Statistical Analysis Plan

Protocol Title:	TNX-CY-PA201 A Phase 2, 14-week Double-Blind, Randomized, Multicenter, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TNX-102 SL Taken Daily at Bedtime in Patients with Multi-site Pain Associated with Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)
Protocol Number:	Protocol No. TNX-CY-PA201, Amendment 02 (13 October 2022)
Investigational Product:	TNX-102 SL (cyclobenzaprine HCl sublingual tablets)
Phase:	2
Sponsor:	Tonix Pharmaceuticals, Inc. [redacted]
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ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
AE	Adverse Event
BMI	Body Mass Index
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DDFM	Denominator degrees of freedom
ESS	Epworth Sleepiness Scale
ET	Early Termination
FDA	Food and Drug Administration
ICH	International Council for Harmonisation
IND	Investigational New Drug
ISI	Insomnia Severity Index
ITT	Intent-to-Treat
LOE	Loss of efficacy
MAR	Missing at random
MBM	Michigan Body Map
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
PASC	Post-Acute Sequelae of SARS-CoV-2 Infection
PCFS	Post-COVID-19 Functional Status
PGI-C	Patient Global Impression of Change
PROMIS	Patient Reported Outcomes Measurement Information System
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe acute respiratory syndrome
SD	Standard Deviation
SDS	Sheehan Disability Scale
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TNX-102 SL tablets	Cyclobenzaprine HCl Sublingual Tablets
WHO	World Health Organization
WHO-DD	World Health Organization – Drug Dictionary

1. BACKGROUND

This Statistical Analysis Plan (SAP) for Protocol No. TNX-CY-PA201/Prevail Study has been written based on the protocol and taking into account recent Food and Drug Administration (FDA) feedback and expectations for pain trials.

2. OVERVIEW

This SAP describes the planned analysis and reporting for Protocol TNX-CY-PA201 (A Phase 2, 14-week Double-Blind, Randomized, Multicenter, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TNX-102 SL Taken Daily at Bedtime in Patients with Multi site Pain Associated with Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)).

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA, European Medicines Agency, 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 (Version 1.1 dated 20JUN2023), the following documents were reviewed in addition to the literature references cited in this SAP:

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 5.6 mg daily at bedtime in the treatment of patients with multi-site pain associated with Long COVID.

3.1.2 Secondary Objectives

The secondary objective is to evaluate the safety and tolerability of TNX-102 SL 5.6 mg daily at bedtime in the treatment of multi-site pain associated with Long COVID.

3.2 Study Endpoints

3.2.1 Efficacy Endpoints

The primary efficacy endpoint is:

- Change from Baseline in the diary NRS weekly average of daily self-reported worst Long COVID pain intensity scores at the Week 14 endpoint

3.2.2 Secondary Endpoints

Key secondary efficacy endpoints include:

- Change from Baseline in the weekly average of the daily diary NRS assessment of sleep quality at the Week 14 endpoint
- Change from Baseline in the PROMIS score for fatigue at the Week 14 endpoint
- Change from Baseline in the PROMIS score for cognitive function at the Week 14 endpoint

Other secondary efficacy endpoints include:

- Change from Baseline in the Patient Reported Outcomes Measurement Information System (PROMIS) score for sleep disturbance at the Week 14 endpoint
- Proportion of patients with a Patient Global Impression of Change (PGI-C) rating of “very much improved” or “much improved” at the Week 14 endpoint
- Change from Baseline to Week 14 in the Sheehan Disability Scale (SDS)
- Change from Baseline to Week 14 in the Insomnia Severity Index (ISI)
- Change from Baseline to Week 14 in the Epworth Sleepiness Scale (ESS)

3.2.3 Exploratory Endpoints

Exploratory efficacy endpoints include:

- Proportion of patients with a ≥ 30% improvement from Baseline to Weeks 1−14 in the daily self-reported worst Long COVID pain intensity score
- Proportion of patients with a ≥ 50% improvement from Baseline to Weeks 1−14 in the daily self-reported worst Long COVID pain intensity scores
- Proportion of Patients with a PGI-C rating of "very much improved" or "much improved" at each post-randomization clinic visit
- PGI-C (1-7) rating at each post-randomization clinic visit
- Change from Baseline in the PROMIS score for sleep disturbance at each post-randomization clinic visit
- Change from Baseline in the PROMIS score for fatigue at each post-randomization clinic visit
- Change from Baseline in the PROMIS fatigue symptom questions 1,3,4 (individually and summed) at each post-randomization clinic visit
- Change from Baseline in the PROMIS fatigue impact questions 6,7,8 (individually and summed) at each post-randomization clinic visit
- Change from Baseline in the PROMIS score for cognitive function at each post--randomization clinic visit
- 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 diary assessment of worst pain intensity scores at Weeks 1−14
- Change from Baseline in laboratory markers of inflammation
- Change from Baseline to Week 14 in the Post-COVID-19 Functional Status Scale (PCFS)
- Change from Baseline in the total number of the modified Michigan Body Map pain regions identified as having pain at each post-randomization clinic visit
- Change from Baseline in average NRS Long COVID pain intensity across the 7 pain regions in modified Michigan Body Map at each post-randomization visit; regions without pain identified will be assigned a value of 0
- Change from Baseline in average NRS Long COVID pain intensity within the index site region on the modified Michigan Body Map at each post-randomization visit
- Change from Baseline in average NRS Long COVID pain intensity within the worst region for a given visit on the modified Michigan Body Map at each post-randomization visit; this will compare the value for the worst region at a visit and the worst region at baseline
- Subgroup analyses of the above endpoints by severity of their SARS-CoV-2 infection using groupings of the WHO ordinal scale of COVID severity as data allow

- Subgroup analyses of the above endpoints by COVID vaccine status

3.2.4 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).

4. OVERALL STUDY DESIGN AND PLAN

This is a Phase 2, randomized, parallel-group, double-blind, placebo-controlled, 14-week study designed to evaluate the efficacy and safety of TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) taken once daily at bedtime for the management of multi-site pain associated with Long COVID. The study is to be conducted at approximately 30 investigational sites in the US.

The study will consist of a Screening Visit (Visit 1, Days -35 to -8), a Washout and Screening period of at least 7 days (for those patients not requiring washout) and no more than 35 days, inclusive of a 7-day baseline data collection phase immediately preceding the Baseline Visit. Eligible patients who provide written informed consent will have study assessments performed at Screening. Due to limitations in the diary completion window, patients who 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.

At Screening Visit 1 and after signing the written informed consent, any required washout should be discussed with the patient and plans made for an appropriate schedule for reducing/stopping any excluded medications. This down-titration and discontinuation of excluded medications must be accomplished so that the patient is free of excluded medications for at least 14 days prior to beginning of the collection of Baseline diary data that takes place during the 7 days leading up to the Baseline/Randomization Visit. Any additional time required for down-titration would be in addition to this washout requirement. For extenuating circumstances, the total duration of the Screening period may be increased to up to a maximum of 49 days with Medical Monitor approval. All excluded medications will be stopped during the Washout period through the Week 14/ Early Termination (ET) Visit (Visit 6).

Patients will be trained on use of an eDiary system at Visit 1.

During the 7-day run-in Phase (7 days immediately preceding Visit 2 [Baseline/Randomization Visit; Day 1]) patients will be asked to record their worst daily Long COVID pain intensity on the 11-point (0−10) NRS scale using 24-hour recall and assess sleep quality from the previous evening, also using an 11-point NRS scale. The average of the 7 days immediately preceding Visit 2 (Baseline Randomization Visit; Day 1) will serve as the Baseline pre-treatment scores.

After completing any required washout of excluded therapies 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), when they will be randomly assigned to receive TNX-102 SL or matching placebo sublingual tablets in a 1:1 ratio.

During the treatment phase, each evening, the system will prompt the patient to reflect on the past 24 hours and record their worst pain intensity, assess their sleep quality from the previous evening, and log study drug dosing from the previous night (post -randomization).

Patients will take the study drug SL once daily at bedtime, starting on the day of randomization (Day 1), for 14 weeks. For the first 2 weeks of treatment, patients will start on TNX-102 SL 2.8 mg/day (1 tablet) or placebo. Patients will continue to record their worst daily pain, assess their sleep quality from the previous evening, and log study drug compliance.

All patients will then return to the clinic at Week 2 (Visit 3) for efficacy and safety assessments and assessment of study drug compliance. The study drug dose will be increased to 2 tablets (5.6 mg; 2 x 2.8 mg TNX-102 SL tablets or placebo) or 2 placebo tablets taken SL and simultaneously daily at bedtime. Patients will next return to the clinic at Week 6 (Visit 4) for assessment of safety, efficacy, study drug compliance, and dose tolerability at the 5.6-mg dose. In scenarios in which TNX-102 SL 5.6 mg (or 2 placebo tablets) is considered intolerable due to adverse event(s) (AEs) and would otherwise lead to study discontinuation, with Medical Monitor approval, the Investigator may lower the daily dose to 1 tablet every night (TNX-102 SL 2.8 mg or 1 placebo tablet). If/when it is deemed clinically warranted by the Investigator, rechallenge with 2 tablets TNX-102 SL 2.8 mg (5.6 mg dose)/placebo may be attempted or the patient may remain on the lower dose for the remainder of the study. 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 it 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 clinic for safety, tolerability, and efficacy assessments, and assessments of study drug compliance at Week 2 (Visit 3), Week 6 (Visit 4), Weeks 10 (Visit 5) and 14 (Visit 6) or ET.

Approximately 2 weeks after Week 14 (Visit 6), there will be a Post-study Safety Follow-up telephone call (Visit 7), and approximately 4 weeks after Week 14, there will be a 1-Month Post-study Safety Follow-up telephone call (Visit 8).

Due to the exceptional circumstances caused by the COVID-19 pandemic, an option for a telephone visit will be available for Weeks 2, 6, 10 (Visits 3, 4, 5), and, only with Medical Monitor approval, Week 14/Visit 6 (or ET) for those unable to attend an in-clinic visit due to the COVID-19 pandemic. However, all visits should be conducted in person whenever possible.

The total duration of the study, including screening and follow-up, may be as long as 25 weeks. The maximum treatment duration will be 14 weeks.

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) to be eligible for randomization:

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

a. A mean worst daily Long COVID pain intensity score ≥ 4 and ≤ 9 on the 11-point (0−10) NRS for the 7 days immediately preceding Visit 2, and

b. No more than 2 individual days with a Long COVID pain 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. Long COVID pain scores recorded on at least 5 out of the 7 days immediately preceding Visit 2

Patients will be randomly assigned to receive TNX-102 SL or matching placebo sublingual tablet in a 1:1 ratio.

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, if the patient reports intolerable side effects that are likely to result in premature discontinuation from the study, then the dose of study drug may be reduced to 1 tablet sublingually nightly, with Medical Monitor approval. Any reduction in study drug dose must be documented in the case report form (CRF). The goal is for the patient to be on a stable and final dose of study drug starting from the Week 2 Visit, at the highest dose tolerated (preferably 2 tablets daily at bedtime). It is anticipated that only a small portion of patients will require dosage reduction, as TNX-102 SL 5.6 mg has been well-tolerated in previous Phase 3 studies of TNX-102 SL. Moreover, the gradual titration from 1 tablet for the first 2 weeks to 2 tablets for the remainder of the study should help with acclimation to the higher dose.

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.

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 data base. 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 0.3.

7. ANALYSIS POPULATIONS

In the case that the study goes to full enrollment or has a sample size increase, the following analysis populations are planned for this study:

- All Patients: used for summaries of dispositions of patients; tabulations of dispositions may also use the populations below.
- Safety population: all patients who receive at least one dose of the investigational product. All safety analyses will be performed using this population, analyzed as treated.
- Intention-to-treat (ITT) population: all patients who are randomized and have at least one post-baseline daily diary entry. 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 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.

For continuous endpoints where treatment groups are compared via linear models with the difference in LS means, the effect size will be calculated and included as a summary statistic using the difference in LS means and its standard error, transformed to a standard deviation.

Study day is defined as assessment date – first dose date +1 for dates after the first dose date and assessment date – first dose date for dates prior to the first dose.

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

8.1.1 Study Success, Adjustments for Multiplicity and Other Alpha Control

8.1.1.1 Study Success

[redacted] If the effect size observed for the primary analysis is greater than 0.20, the trial will be considered to have achieved proof of concept and would support further research of the product in this indication.

In the event that statistical significance for the primary is achieved, the multiplicity algorithm below will apply. If statistical significance is not obtained, but proof of concept is declared on the primary, there will be no formal hierarchy or thresholds subsequently considered for secondary endpoints.

8.1.1.2 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 key secondary endpoints in an ordered fashion. If the analysis for a key secondary endpoint does not produce a statistically significant result, then the remaining key 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:

- Change from Baseline in the weekly average of the daily diary NRS assessment of sleep quality at the Week 14 endpoint
- Change from Baseline in the PROMIS score for fatigue at the Week 14 endpoint
- Change from Baseline in the PROMIS score for cognitive function at the Week 14 endpoint

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) where the given data are collected, 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.

For example, a patient with valid 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 without valid 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 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.

For the primary analysis, no missing values will be imputed; a sensitivity analysis may be performed using the following imputation algorithm:

[redacted]

Daily sleep diary data may 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 may 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 PGI-C at a given visit will be considered non-responders at that visit for the purposes of treatment comparisons; 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. 30% and 50% responders will be handled similarly with missing values being imputed as non-responders.

No missing safety data will be imputed.

8.2 Efficacy Assessments

8.2.1 Weekly Average of Daily Worst Long COVID Pain Intensity Score

The daily eDiary is an important aspect of this study, and all patients must receive training explaining what is being asked of them, when to complete the diary, and how to use the diary system effectively. Patients will be trained on use of the diary system at Visit 1. Additionally, patients should complete the training on accurate pain reporting and placebo response reduction training as required.

During the 7-day run-in Phase (7 days immediately preceding Visit 2 [Baseline/Randomization Visit; Day 1]) patients will be asked to record their worst daily Long COVID pain intensity on the 11-point (0−10) NRS scale using 24-hour recall and to assess sleep quality from the previous evening, also using an 11-point NRS scale. The average of the 7 days immediately preceding Visit 2 (Baseline Randomization Visit; Day 1) will serve as the Baseline pre-treatment scores.

During the treatment phase, each evening, the system will prompt the patient to reflect on the past 24 hours and record their worst pain intensity, assess their sleep quality from the previous evening, and log study drug dosing from the previous night (post -randomization).

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

The diary should be started the evening of Visit 1 and completed daily until Visit 6 (Week 14). Patients should be instructed to complete the diary in the evening before dosing. Once the patient has properly identified themselves, the diary will prompt answers to the following:

- Rate your worst Long COVID pain intensity during the last 24 hours on a scale from 0-10, where 0 is “no pain” and 10 is “pain as bad as you can imagine”. Rate your sleep quality last night on a scale from 0−10 where 0 is the “best possible sleep” and 10 is the “worst possible sleep”.

After randomization to study drug at Visit 2, the following questions will be added to the daily diary (starting in the evening of the day after randomization, Day 2):

- Did you take your study drug last night? (Yes/No)
- If yes, how many tablets of study drug did you take last night? (1 tablet/2 tablets)

These daily values will be averaged into a weekly mean; since a mean is used in the calculation of the primary endpoint, it is not necessary to replace values missing on random intermittent days.

As described above, 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 D.

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 time point for diary outcomes (as well as any prior weeks for which data are present). 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 Weekly Average of Daily Sleep Quality Score

The weekly average of daily sleep quality score will be obtained in the same manner as the weekly average of the daily worst long COVID pain intensity 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 Modified Michigan Body Map

The Michigan Body Map (MBM) is based on the 2011 FM Survey Criteria, a tool that is commonly used to assess for the presence of multi-site pain in fibromyalgia (FM), a disorder characterized by widespread body pain, along with comorbid symptomatology similar to that experienced by patients with Long COVID. The 2011 FM Survey Criteria include the assessment of pain in 19 specific body areas using the Widespread Pain Index (WPI). The areas from the WPI are then combined with the Symptom Severity scale to assess the presence and severity of FM. The MBM is a graphic mannequin with the 19 areas from the WPI superimposed upon it in anatomically relevant locations. The MBM also contains 16 additional areas for more general use. The MBM, and its online version, have been validated in patients with chronic pain.

Tonix Pharmaceuticals has modified the MBM (mMBM) in consultation with its authors. The

[redacted]

Two versions of the mMBM will be used in the study, the Screening version and the Baseline/Post-Randomization Version. The screening Version will assess a patient's eligibility to enter the study, based on the number of body regions with pain and the Baseline/Post-Randomization Version will be used for assessment of outcomes. The two versions are described in more detail below.

At screening

At screening (Visit 1), the patient will complete the "Screening Visit" version of the mMBM with a 3 month look-back period, which includes:

- [redacted]
- [redacted]

Note: In order to be eligible for the study, the patient must have Long COVID pain in at least 4 out of 7 body regions on Part 2 of the screening mMBM.

At Baseline/Post-Randomization Visits (Visit 2-Visit 6)

At randomization through the end of the study, the patient will complete "Baseline/Post-Randomization" version of the mMBM with a 7-day look-back period, which includes:

- [redacted]
- [redacted]

The region of pain that is selected as "most bothersome" at the Baseline Visit will be referred to as the "index site" thereafter. The "index site" will be followed from the Baseline Visit through V6 as a part of the exploratory analyses. Additional analyses related to the mMBM have been incorporated as exploratory endpoints as well. Refer to Appendix 2 of the Protocol for an exact

copy of the mMBM and definition of body regions.

The following endpoints will be derived using the mMBM:

- Change from Baseline in the total number (1-7) of the modified Michigan Body Map pain regions identified as having pain at each post-randomization clinic visit
- Change from Baseline in average NRS Long COVID pain intensity across the 7 pain regions in the modified Michigan Body Map at each post-randomization visit; regions without pain identified will be assigned a value of 0
- Change from Baseline in NRS Long COVID pain intensity within the index site region on the modified Michigan Body Map at each post-randomization visit
- Change from Baseline in NRS Long COVID pain intensity within the worst region for a given visit on the modified Michigan Body Map at each post-randomization visit; this will compare the value for the worst region at a visit and the worst region at baseline

8.2.4 Sheehan Disability Scale

SDS is a brief self-reporting tool that rates the extent to which work/school, social life, and home life or family responsibilities are impaired by the symptoms on a 10-point visual analog scale. The 3 items can also be summed into a single dimensional measure of global functional impairment that ranges from 0 (unimpaired) to 30 (highly impaired). If a patient is not working/in school for reasons unrelated to their disease state, that item is not completed; in this case, the average of the two other items will be imputed for this measure when calculating the total score (but not for reporting on that individual measure).

8.2.5 PROMIS Scales

The PROMIS Short-Form Fatigue, Sleep Disturbance, and Cognitive Function – Abilities Scale 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. Each 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.

$$\text{New raw score} = (\text{Raw score} / \#\text{ of items answered}) \times \#\text{ of total items}$$

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, Appendix B for Sleep Disturbance and Appendix C for Cognitive Function – Abilities scale. 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 Patient Global Impression of Change (PGI-C)

PGI-C is a question completed by the patient at Weeks 2, 6, 10, and 14. The patient will rate the change in their Long COVID symptoms (specifically pain, sleep disturbance, fatigue, and/or

memory/concentration issues) 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 PGI-C 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 PGI-C score will be considered a non-responder for that visit.

8.2.7 Post-COVID-19 Functional Status (PCFS) scale

The PCFS scale is an ordinal scale for assessment of patient-relevant functional limitations over time after COVID-19 infection.

The scale rates the functional status of patients as:

0 = No functional limitations
1 = Negligible functional limitations
2 = Slight functional limitations
3 = Moderate functional limitations
4 = Severe functional limitations
D = Death

Missing values will not be imputed.

8.2.8 Insomnia Severity Index (ISI) – Patient version

The ISI is a 7-item self-reported questionnaire assessing the nature, severity, and impact of insomnia.

The usual recall period is the “last month” and the dimensions evaluated are severity of sleep onset, sleep maintenance and early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties.

The scores range from 0 (no problem) to 4 (very severe problem) yielding a total score ranging from 0 to 28. The total score is interpreted as:

0–7 = absence of insomnia
8–14 = sub-threshold insomnia
15–21 = moderate insomnia 22–
28 = severe insomnia

Missing items will be imputed with the average of the non-missing items, as long as at least 4 items are completed.

8.2.9 Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire with 8 questions. The patient rates from 0 to 3 their usual chances of dosing off or falling asleep while engaged in 8 different activities. The total score can range from 0 to 24, with higher rating indicating higher average sleep propensity in daily life.

Missing items will be imputed with the average of the non-missing items, as long as at least 4 items are completed.

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 major vs minor, 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, body mass index (BMI), family status, education, employment status, and MINI modules A, C, I, J, K, O)
- Tobacco/nicotine, alcohol, and THC/cannabis use history

Medical History will be coded using a current version 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

Population

The analysis population will be patients with PASC as defined by the protocol inclusion/exclusion criteria.

Variable

The primary endpoint will be the change from baseline to Week 14 in the diary NRS weekly average of daily self-reported worst Long COVID pain intensity scores.

Intercurrent Events

For all intercurrent events, data will be analyzed as observed and missing data (both intermittent and following discontinuation) will be assumed to be missing at random. All patients that complete at least one diary pain entry will contribute to the model estimation.

Population-Level Summary

The population-level summary will be the difference in least-square means between treatment arms (analyzed as randomized) at Week 14 from the primary analysis model. See Section 10.1.2 for details.

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 without imputation under the assumption that data are missing at random. The model will include the fixed, categorical effects of treatment, 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 (DDFM) with the unstructured matrix; other covariance structures will utilize the sandwich matrix and the SAS® default DDFM. Week 14 will serve as the primary time point of interest. 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 a two-sided alpha of 0.05.

10.1.3 Sensitivity Analysis

The following sensitivity analysis may be performed:

Data will be imputed using multiple imputation as described in Section 8.1.4. Models identical to the primary analysis described above will be fit for the 20 MI repeated sets; LS means and

differences across the twenty MI reps will be combined using SAS® procedure MIANALYZE (Rubin, 1976). Week 14 will serve as the primary time point of interest. 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 a two-sided alpha of 0.05.

10.2 Secondary and Exploratory Efficacy Analyses

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

10.2.1 Continuous Key Secondary 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 10.1.2 for the analysis approach.

Outcomes using these analyses will include:

- Change from Baseline in the weekly average of the daily diary NRS assessment of sleep quality at the Week 14 endpoint
- Change from Baseline in the PROMIS score for fatigue at the Week 14 endpoint
- Change from Baseline in the PROMIS score for cognitive function at the Week 14 endpoint

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.

This will be repeated on the outcomes above, but using observed data only without imputation.

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).

10.2.2 Other Continuous Secondary and Exploratory Endpoints

Descriptive statistics will be reported for each endpoint, time point and treatment for both the observed values and the changes from baseline.

The with the exception of ISI and PCFS (collected just once post-baseline), change from baseline in each endpoint from baseline to each visit in the TNX-102 SL and placebo arms will be analyzed using a restricted maximum likelihood (REML) based repeated measures approach with no imputation. Week 14 will serve as the primary time point of interest. Models will include the fixed, categorical effects of treatment, 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 (DDFM) with the unstructured matrix; other covariance structures will utilize the sandwich matrix and the SAS®

default DDFM. Significance testing will be based on least-squares means and two-sided 95% confidence intervals will be presented.

For ISI and PCFS, an ANCOVA model will be fit on the change from baseline to Week 14. Fixed effects will include categorical effects for treatment and a covariate for the baseline value of each scale. Significance testing will be based on least-squares means and two-sided 95% confidence intervals will be presented.

Secondary Efficacy Endpoints analyzed this way will include:

- Change from Baseline to Week 14 in the Sheehan Disability Scale (SDS)
- Change from Baseline in the Patient Reported Outcomes Measurement Information System (PROMIS) score for sleep disturbance at the Week 14 endpoint
- Change from Baseline to Week 14 in the Insomnia Severity Index (ISI)
- Change from Baseline to Week 14 in the Epworth Sleepiness Scale (ESS)

Exploratory endpoints analyzed this way will include:

- Patient Global Impression of Change (PGI-C) Scored 1-7 at Week 14 (without the fixed covariates of baseline value and baseline value score-by-study week interaction)
- Change from Baseline in the PROMIS score for sleep disturbance at each post--randomization clinic visit
- Change from Baseline in the PROMIS score for fatigue at each post-randomization clinic visit
- Change from Baseline in the PROMIS fatigue symptom questions 1,3,4 (individually and summed) at each post-randomization clinic visit
- Change from Baseline in the PROMIS fatigue impact questions 6,7,8 (individually and summed) at each post-randomization clinic visit
- Change from Baseline in the PROMIS score for cognitive function at each post--randomization clinic visit
- 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 diary assessment of worst pain intensity scores at Weeks 1−14
- Change from Baseline in laboratory markers of inflammation
- Change from Baseline to Week 14 in the Post-COVID-19 Functional Status Scale (PCFS)
- Change from Baseline in the total number of the modified Michigan Body Map pain regions identified as having pain at each post-randomization clinic visit
- Change from Baseline in average NRS Long COVID pain intensity across the 7 pain regions in modified Michigan Body Map at each post-randomization visit

- Change from Baseline in average NRS Long COVID pain intensity within the index site region on the modified Michigan Body Map at each post-randomization visit
- Change from Baseline in average NRS Long COVID pain intensity within the worst region for a given visit on the modified Michigan Body Map at each post-randomization visit

As noted above, results of Week 14 are of primary interest, with other time points being exploratory. For PROMIS fatigue, the questions regard symptoms and impacts will be analyzed independently and additional post-hoc analyses may be completed to evaluate how they contribute to the overall score.

10.2.3 Categorical Endpoints

A categorical analysis of PGI-C 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. In the case of sparse data (<5 patients expected in a cell), Fisher's exact test will be employed. A summary of frequency counts for all PGI-C responses for each time point will be presented; Week 14 is of primary interest and all other time points are considered exploratory.

Exploratory analyses of the following endpoints will use identical methodology as the PGI-C analysis:

- Proportion of patients with a ≥ 30% improvement from Baseline to Weeks 1−14 in the daily self-reported worst Long COVID pain intensity score
- Proportion of patients with a ≥ 50% improvement from Baseline to Weeks 1−14 in the daily self-reported worst Long COVID pain intensity scores

The number and percentage of patients in each PCFS category will be reported at each visit where it is collected.

10.3 Subgroup Analyses

Exploratory subgroup analyses of the primary, secondary and exploratory analyses may be performed. These may include:

- Subgroup analyses by severity of the patients' SARS-CoV-2 infection using groupings of the WHO ordinal scale of COVID severity as data allow
- Subgroup analyses by COVID vaccine status

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
- Vital Signs
- Physical Examinations and examinations of the oral cavity

11.1 Adverse Events

All AEs, TEAEs, and SAEs will be coded using a current version of the MedDRA Dictionary.

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, and TEAEs by strongest relationship to study drug.

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

In the AE data listings, all AEs will be displayed. 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 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 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 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.

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.

The number of patients with increase over baseline in suicidal ideation at any time point will be reported. The maximum ideation across all visits for a patient will also be summarized with counts and percentages both for all patients and among patients with an increase in ideation. Likewise, the count and percentage of patients with any suicidal behavior will be reported along with a summary of the most extreme behavior each patient reported.

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 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.

11.5 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 a current 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 responds 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

[redacted] Consequently, a number of analyses were simplified or removed from the SAP that were planned in the protocol.

- The interim analysis was removed, and the required alpha spend eliminated.
- The imputation algorithm was removed from the primary analysis and shifted to an optional sensitivity analysis. As such, the ITT population was updated to include the requirement that patients have at least one post-baseline diary entry.
- Lab summaries were eliminated; lab results will be presented in listings
- C-SSRS summaries were simplified
- Site covariate removed due to low patient counts spread over many sites

14. REFERENCES (AVAILABLE UPON REQUEST)

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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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 Summed 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

Adult v2.0 - Cognitive Function Abilities Subset 8a		
Short Form Conversion Table		
Raw Score	T-Score	SE*
8	23.27	4.36
9	26.59	3.47
10	28.63	3.13
11	30.23	2.93
12	31.63	2.76
13	32.87	2.64
14	34.01	2.56
15	35.07	2.51
16	36.07	2.48
17	37.04	2.46
18	37.97	2.45
19	38.90	2.44
20	39.81	2.44
21	40.71	2.44
22	41.61	2.45
23	42.51	2.46
24	43.42	2.46
25	44.34	2.48
26	45.27	2.49
27	46.21	2.50
28	47.18	2.52
29	48.16	2.53
30	49.17	2.55
31	50.21	2.56
32	51.29	2.59
33	52.42	2.63
34	53.63	2.68
35	54.94	2.78
36	56.39	2.93
37	58.03	3.14
38	59.95	3.41
39	62.52	3.90
40	67.09	5.24
*SE= Standard Error on T-score metric		

15.4 Appendix D

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

15.5 Appendix E

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

4892962

3752934

5798332

3796594

6437925

3949255

3597909

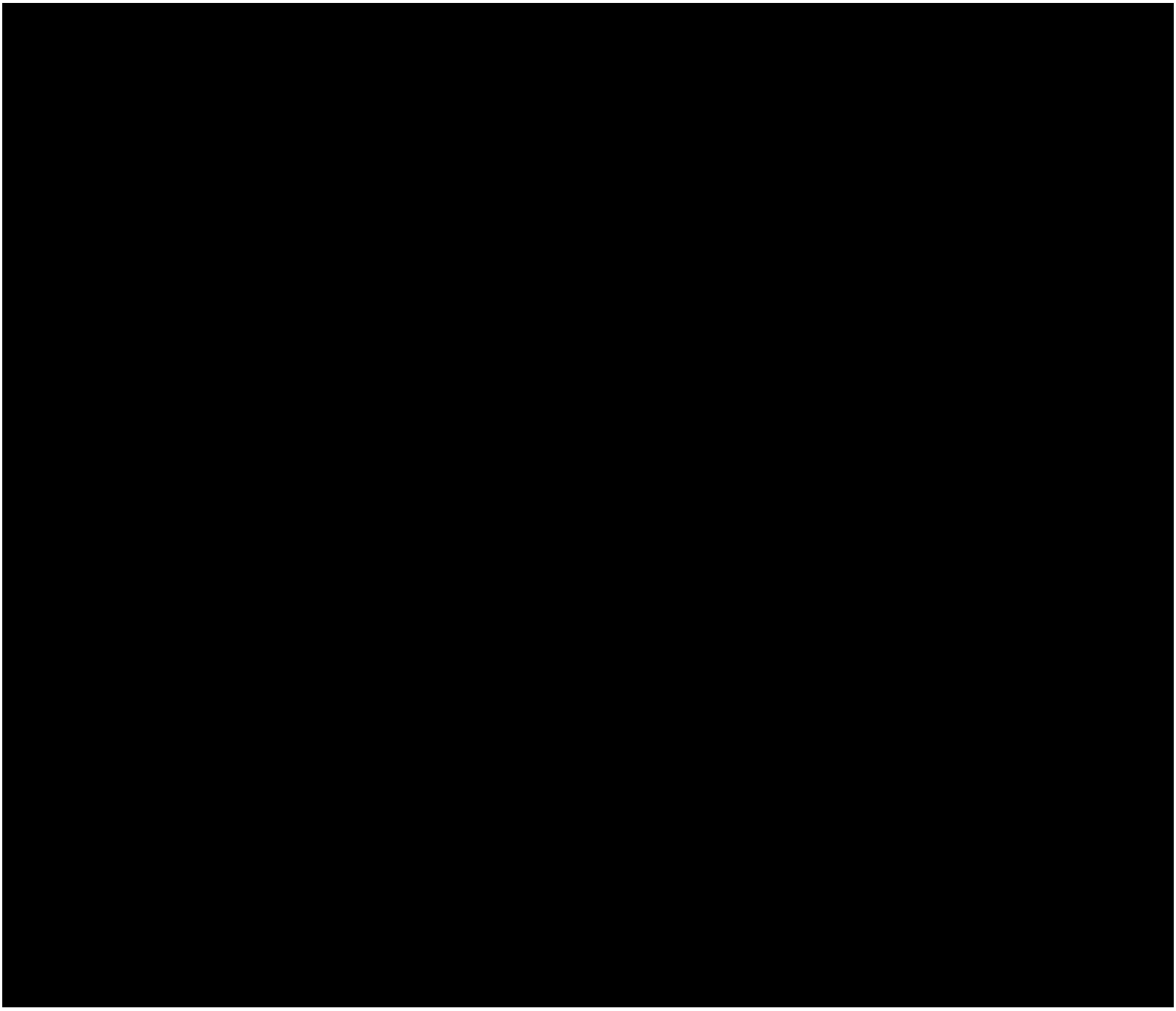
3067243

7256068

6953553

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.

Intermediary Delivery Events	Status	Timestamp



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