Statistical Analysis Plan

Protocol Title:	TNX-CY-F307 A PHASE 3, DOUBLE-BLIND, RANDOMIZED, MULTICENTER, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TNX-102 SL TAKEN DAILY AT BEDTIME IN PATIENTS WITH FIBROMYALGIA ("RESILIENT STUDY")
Protocol Number:	Protocol No. TNX-CY-F307, Amendment 02 (15 June 2023)
Investigational Product:	TNX-102 SL (cyclobenzaprine HCl sublingual tablets)
Phase:	3
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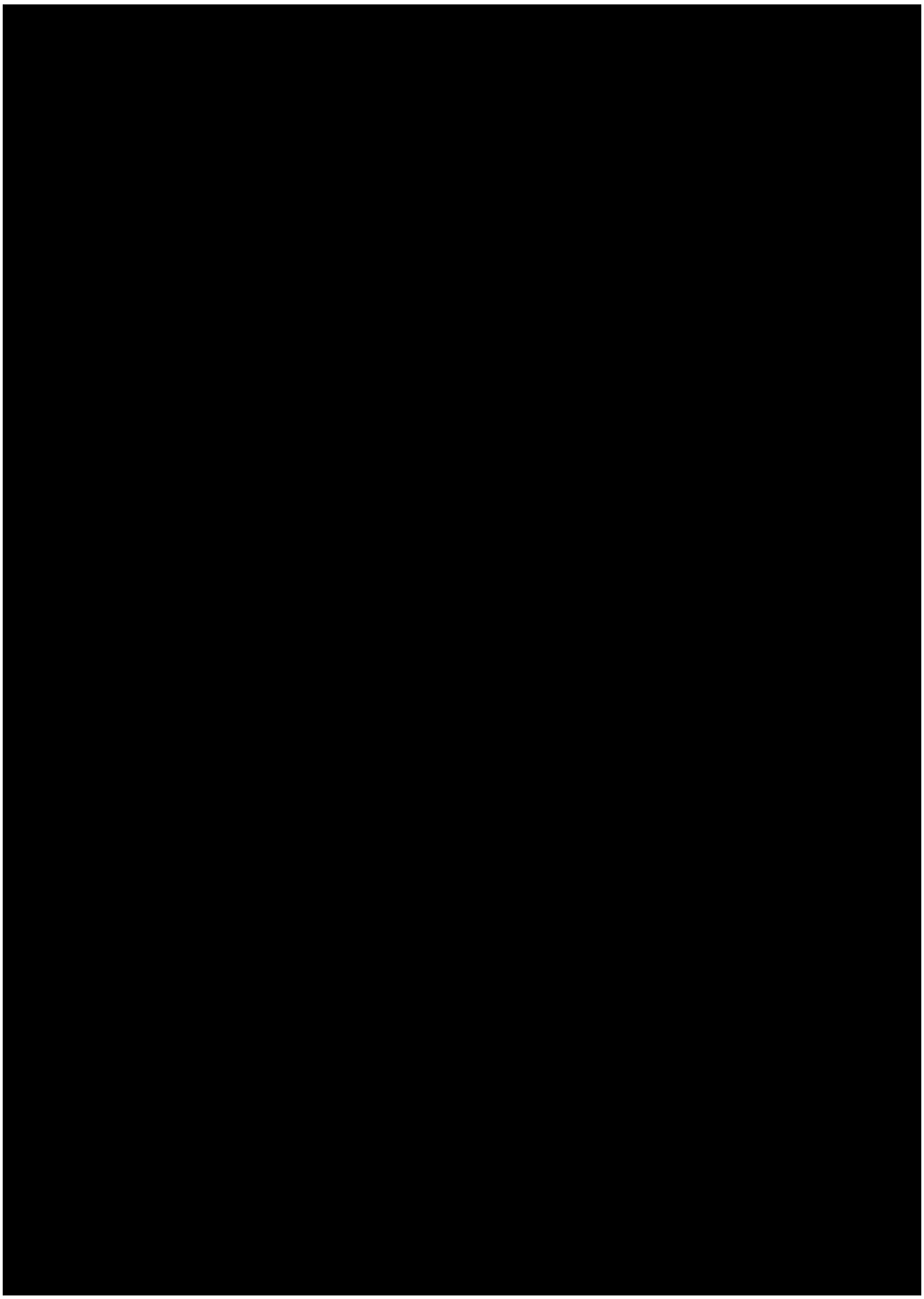

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ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
AE	Adverse Event
ALT	Alternate
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical (WHO Drug Classification System)
BDI-II	Beck Depression Inventory II
BMI	Body Mass Index
CFB	Change from Baseline
CRF	Case Report Form
CSFQ-14	Changes in Sexual Functioning Questionnaire Short-Form
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
EMA	European Medicines Agency
ET	Early Termination
FDA	Food and Drug Administration
FIQR	Fibromyalgia Impact Questionnaire (Revised)
FM	Fibromyalgia
GxT	Genotype by Treatment
GWAS	Genome Wide Association Study
ICH	International Council for Harmonisation
IND	Investigational New Drug
ITT	Intent-to-Treat
LOE	Loss of efficacy
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model Repeated Measures
MNAR	Missing not at random
N	Number of patients
NRS	Numeric Rating Scale
Nt	Nucleotide
PGIC	Patient Global Impression of Change
PROMIS	Patient Reported Outcomes Measurement Information System
REML	Restricted Maximum Likelihood
REF	Reference
Rs	Reference SNP
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF	Short Form
SNP	Single-Nucleotide Polymorphism
SOC	System Organ Class

TEAE	Treatment-emergent Adverse Event
TNX-102 SL tablets	Cyclobenzaprine HCl Sublingual Tablets
WES	Whole exome sequence
WHO	World Health Organization
WHO-DD	World Health Organization – Drug Dictionary

1. BACKGROUND

This Statistical Analysis Plan (SAP) for Protocol No. TNX-CY-F307/RESILIENT Study has been written based [redacted]

2. OVERVIEW

This SAP describes the planned analysis and reporting for Protocol TNX-CY-F307 (A Phase 3, Double-Blind, Randomized, Multicenter, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TNX-102 SL Taken Daily at Bedtime in Patients with Fibromyalgia).

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the 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.

In preparing this SAP (Final Version 1.0 dated 17OCT2023), the following documents were reviewed in addition to the literature references cited in this SAP:

- [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.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective is to evaluate the efficacy of TNX-102 SL taken at bedtime over 14 weeks of treatment using an 11-point (0-10) numerical rating scale (NRS).

3.1.2 Secondary Objectives

The secondary objective is to evaluate the safety of TNX-102 SL taken at bedtime over 14 weeks of treatment.

3.2 Study Endpoints

3.2.1 Efficacy Endpoints

The primary efficacy endpoint is:

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

Key secondary efficacy endpoints include:

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

3.2.2 Exploratory Endpoints

Exploratory efficacy endpoints include:

- Change from baseline in the in-clinic assessment of pain - 24-hour recall
- Change from baseline in the in-clinic assessment of pain - weekly recall
- Proportion of patients with a ≥30% improvement from baseline to Weeks 1-14 in the daily self-reported pain severity score
- Proportion of patients with a ≥50% improvement from baseline to Weeks 1-14 in the daily self-reported average pain severity scores
- Proportion of patients with a PGIC rating of "very much improved" or "much improved" at all post-randomization clinic visits

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

3.2.3 Safety Endpoints

Safety is assessed by the monitoring and recording of Adverse Events (AEs), clinical laboratory tests, vital signs, and physical examinations including examinations of the oral cavity, as well as the monitoring of suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS), and the monitoring of depression status via the Beck Depression Index (BDI-II).

4. OVERALL STUDY DESIGN AND PLAN

This is a Phase 3, randomized, parallel-group, double-blind, placebo-controlled, 16-week study designed to evaluate the efficacy and safety of TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) taken daily at bedtime for the treatment of fibromyalgia. The study is to be conducted at approximately 30-40 investigational sites in the United States.

The study will consist of a Screening Visit (Visit 1, Days -35 to -8), a Baseline/Randomization Visit (Visit 2, Day 1), a Week 2 Visit (where the dose will be increased to 5.6 mg/day), and 3 more treatment visits (Weeks 6, 10 and 14 or Early Termination). The period between the Screening and Baseline Visit wills be at least 7 days, in order to allow for at least one week of daily pain data collection, and up to 35 days, to accommodate any necessary scheduling challenges or prohibited medication washout time. For extenuating circumstances, the duration of the Screening period may be increased to up to 49 days with Medical Monitor approval, and an option for a telephone visit will be available for Weeks 2, 6, and 10 for those unable to attend an in-clinic visit due to circumstances related to the COVID-19 pandemic. Additionally, a Week 14/ET telephone visit or home visit by site staff may be allowed on a case-by-case basis, approved by the Medical Monitor, if the only other choice is losing the patient completely from the study if patient absolutely cannot come in to the clinic for the visit. A safety follow up telephone visit will occur at Week 16. The total duration of the study, including Screening, will be approximately 17-21 weeks. The maximum treatment duration will be 14 weeks.

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

Patients will be trained on the use of the electronic daily diary and will be asked to complete a brief training at each study visit starting from Screening Visit 1. Patients will be asked to record their average daily pain intensity on the 11-point (0-10) NRS scale using 24-hour recall, and to provide an assessment of sleep quality from the previous evening, also using an 11-point NRS scale. Each evening, when the patient completes the diary, the system will prompt the patient regarding daily average pain intensity, sleep quality from the previous night, and study drug dosing (post-randomization). Due to limitations in the diary completion window, patients that are planning on international travel during the study period should not be considered for the study. Patients whose employment involves overnight shifts also should not be considered for the study due to the restricted completion window and the requirement for consistent bedtime dosing.

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

At Screening Visit 1 and after signing the written informed consent, any required washout should be discussed with the patient and plans made for an appropriate schedule for reducing/stopping any excluded medications. This down titration and withdrawal must be accomplished so that the patient is medication-free for at least 21 days prior to randomization. This will provide 14 days

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

Patients will take the study drug sublingually daily at bedtime, starting in the evening of the day that they are randomized (Day 1, Visit 2), for 14 weeks. Patients will be instructed to take one tablet (2.8 mg) sublingually daily at bedtime for the first 2 weeks (Days 1-14). Patients will then return to the clinic at Week 2 (Visit 3) for efficacy and safety assessments, assessment of study drug compliance, and the study drug dose will be increased to two tablets (2 x 2.8 mg) taken sublingually and simultaneously daily at bedtime. Patients will next return to the clinic at Week 6 (Visit 4) for efficacy and safety assessments, assessment of study drug compliance, and an assessment of dose tolerability at the 5.6 mg dose. If the patient reports intolerable side effects at this visit (Visit 4), the Investigator may consider a reduction in dose to one tablet sublingually every night (with Medical Monitor approval), either temporarily or for the remainder of the study, depending on what the Investigator considers clinically appropriate. It will be emphasized to Investigators that such dosage reduction should only be considered when the patient's intolerability is sufficient to cause the patient to consider discontinuing from the study. It will be emphasized to participating patients that they should only make changes in study drug dose upon consultation with the Investigator, and they should notify the clinic immediately if they think the dosage needs to be adjusted. Ideally, any changes in dose should only be made at a scheduled visit, but, if necessary to change dose between visits, the change should only be made upon the recommendation of the Investigator after discussion between the patient and the Investigator. Patients will return to the study center for safety and efficacy assessments, and assessments of study drug compliance and tolerability at Weeks 10 (Visit 5), and 14 (Visit 6) or Early Termination. Approximately 2 weeks after Week 14 (Visit 6), there will be a Post-study Safety Follow-up telephone call (Visit 7).

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

4.1 Selection of Study Population

For a complete list of inclusion and exclusion criteria please refer to the study protocol.

4.2 Method of Treatment Assignment and Randomization

The following randomization criteria must be satisfied at the Baseline visit (Visit 2) in order for the patient to continue in the study and be randomized:

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

d. Pain scores must be recorded on at least 5 out of the 7 days immediately preceding Visit 2.

Before the start of the study, a computer-generated randomization schedule will be prepared. Based on the randomization schedule, eligible patients will be randomly assigned in a 1:1 ratio to receive TNX-102 SL tablets or placebo tablets for 14 weeks.

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

4.3 Treatment Blinding

This is a double-blind study. Unless otherwise specified, all study personnel are to remain blinded to study drug. Treatment assignments will not be revealed until all patients have completed the study and the database has been finalized and closed.

If AEs occur that are considered to be intolerable, the investigator must decide whether it is necessary for the patient to discontinue study drug; however, the investigator should not be unblinded unless it is imperative for the patient's overall safety to determine whether the patient received active study drug (e.g., in the event of overdose).

4.4 Minimization of Missing Data

The Sponsor believes it has incorporated strong steps into the study design to ensure minimization of missing data during the treatment period. Multiple analysis techniques to examine the impact of missing data on the robustness of results will be carried out. Additionally, with Medical Monitor approval, investigators have the option after the Week 2 visit when dose escalation has occurred, to reduce the treatment dose back to one tablet of TNX-102 SL 2.8 mg or one tablet of placebo if the higher dose is resulting in tolerability issues that would otherwise lead to study discontinuation. The importance of minimizing the amount of missing data will be discussed with all study investigators, and their awareness of the importance of patient compliance and minimal dropout rates is factored into their recruiting plans and daily patient management. In addition, investigators are advised to contact the Medical Monitor for guidance on available management options when needed to avoid patients withdrawing from the study.

4.4.1 Opioid Usage

In order to minimize confounding issues related to concomitant usage of opioids, investigators have been asked to identify candidates for this clinical trial that are not currently using chronic opioids. However, it is understood by the Sponsor that opioid usage is sometimes unavoidable for acute conditions. In the event that an opioid is required for the management of an acute pain condition, the patient will be instructed to contact the site immediately so that appropriate management decisions can be implemented and accurate medication records obtained. In addition, when feasible, study visits may be delayed to avoid the contamination of data by recent

opioid usage. At a minimum, no opioid/narcotic should be utilized within 2 days of a study visit, and ideally there will be no usage during the 7 days prior to any visit.

A listing of concomitant medication CRF data identifying the use of opioids will be reviewed by the project team and approved by the Sponsor prior to database lock and unblinding, and will be used to flag records in the analysis database and in the by-patient concomitant medication listings. These flagged records will also be utilized to identify records to be censored in the sensitivity analysis described in Section 10.1.3.

4.4.2 Intermittent Missing Data

Intermittent missing daily data will not be imputed and weekly averages will be calculated using available values, even if only a single value is available for a week. Intermittent missing data (weekly averages and/or in-clinic assessments) occurring prior to discontinuing use of study drug is assumed to be missing at random, and analyses have been chosen to mitigate the impact of these missing data (Section 10.1).

5. ANALYSIS AND REPORTING

All final, planned analyses will be performed after the last patient has completed the last study visit and end-of-study assessments and all relevant study data have been processed and integrated into the analysis database. Any post-hoc, exploratory analyses completed to support planned study analyses, but 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 as such in the text of the CSR.

6. SAMPLE SIZE DETERMINATION

The study is planned to enroll approximately 470 patients total in a 1:1 randomization, that is, 235 patients in each of the TNX-102 SL and placebo arms. Using a two-sided t-test with an alpha level of 0.05, a sample size of 235 per group provides a power of approximately 90% if the effect size is 0.30.

7. ANALYSIS POPULATIONS

The following analysis populations are planned for this study:

- **All subjects:** Used for summaries of dispositions of patients; tabulations of dispositions may also use the populations below.
- **Safety population:** all patients who took investigational product. Patients that were issued study drug, but do not return all of it will be included in the safety population. All safety analyses and demographic/baseline characterization will be performed using this population, analyzed as treated.
- **Intention-To-Treat (ITT) population**: all patients who were randomized. This is the primary population for efficacy analyses, and patients will be analyzed based on their randomized treatment.

8. GENERAL ISSUES FOR STATISTICAL ANALYSIS

8.1 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 and visit. All patients for a population in each treatment group will be grouped together; patients that reduce dose from two tablets per day to one tablet per day will be not be reported separately for the analyses described in this SAP, unless otherwise noted. If there are more than 10% of patients in the active arm with a dose reduction at any point in the study, summary statistics on key outcomes may be reported for patients with dose reductions.

Baseline characteristic and safety tables will be completed for the Safety Population unless otherwise specified. Efficacy tables will be presented for the ITT Population.

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.

Baseline values are defined as the last non-missing measurement prior to the first dose of study drug. For scores obtained via diary, baseline will be defined as the average of the scores from the 7 days prior to the baseline visit. Change from baseline will be defined as the post-baseline visit value minus the baseline value.

Study day is defined as assessment date – first dose date +1 for dates on/after first dose date and assessment date – first dose date for those before.

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

8.1.1 Adjustments for Multiplicity

8.1.1.1 Multiplicity

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

The order of key secondary endpoints in which they are to be tested is as follows:

- Proportion of patients with a PGIC rating of “very much improved” or “much improved” at Week 14
- Change from baseline in the FIQR symptoms domain score at Week 14
- Change from baseline in the FIQR function domain score at Week 14

- Change from baseline in the PROMIS score for sleep disturbance at Week 14
- Change from baseline in the PROMIS score for fatigue at Week 14
- Change from baseline to Week 14 in the weekly average of the daily diary assessment of sleep quality.

No other adjustments for multiplicity will be made and other p-values displayed in the output will be considered for descriptive summary purposes only and will not be used for formal inference. Additional details regarding statistical analysis for the listed endpoints can be found in Section 10.

8.1.2 Data Handling for Patients Who Withdraw/Drop Out from the Study

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 (Week 2, 6, 10, 14), using midpoints 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 (see below).

For example, a patient with a non-missing Week 10 clinic assessment collected on Day 72 that has early termination data collected on Day 79, would have the early termination data mapped to Week 10; however, since Day 72 data is present and closer to the target date, it would be analyzed and the Day 79 data would be excluded. A patient with missing Week 10 data who early terminates on Day 79 would have the Day 79 data analyzed with the Week 10 data.

Patients who provide 14 weeks of diary pain data will be analyzed as completers for purposes of the primary analysis, even if for some reason they are unable to attend a Week 14 final study visit. As a specific example, a patient who successfully provides 14 weeks of diary data as described in Section 8.2.1, but who is unable to attend a final study visit during the required time window because of travel or other circumstances, would be analyzed as a completer for purposes of the primary endpoint, but would be missing non-diary based secondary outcome measures at the Week 14 endpoint.

For safety data, the last observation available will be summarized in addition to the presentation above (grouping ET visits with the closest planned visit); this will combine the ET visit data with the completers' Week 14 data, regardless of when the ET occurred.

8.1.3 Site Covariate

For the purposes of modeling and imputation, all sites with less than 10 patients will be pooled into a single large site. In listings and analyses by site, patients will appear under their study site identifier (not the pooled site).

8.1.4 Imputation of Missing Data

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

Missing weekly pain scores for participants in the ITT population will be imputed via multiple imputation (MI). [redacted]

The steps will be as follows:

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

Daily sleep diary data will be handled in an identical manner to the pain scores.

Continuous outcomes included in the list of key secondary outcomes that are collected in-clinic will be handled as above, minus the step of creating weekly averages of daily values and with steps being done by visit instead of week.

Patients with missing PGIC at a given visit will be considered non-responders at that visit for the purposes of treatment comparisons and efficacy claims; additional tabulations will summarize the number and percentage in each category out of non-missing values as well as a count of the missing values.

No missing safety data will be imputed.

8.2 Efficacy Assessments

8.2.1 Average Daily Pain Score

The average daily pain score will be obtained using the daily, 24-hour recall, NRS pain data collected with the diary system. Since a mean is used in the calculation of the primary endpoint, it is not necessary to replace values missing on random intermittent days.

The baseline pain score will be defined as the average of the pain scores from the 7 days prior to the baseline visit. Pain scores must be recorded on at least 5 out of the 7 days immediately preceding the baseline visit in order for the patient to qualify for randomization.

The mean of the daily, patient self-reported, 24-hour recall, pain severity scores for the 7 days of each week will serve as the pain score for that study week. All available values will be used; if a patient has at least one value for the week, the week is non-missing. Because there is a -4 day and +7 day window around the scheduling of Visit 6 (Day 99), the study weeks will be anchored by the timing and completeness of their final study visit. Ideally, patients appearing in-clinic on Day 99 (defining randomization as Day 1), would have last filled out their diary on Day 98; therefore, "Week 14" would include Days 92-98; the protocol-defined window allows visit 6 as early as Day 95, resulting in a nominal "Week 14" including Days 88-94. Likewise, patients may appear in-clinic per protocol as late as Day 106, resulting in a "Week 14" interval running from Day 99-105.

Due to impacts from the COVID-19 pandemic, the criteria for calculating the Week 14 average will be marginally relaxed beyond the protocol-specified visit windows to allow for additional flexibility by permitting data collected during Week 13 to be used to calculate the Week 14 average: working backwards from Day 98, the first non-missing day (as early as Day 91) will serve as the LAST day of Week 14 for the purpose of anchoring and any non-missing values in the 6 days prior to that day will contribute to the average. If a patient does not have a non-missing value on/after Day 91, any available data from Day 85-91 will be averaged as Week 14 and Day 91 will serve as the anchor. Patients without data on/after Day 85 will be missing for Week 14 and handled as described below. Specific examples of calculating the Week 14 pain score are described in Appendix C.

Each week prior to Week 14 will be based on 7-day intervals; depending on the interval selected for "Week 14", this will result in Week 1 having less than 7 days or some "extra" days prior to Week 1. Extra days will be dropped and not included in the analysis; in the case of less than 7 days, the available days will be averaged, as long as there are non-missing values. The earliest day included in the Week 1 average will be the data entered the day after randomization (covering roughly the 24 hours following their first dose of study drug).

For patients who withdraw from the study early, that do not have a final study visit or complete the study but do not have data in the 7 days preceding their last visit, the last day of diary data (at or prior to Day 106) will serve as the anchor point for dividing the available data into weeks. First, the nearest nominal end day for a weekly period is identified and this week will be the assigned the data from the 7 days immediately preceding the anchor date. For example, if a patient early terminates on study Day 24, the Week 3 (nominally ending on day 21) average will be based on the 7 days prior to Day 24 (Days 17-23). Lost to follow-up patients that continue to fill out the diary into Week 14 and beyond will have non-missing values for the Week 14

timepoint for diary outcomes. Day 106 will be the last allowable day to be included in the average.

Week	Nominal Study Day Intervals
Baseline	Day -7 to -1
Day of Randomization	Day 1
Week 1	Day 2 to 7
Week 2	Day 8 to 14
Week 3	Day 15 to 21
Week 4	Day 22 to 28
Week 5	Day 29 to 35
Week 6	Day 36 to 42
Week 7	Day 43 to 49
Week 8	Day 50 to 56
Week 9	Day 57 to 63
Week 10	Day 64 to 70
Week 11	Day 71 to 77
Week 12	Day 78 to 84
Week 13	Day 85 to 91
Week 14	Day 92 to 98

Change from baseline will be defined as the pain score at each week minus the baseline pain score (with baseline and weekly pain scores derived as described above). Thus, negative changes will denote lesser pain and larger negative values will denote greater improvement.

8.2.2 Average Daily Sleep Quality Score

The average daily sleep quality score will be obtained in the same manner as the average daily pain score, via electronic Interactive Response Technology (IRT) system. Derivation of the weekly average sleep quality scores and censoring of data will be treated the same as the weekly average pain scores described in Section 8.2.1, using the same windows based on the date of collection. It should be noted that the sleep prompt asks about the prior night's sleep; thus, patients report their sleep starting the first night that they take randomized drug through the night between day 97-98, if their final visit is day 99. As with pain, negative changes will denote improvement in sleep quality and larger negative values will denote greater improvement.

8.2.3 Patient Global Impression of Change (PGIC)

PGIC is a question completed by the patient at Weeks 2, 6, 10, and 14. The patient will rate the change in their overall fibromyalgia symptoms on a 1-7 Likert scale, where 1 is "Very Much Improved" and 2 is "Much Improved". Scores of 1 and 2 will be considered PGIC responders, and all other scores will be considered non-responders for that visit. The proportion of responders in each treatment arm will be analyzed. Any missing PGIC score will be considered a non-responder for that visit.

An exploratory analysis will include "Minimally Improved" (3) as responders, in addition to scores of 1 and 2.

8.2.4 Revised Fibromyalgia Impact Questionnaire (FIQR)

The FIQR is made up of 3 domains: (1) functional (9 questions); (2) overall impact (2 questions) and (3) symptoms (10 questions). If 2 or more items are missing from the functional domain, the domain will be considered invalid for that visit. Likewise, if *any* item is missing from the overall impact domain or the symptom domain, those domains will be considered invalid.

To account for missing items in the functional domain, the score will be recalculated as:

New score = (Raw score / # of items answered) × # of items in domain

The FIQR total score can be determined after all domain scores have been calculated using the following steps. First, divide the function domain score by 3, divide the overall impact domain score by 1, and divide the symptom domain score by 2. Next, add the three resulting domain scores to obtain the total score of FIQR. If any domain score is missing, then the total is missing.

8.2.5 Patient Reported Outcomes Measurement System (PROMIS) Instruments

8.2.5.1 PROMIS Short-Form (SF) Fatigue and Sleep Disturbance Instruments

The PROMIS Short-Form Fatigue and Sleep Disturbance Instruments each consist of 8 items in which responses are scored 1 to 5 for each item. Scores for all items are totaled to create a raw score. Either instrument will be considered invalid if 50% of the items are missing. If more than 50% of the items are answered, the raw total score will use the following formula to determine a new calculated score to account for missing items.

New raw score = (Raw score / # of items answered) × # of total items

New raw scores that are fractions are rounded up to the nearest whole number. Once a new raw score has been calculated, a T-score will be determined using Appendix A for Fatigue Inventory and Appendix B for Sleep Disturbance. The T-scores will be analyzed.

Note that items 1, 2, and 8 of the PROMIS Sleep Disturbance Instrument will need to have their directionality reversed for calculating the totals.

8.2.6 Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14)

The CSFQ-14 (Keller et al. 2006) is a validated scale with internal reliability designed to allow a patient to self-evaluate his or her sexual behaviors or problems in a number of areas. The CSFQ-14 will be administered at Baseline (Visit 2) and Week 14/ET (Visit 6). It yields a total score, three subscales corresponding to phases of the sexual response cycle (i.e. desire, arousal, orgasm), and five subscales corresponding to important dimensions of sexual functioning. It is considered a useful scale for assessing sexual side effects of medications. For all items, higher scores reflect higher sexual functioning. For 12 of the 14 items, higher sexual functioning corresponds to greater frequency or enjoyment/pleasure (e.g. 1=never to 5 = every day). For two items (item 10, assessing loss of interest after arousal for women and priapism for men, and item

14, assessing painful orgasm), higher sexual functioning corresponds to lower frequency (e.g. 1=every day; 5=never). Items 10 and 14 are included in the total score but not in any subscale scores.

8.3 Safety Endpoints

To handle missing or partial AE and 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.

Adverse events are categorized as pre-treatment adverse events or treatment-emergent adverse events based on the response to the CRF question "Did the AE start prior to the first dose?"

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

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

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 treatment.
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 treatment.
4. If the start date is not missing but the stop date is missing, then the most conservative

approach is taken and the medication is considered to be concomitant.

9. STUDY PATIENTS AND DEMOGRAPHICS

9.1 Disposition of Patients and Withdrawals

The numbers and percentage of patients screened, randomized, completing the study, and withdrawing from the study, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number and percentage of patients in each analysis population will be reported. Additionally, the number and percentage of patients that have an investigator-directed dose reduction from two tablets per day to one tablet per day will be summarized. The disposition and withdrawal summaries will be based on all patients who have data entered into the database.

9.2 Protocol Violations and Deviations

Protocol deviations will be checked on complete data for all patients. Protocol deviations will be summarized by type, status as Important vs Non-important, and by treatment group for the Safety population.

Individual patients with protocol deviations or violations will be listed.

9.3 Demographics and Other Baseline Characteristics

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

Descriptive summaries of demographic and other baseline conditions will include:

- Demographics (age, gender, race/ethnicity, height, weight, BMI, family status, education and employment status)
- Tobacco/nicotine, alcohol, and THC/cannabis use history

Medical History will be coded using version 23.0 of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by SOC and Preferred Term using frequency counts by treatment group. Physical examination data, as well as findings from dedicated oral cavity examinations, will be presented in listings.

10. EFFICACY ANALYSES

10.1 Primary Efficacy Analysis

10.1.1 Estimand

The primary ITT analysis will provide an estimate of the following causal estimand: the difference in the weekly mean change from Baseline of the daily patient self-reported 24-hour recall average pain severity rating using an 11-point (0-10) NRS evaluated at the Week 14 endpoint in all randomized patients attributable to the initially randomized treatment assignment, under the assumption that those withdrawing due to AEs and lack of efficacy revert to the baseline pain levels (on average).

10.1.2 Primary Analysis

The mean change from baseline in the weekly average of daily pain scores from baseline to each week in the TNX-102 SL and placebo arms will be analyzed using a restricted maximum likelihood (REML) based repeated measures approach with data imputed using multiple imputation (see Section 8.1.4). Week 14 will serve as the primary time point of interest. Models will be run on each of the twenty imputation sets individually and will include the fixed, categorical effects of treatment, pooled site, study week, and treatment by study week interaction, as well as the fixed covariates of baseline value and baseline value score-by-study week interaction. An unstructured covariance structure will be used to model the within-patient errors. If this analysis fails to converge, the following structures will be tested in this order: first order ante dependence, heterogeneous first order autoregressive, heterogeneous compound symmetry and compound symmetry with the first to give convergence used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. LS means and differences across the twenty MI reps will be combined using SAS procedure MIANALYZE (Rubin, 1976). Significance testing will be based on least-squares means and two-sided 95% confidence intervals will be presented. The p-values will be compared against two-sided alpha of 0.05.

10.1.3 Sensitivity Analyses

Four sensitivity analyses will be performed:

For the first, pain scores will be censored on the day(s) on which an opioid is utilized. If the patient utilizes an opioid for any indication, then the pain score on each impacted day will be replaced by the score obtained on the day immediately prior to the first day of opioid use (and until the opioid is no longer used). This will be done prior to the weekly averaging, and all other calculations will be performed as described in the primary. This will investigate whether use of concomitant opioids influences the interpretation of study results.

For the second, patients that discontinue due to “withdrawal of consent” or “investigator decision” will be grouped with the LOE and AE dropouts when performing the multiple imputation procedure. This analysis will investigate whether the categorization of these reasons for dropout influences the interpretation of study results.

For the third, ALL patients that discontinue will be grouped with the LOE and AE dropouts when performing the multiple imputation procedure. This analysis will sample from the baseline

distribution of all dropouts and will investigate whether treating dropouts as treatment failures (on average) influences the interpretation of study results.

Finally, a tipping point analysis will be performed on the values for the primary analysis. A shift parameter will be applied to the active treatment arm starting at .25 and increasing in increments of .25 through either 5 or when the outcome is no longer significant. This will only be performed if the primary analysis is significant. This will test the overall robustness of the primary analysis.

10.2 Secondary Efficacy Analyses

Secondary efficacy analyses will be based on the ITT population only.

Continuous Endpoints

For the purposes of possible label claims and reported p-values entered into the multiplicity algorithm, an approach identical to the primary analysis will be used for all continuous outcomes. See Section 8.1.4 for the imputation algorithm and Section 10.1.2 for the analysis approach.

Outcomes using these analyses will include:

- Change from baseline in the FIQR symptoms domain score
- Change from baseline in the FIQR function domain score
- Change from baseline in the PROMIS score for sleep disturbance
- Change from baseline in the PROMIS score for fatigue
- Change from baseline in the weekly average of the daily diary assessment of sleep quality.

For each, all time points will be summarized, but the primary time point of interest is Week 14. Time points other than Week 14 are considered exploratory. The estimand for each is identical to the primary, substituting for the endpoint in question.

For the sleep quality assessment collected via a daily patient diary, the baseline score and the weekly scores for each patient will be calculated as the weekly average score based on the mean of the scores recorded for that study week (Section 8.2.2).

In addition to the above analyses using the primary imputation and model, analyses will be repeated on the outcomes above, but using observed data only without imputation.

Categorical Endpoints

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

10.3 Exploratory Analyses

All efficacy analyses at time points other than Week 14 are considered exploratory as described above.

Additional exploratory efficacy endpoints include:

- FIQR total score, overall impact domain score, and individual item scores at all post-randomization clinic visits
- Proportion of patients with a ≥30% improvement from baseline to Weeks 1-14 in the daily self-reported pain severity score
- Proportion of patients with a ≥50% improvement from baseline to Weeks 1-14 in the daily self-reported average pain severity scores
- Proportion of patients with a PGIC rating of "minimally improved," "very much improved" or "much improved" at all post-randomization clinic visits
- PGIC as a continuous variable with 1-7 scoring
- CSFQ-14 at Week 14
- In-clinic assessment of pain (24-hour & weekly recall)

The PGIC, 30% and 50% improvement responder endpoints will be analyzed with a difference in proportions Z test (equivalent to a Pearson's Chi Squared). Patients with missing data will be considered non-responders. The percentages of responders and the 95% CIs of the percentages as well as the difference in the percentages and its 95% CI will be reported.

In addition to the responder analysis in the secondary outcomes, PGIC will be analyzed as a continuous variable scoring the responses 1-7. Results will be reported by treatment with summary statistics and an MMRM Model will be used to compare treatments. The model will include the fixed, categorical effects of treatment, pooled site, study week, and treatment by study week interaction. An unstructured covariance structure will be used to model the within-patient errors. If this analysis fails to converge, the following structures will be tested in this order: first order ante dependence, heterogeneous first order autoregressive, heterogeneous compound symmetry and compound symmetry with the first to give convergence used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Significance testing will be based on least-squares means using a two-sided alpha=0.05 test and two-sided 95% confidence intervals will be presented.

The CSFQ-14 is completed at baseline and Week 14/ET. It has a male and a female version, which will be analyzed separately. The CSFQ-14 will be analyzed for its total score, three subscales on phases of sexual response, and five subscales for dimensions of sexual functioning by using an Analysis of Covariance (ANCOVA) model. The model will include the fixed, categorical effects of treatment and pooled site, plus a baseline covariate corresponding to the subscale (or total) being analyzed. Significance testing will be based on least-squares means using a two-sided alpha=0.05 test and two-sided 95% confidence intervals will be presented. This outcome is considered to be supportive of the product's safety; other exploratory analyses are for further support of product efficacy.

The FIQR exploratory endpoints and the in-clinic pain assessments will be analyzed using an MMRM including the fixed, categorical effects of treatment, pooled site, study week, and treatment by study week interaction, as well as the fixed covariates of baseline value and baseline value score-by-study week interaction. An unstructured covariance structure will be used to model the within-patient errors. If this analysis fails to converge, the following structures will be tested in this order: first order ante dependence, heterogeneous first order autoregressive, heterogeneous compound symmetry and compound symmetry with the first to give convergence used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Note that the screening values will be used as baseline for the in-clinic pain outcomes.

10.3.1 Exploratory Analyses of Single-Nucleotide Polymorphism (SNP) Subgroups

The response to TNX-102 SL therapy will be analyzed in subgroups defined by genetic analysis. Blood samples were collected from patients in TNX-CY-F307 after obtaining patient's signed pharmacogenomic informed consent form and Institutional Review Board approval. Laboratory quality germline DNA sequencing from this subgroup will be used to determine the genotypes and group patients by genetically defined alleles for exploratory analyses of treatment response.

The primary and key secondary efficacy analyses for the subgroups of patients with each of these genetically-defined alleles, and certain combinations, will be presented for the current study F307 to confirm the strength of the results observed for TNX-CY-F304 and TNX-CY-F306. Analysis methods will be identical to those used for the full population, but applied to subsets of the study participants defined by the genetically defined alleles. The pooled site variable as generated for the full population will be utilized where specified, but should convergence issues arise, a pooled site variable specific to the subpopulation will be created. The overall summary of adverse events and summary of AEs by system organ class and preferred term will also be reported for these subgroups (see section 11.1 for the description of these displays).

10.4 Analyses by Dose

Given that TNX-102 SL is generally well tolerated, it is unlikely that a large number of patients will have a dose reduction to one tablet and hence it is nearly certain that an insufficient number will have such a reduction so as to allow the multiple imputation algorithm to return stable results taking dose into account. If more than 10% of the patients in the active arm have a dose reduction at any point in the study, summary statistics on observed values for the primary and key secondary outcomes will be reported for placebo and each dose, with active treatment patients grouped by whether they had a PI-directed dose reduction at any time point, regardless of the dose they were on at a particular time point. Placebo patients that had a "dose reduction" will not be grouped separately.

10.5 Additional Subgroup Analyses

[redacted]

[redacted]

11. SAFETY AND TOLERABILITY ANALYSES

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

- Adverse Events
- Clinical Laboratory Investigations
- C-SSRS
- BDI-II
- Vital Signs
- Physical Examinations and examinations of the oral cavity
- CSFQ-14

11.1 Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA Dictionary Version 23.0.

The collection of adverse events will begin at the time the patient is consented and screened for the study. Treatment-emergent adverse events (TEAEs) are defined as either new onset AEs with an onset at the time of or following the start of treatment, as indicated by a "no" answer to "Did AE start prior to the first dose?", or a recurrence of an AE (or medical history) present prior to randomization but increasing in severity, frequency or relationship at the time of or following the start of treatment.

An AE summary table will be presented for the following:

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

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

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

In the AE data listings, all AEs will be displayed. AEs that occur prior to randomization will be considered pre-treatment AEs, and will be determined by a "yes" response to the CRF question, "Did the AE start prior to the first dose?" AEs that start on the date of randomization but have a "yes" response to this question will be categorized as pre-treatment AEs. TEAEs will be defined

from the date of randomization and a "no" response to the CRF question, "Did the AE start prior to the first dose?"

11.1.1 Adverse Events Leading to Discontinuation of Study Drug

A summary of incidence rates (frequencies and percentages) of TEAEs 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.

11.1.2 Serious Adverse Events

A summary of incidence rates (frequencies and percentages) of serious adverse events (SAE) 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.

11.1.3 Oral TEAEs

In light of the study drug's sublingual route of delivery, patients will undergo a detailed examination of the oral cavity at screening and brief examinations at all other visits.

AEs involving the oral cavity may be spontaneously reported by the patient, observed during an oral cavity examination, or both. Oral cavity AEs will be identified by a "yes" response to the CRF question, "Is the AE in the oral cavity?" Additional information will be collected on oral cavity AEs (based on a "yes" response to the above question), including whether the AE occurs immediately or very soon after dosing, an approximation of the duration of the AE (less than or greater than 60 minutes), and whether the AE is still present the next morning upon awakening.

A separate by-patient listing of oral cavity AEs (including pre-treatment oral cavity AEs) will be provided.

11.1.4 Deaths

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

11.2 Clinical Laboratory Evaluations

Laboratory data (analytes for Chemistry and Hematology) will be summarized by treatment and visit for the Safety Population. Descriptive summaries of actual values and changes from baseline will be presented by study visit and last available assessment for each clinical laboratory analyte and each treatment group. 95% confidence intervals will be presented for change from baseline. 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 with their corresponding normal ranges, and those values that are outside the normal range will be flagged. For each laboratory analyte, shifts in assessments of abnormality from baseline to each scheduled time point will be presented in shift tables.

A by-patient listing of all clinical laboratory (Chemistry, Hematology and Urinalysis) data will also be provided.

11.3 Columbia Suicide Severity Rating Scale (C-SSRS)

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

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 non-suicidal behavior at the screening and baseline visit will be summarized by visit and treatment group.

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

Category	Items
A) Suicidal Ideation	(1) Wish to be dead
	(2) Non-specific active suicidal thoughts
	(3) Active suicidal ideation with any methods (not plan) without intent to act
	(4) Active suicidal ideation with any some intent to act, without specific plan
	(5) Active suicidal ideation with specific plan and intent
B) Suicidal Behavior	(6) Preparatory acts or behavior
	(7) Aborted attempt
	(8) Interrupted attempt
	(9) Actual attempt
	10) Completed suicide
	Suicidal Behavior present (composite of items 6-10)
	Non-Suicidal Self-Injurious Behavior

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

11.4 Beck Depression Inventory II

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

11.5 Vital Signs

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

11.6 Physical Examination and Oral Cavity Exam

A standard physical examination will be performed at Screening, Baseline, and Week 14. In addition, a separate examination of the oral cavity will be performed at each visit (Screening through Week 14). Oral cavity examination findings will be documented separately from other physical examination findings. Note that the oral exam did not include examination of the pharynx; any findings there would be recorded with the physical exam, and also on the AE page, if appropriate.

A data listing of the results at each scheduled visit will be presented for both the standard physical examination and the examination of the oral cavity.

12. MEDICATIONS

12.1 Concomitant Medication

All medications will be coded using the MAR2020 version of the World Health Organization Drug Dictionary. 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 Levels 1 and 3 and preferred term.

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.

Prior and Concomitant medications will be summarized. All medications will be presented in a listing.

Please refer to Section 8.3 to impute the partial start date and end date of concomitant medication.

12.2 Opioid Medications

A list of patients' concomitant medication records from the CRF data identifying opioid usage will be reviewed by the project team and approved by the sponsor prior to database lock. This listing will be used to flag opioid records in the analysis database and in the by-patient concomitant medication listings.

12.3 Exposure and Compliance

The treatment duration will be calculated and summarized based primarily on CRF data for first and last dose dates (number of days=last dose date – first dose date+1). If these values are missing or patients' diary data indicate dates that exceed this period, the diary dates will be utilized.

Days of exposure will be based on patients' responses to the daily questions regarding medication usage. The number of days on study drug is the total number of days a patient respond that study drug was taken. If the CRF data for the last dose date is a date not included in the diary, it will be added to the count (this should be true for most completing patients since they do not fill out a diary the day of their last visit). The number of patients with total exposure by visit weeks (≤2 weeks, 2 to ≤4, 4 to ≤8, 8 to ≤12, 12 to ≤14 and >14 weeks) will be presented. Missing days where the patient did not complete the diary will be treated as though study drug was not taken. Days of exposure will also be calculated for the days on each dose of study drug.

Additionally, the number and percentage of patients that drop back to one tablet per day will be summarized and the week in which they reduced their dose will be tabulated (among those that had a dose reduction).

Compliance will be similarly summarized across all study visits for each treatment arm. Study drug compliance as a percentage will be defined as the exposure days defined above divided by the total number of expected days on treatment multiplied by 100. The expected number of days will be the date of last diary recorded dose-randomization date +1. This compliance reporting

will take into account whether or not they took any medication, but will not account for the number of tablets they took on a given day.

Compliance will be summarized with descriptive statistics by treatment arm. The number and percentages of patients within certain categories of compliance (e.g. < 60%, 60% to < 80%, 80% to ≤ 100%, greater than 100%) will also be presented.

A listing of drug accountability data based on CRF data will be provided.

13. CHANGES FROM PLANNED ANALYSIS

Analysis of PGIC as a continuous variable with values 1-7 added.

14. REFERENCES (AVAILABLE UPON REQUEST)

15. APPENDICES

15.1 Appendix A

Fatigue 8a - Adult v1.0 *Short Form Conversion Table*					
Raw Score	**T-score**	**SE***	**Raw Score**	**T-score**	**SE***
8	33.1	4.8	25	58.5	1.7
9	38.5	2.7	26	59.4	1.7
10	41	2.2	27	60.4	1.7
11	42.8	2	28	61.3	1.7
12	44.3	1.9	29	62.3	1.7
13	45.6	1.8	30	63.3	1.7
14	46.9	1.8	31	64.3	1.7
15	48.1	1.8	32	65.3	1.7
16	49.2	1.8	33	66.4	1.7
17	50.4	1.8	34	67.5	1.7
18	51.5	1.7	35	68.6	1.7
19	52.5	1.7	36	69.8	1.8
20	53.6	1.7	37	71	1.8
21	54.6	1.7	38	72.4	2
22	55.6	1.7	39	74.2	2.4
23	56.6	1.7	40	77.8	3.7
24	57.5	1.7			
*SE = Standard Error on T-score metric					

15.2 Appendix B 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		

15.3 Appendix C

The following conventions will be used for calculation of a patient's nominal Week 14 score. All other week scores are calculated relative to the nominal Week 14 interval.

Landmark Endpoint Visit Day	Last Available Diary Score Recorded	Days Used to Calculate "Week 14"	Comment
99	98	92-98	Ideal condition with final study visit on Day 99, last diary data will be day 98.
100	99	93-99	
101	100	94-100	
102	101	95-101	
103	102	96-102	
104	103	97-103	
105	104	98-104	
106	105	99-105	
Out of window (late)	106+	99-105	Since the Week 14 endpoint is Day 99 -4/+7 days, days after 106 are outside the Week 14 nominal interval. Any scores recorded after day 106 will be ignored.
98	97	91-97	
97	96	90-96	
96	95	89-95	
95	94	88-94	
94	93	87-93	Out of window, but allowed
93	92	85-92	Out of window, but allowed
92	91	85-91	Out of window, but allowed
<92	<91	85+	Must have a valid score occurring on/after day 85 or will be missing for week 14

15.4 Appendix D

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

5465464

3779512

9776222

6324863

3985432

7982341

8675309

4456933

7529612

6282513

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 in the last by 1. All seeds used will be documented in the programming specifications and the programs themselves.

15.5 Appendix E

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.

15.5.1 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., 2001-08-01) 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 and a date stamp on the bottom of each output.

15.5.2 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 Patients, (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., ITT >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 Patients with non-missing values.
- All population summaries for categorical variables will include all categories that were planned and for which the patients 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.