NCT04044664

NYX-783-2004

A Study to Evaluate the Safety and Efficacy of NYX-783 in Subjects with Post-Traumatic Stress Disorder

SAP

18 Sept 2020

[redacted]

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Final 1.0	04AUG2020	[redacted]	Initial Version
Final 1.1	18SEP2020	[redacted]	-[redacted] -Add COVID-19 impact analysis -Update on compliance

[redacted]

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[redacted]

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Aptinyx protocol number NYX-783-2004 (A Study to Evaluate the Safety and Efficacy of NYX-783 in Subjects with Post-Traumatic Stress Disorder), dated 01-May-2020 amendment 3. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

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

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to Aptinyx's study NYX-783-2004.

[redacted]

2. Study Objectives and Endpoints

2.1. Study Objectives

The overarching goal of this exploratory study is to investigate the safety and tolerability of NYX-783 in a Post-Traumatic Stress Disorder (PTSD) population, and to characterize the response profile of PTSD symptoms to NYX-783 treatment, as assessed by the intrusion, avoidance, and negative alterations in cognition and mood, and arousal & reactivity subscores as well as the total score on the Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (CAPS-5)

2.1.1. Primary Objective

The primary objective is to assess the effects of NYX-783 compared to placebo on reducing the severity of PTSD symptoms as measured by the Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (CAPS-5).

[redacted]

2.1.2. Secondary Objectives

The secondary objectives are

- To assess the effect of NYX-783 compared to placebo in the following outcomes: a) change in symptoms of PTSD as measured by the PTSD-Checklist for DSM-5 (PCL-5), b) change in sleep quality as measured by the Pittsburgh Sleep Quality Index (PSQI) Global Score, and c) change in cognitive function as measured by the Symbol Coding from the Brief Assessment of Cognition (BAC Symbol Coding).
- To assess the effect of NYX-783 compared to placebo in the change in global clinical severity of PTSD symptoms as measured by the Clinical Global Impressions-Severity (CGI-S) scale.
- To compare NYX-783 vs. placebo in the change in levels of anxiety and depression as measured by the Hospital Anxiety and Depression Scale (HADS).
- To assess the safety and tolerability of NYX-783 compared to placebo.

2.1.3. Exploratory Objectives

The exploratory objectives are

[redacted]

[redacted]

2.2. Study Endpoints

2.2.1. Efficacy Endpoints

2.2.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the change in CAPS-5 total score and subscores following 4 weeks of treatment in each respective Stage (Stage 1 [baseline to Week 4] and Stage 2 [Week 4 to Week 8]) .The primary endpoint will be evaluated using the weighted combination of the estimated treatment effects from stage-specific models.

2.2.1.2. Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints of this study include the following

- Change in symptoms of PTSD as measured by the PCL-5 following 4 weeks of treatment in each respective Stage (Stage 1 [baseline to Week 4] and Stage 2 [Week 4 to Week 8])
- Change in sleep quality as measured by the PSQI Global Score and the PSQI Addendum for PTSD (PSQI-A) Global Score following 4 weeks of treatment in each respective Stage (Stage 1 [baseline to Week 4] and Stage 2 [Week 4 to Week 8])
- Change in cognitive function as measured by the Symbol Coding from BAC Symbol Coding following 4 weeks of treatment in each respective Stage (Stage 1 [baseline to Week 4] and Stage 2 [Week 4 to Week 8])
- Change in CGI-S following 4 weeks of treatment in each respective Stage
- Change in Hospital and Anxiety Depression Scale for Anxiety (HADS-A) and Hospital and Anxiety Depression Scale for Depression (HADS-D) subscores following 4 weeks of treatment in each respective Stage (Stage 1 [baseline to Week 4] and Stage 2 [Week 4 to Week 8])

2.2.1.3. Exploratory Efficacy Endpoint(s)

The exploratory efficacy endpoint of this study include the following:

[redacted]

[redacted]

2.2.2. Safety Endpoints

2.2.2.1. Secondary Safety and Tolerability Endpoint(s)

Safety and tolerability endpoints for this study will be based on: incidences of adverse events (AEs) and any changes in vital signs, physical examination findings (including weight), 12-lead ECG results, clinical laboratory values, and suicidality assessments (Sheehan Suicidality Tracking Scale [STS-S]).

3. Overall Study Design and Plan

3.1. Overall Design

3.2. Sample Size and Power

Response to treatment will be measured using the CAPS-5 score change from baseline to Week 4 (Stage 1) and from Week 4 to Week 8 (Stage 2). If the effect size of NYX-783 is in line with the effect sizes observed in similar historical studies, this study is powered at approximately 80% to reject the null hypothesis at a one-sided $\alpha = 0.10$ level for any single specified efficacy comparison. The sample size estimate (n=156) assumes a 15% dropout during Stage 1 and 11% dropout during Stage 2, based on the treatment comparisons specified for Amendment 2 of the protocol. The sample size may be adjusted if the actual dropout rate exceeds this assumption; patients randomized based on earlier protocol versions will be included in data listings, but will not be included in data summaries or inferential analyses.

3.3. Study Population

The study population consists of adult subjects diagnosed with Post-Traumatic Stress Disorder (PTSD). The goal of the study is to recruit subjects with a clearly identifiable primary traumatic event during adulthood.

3.4. Treatments Administered

NYX-783 is formulated for this study as 50 mg, and 10 mg capsules for oral administration. Matching placebo capsules for oral administration are also provided. The study will be conducted as a placebo-controlled, double-blind study. The Treatment period will be conducted in 2 Stages to examine the efficacy and safety of NYX-783 compared to placebo in the treatment of PTSD symptoms.

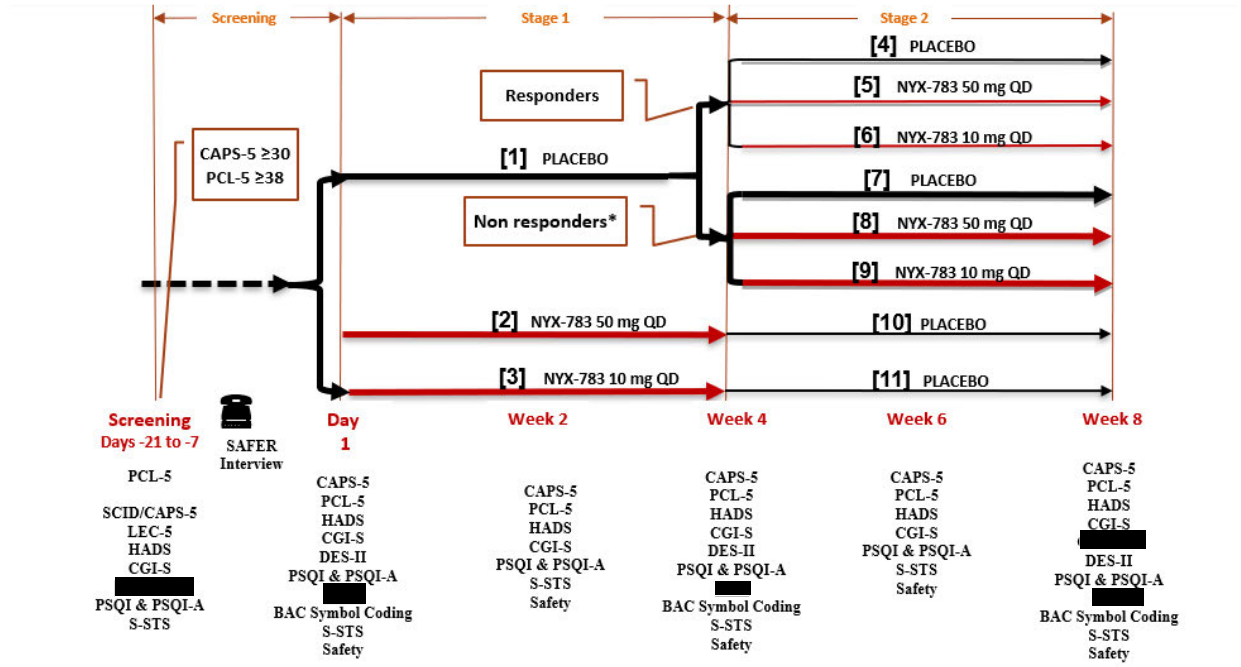
3.5. Method of Assigning Subjects to Treatment Groups

On Day 1, subjects will be randomized to receive placebo, NYX-783 50 mg QD, or NYX-783 10 mg QD in a 4:1:1 ratio, respectively. Placebo responders and placebo non-responders (CAPS-5 total score reduction from baseline ≤35% and total CAPS-5 total score ≥26 at Week 4) will be identified at the completion of Stage 1 (Weeks 1-4) in a blinded fashion; then, each group (i.e., placebo responders and placebo non-responders) will be re-randomized in a blinded fashion to placebo, NYX-783 50 mg QD, NYX-783 10 mg QD in a 3:2:2 ratio, respectively, for Stage 2 (Weeks 4-8)

[redacted]

treatment. Subjects who received active treatment during Stage 1 will receive placebo in Stage 2.

Figure 1: Study Design



* Placebo non-responder: CAP-S-5 reduction from baseline ≤ 35% and CAPS-5 total score ≥ 26 at Week 4.
BAC Symbol Coding, Symbol Coding from the Brief Assessment of Cognition; CAPS-5, Clinicians Administered PTSD Scale for DSM-5; [redacted] CGI-S, CGI-Severity; HADS, Hospital Anxiety and Depression Scale; LEC-5, Life Events Checklist for DSM-5; PCL-5, PTSD Checklist for DSM-5; PSQI, Pittsburgh Sleep Quality Inventory; PSQI-A, PSQI-Addendum for PTSD; SCID-5, Structured Interview for DSM-5; [redacted] S-STS, Sheehan Suicidality Tracking Scale. ☎ Phone Interview

Figure from protocol Section 7.1 Overall Study Design and Plan: Description.

3.6. Blinding and Unblinding

The study will be conducted as a placebo-controlled, double-blind study. The authorized investigative site personnel will obtain blinded kit assignments using an interactive response technology (IRT) system. The blinded dose information may only be obtained by the investigator (or designee) in an emergency, where the information may have an impact on further treatment decisions or aid in the emergency treatment of the subject.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1

[redacted]

Table 1: Schedule of Events

Phases/Visits / Tasks / Events	Screening		Double-blind Treatment Phase					Early Termination	Safety Follow-Up
	Visit 1 Screening	SAFER	Day 1	Week 2	Week 4	Week 6	Week 8		
			Stage 1						
					Stage 2				
Days relative to start dosing of study drug	**-21 to -7**	**-7[a]**	**1**	**14[a]**	**28[a]**	**42[a]**	**56[a]**	**NA**	**63[ap]**
ENTRY / SAFETY/ ADMINISTRATIVE									
Informed consent	X								
[redacted]									
Inclusion/exclusion criteria	X	X[j]	X						
Demographics / habits[b]	X								
Medical/psychiatric history	X		X						
PTSD diagnosis (CAPS-5)	X	X[j]							
SAFER interview (Confirmation of PTSD diagnosis and overview of inclusion/exclusion criteria)		X[j]							
LEC-5 (Part of PCL-5 with LEC-5 and Criterion A)	X								
S-STS	X[s]		X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	
Vital signs[c]	X		X	X	X	X	X	X	X[r]
Height	X[e]								
Weight	X[e]		X	X	X	X	X	X	X[r]
Physical examination	X				X		X	X	X[r]
12-lead ECG[d]	X		X		X		X	X	X[r]
Randomization			X		X				
Prior and concomitant medications	X		X	X	X	X	X	X	X
Study drug dispensing[o]			X	X	X	X			
Study drug administration			X[k]	X	X[l]	X	X		
Study drug compliance monitoring[f]			X	X	X	X	X	X	
Adverse events[g]	X	X	X	X	X	X	X	X	X
LABORATORY TESTS									
Clinical chemistry[q]	X		X	X	X	X	X	X	X[r]
Hematology	X		X		X		X	X	X[r]
HIV and hepatitis tests	X								

[redacted]

[redacted]									
Pregnancy test[v]	X[h]		X[i]		X[i]		X[i]	X[i]	
Drug and alcohol screen	X[h]		X[i]		X[i]		X[h]	X[h]	
Urinalysis	X		X		X		X	X	X[r]
Clinical Measures									
CAPS-5	X[s]		X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	
PCL-5	X[s]		X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	
HADS[t]	X		X	X	X	X	X	X	
CGI-S	X		X	X	X	X	X	X	
PSQI	X		X	X	X	X	X	X	
PSQI-A	X		X	X	X	X	X	X	
[redacted]									
DES-II			X		X		X	X	
[redacted]									
BAC-Symbol Coding			X		X		X	X	

Abbreviations: BAC-Symbol Coding = Symbol Coding from the Brief Assessment of Cognition; CAPS-5 = Clinician Administered PTSD Scale for DSM-5; [redacted] CGI-S = Clinical Global Impression – Severity; DES-II = Dissociative Experiences Scale-II; DNA = Deoxyribonucleic acid; ECG = electrocardiogram; HADS = Hospital Anxiety and Depression Scale; HIV = human immunodeficiency virus; LEC-5 = Life Events Checklist for DSM-5; [redacted] PCL-5 = PTSD Checklist for DSM-5; [redacted] PSQI = Pittsburgh Sleep Quality Index; PSQI-A = Pittsburgh Sleep Quality Index Addendum; PTSD = Post-Traumatic Stress Disorder; SCID-5-CT = Structured Clinical Interview for DSM-5 (Clinical Trials Version); [redacted] = Sheehan Suicidality Tracking Scale.

a) Visit window is ± 3 days.
b) Includes alcohol or illicit drug use history, employment status, smoking history, and index traumatic event.
c) Collect vital signs after at least 5 minutes of rest, seated or supine.
d) ECG after at least 5 minutes supine rest.
e) Include body mass index calculation.
f) Subjects use smartphone video application monitoring. Investigative site personnel calculate compliance and document accountability via capsule count/blister package inspection.
g) Serious Adverse Event (SAE) reporting begins at time of informed consent and continues until 30 days after the last dose of study drug. Non-serious AE collection commences with the time of first dose of study drug until last day of subject participation in the study.
h) Serum sample.
i) Urine sample or breathalyzer (alcohol screen).
j) Via phone.
k) Doses are to be administered at the clinic on Day1 (after completing other procedures) then on an outpatient basis.

[redacted]

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher).

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD) (or standard error (SE) if appropriate), median, minimum, and maximum. Confidence intervals (CIs) will be added if appropriate.

Categorical (qualitative) variable summaries will be based on frequencies and percentages.

Unless stated otherwise, efficacy data for endpoints included in mixed effects repeated measures model (MMRM) analyses (groups [1], [2], [3], [7], [8], and [9]) will be summarized by visit and treatment group (Placebo, NYX-783 10 mg QD, NYX-783 50 mg QD) to allow for summary data treatment comparisons as per model inference. Efficacy data for Stage 2 groups [4], [5], [6], [10], and [11] will be presented separately.

Unless stated otherwise, safety data will be summarized by Stage and treatment group (Placebo [as Placebo Only and Placebo Stage 2, separately], NYX-783 10 mg QD, NYX-783 50 mg QD); data presented by visit will be displayed based on the treatment group which applies at onset for AEs/collection date.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD, SE) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all statistical tests will be conducted at a 0.10 significance level using one-sided tests and p-values will be reported. Corresponding 80% CIs (the interpretation of which is equivalent to a one-sided 90% CI when restricted to a single bound) will be presented.

4.2. Interim Analysis and Data Monitoring

No interim analyses for review of efficacy are planned for this study.

Data and Safety Monitoring Board (DSMB) will be responsible for the periodic review of available study data. Refer to the DSMB Charter for additional details of deliveries and timings of DSMB meetings.

[redacted]

5. Analysis Populations

The following analysis populations are planned for this study. As per protocol, the 50mg QW group will not be included in analysis population. Main efficacy and safety data for those subjects will be listed.

- **Safety Population (SAF):** The SAF consists of all randomized subjects who receive at least one dose of study drug (active or placebo). SAF inclusion and reporting will be evaluated separately for each Stage so there will be a safety set defined for Stage 1 (randomized subjects who receive at least one dose of study drug (active or placebo) during Stage 1 and a safety set defined for Stage 2 (randomized subjects who receive at least one dose of study drug (active or placebo) during Stage 2). Subjects in the SAF will be analyzed according to the treatment they actually received. For definition of actual treatment see Section 6.1.4. Unless otherwise specified, all safety analyses will be conducted on the Safety Population.
- **Intent-To-Treat (ITT) Population:** The ITT Population will consist of all randomized subjects. Subjects in the ITT Population will be analyzed according to the treatment they are assigned at randomization. The primary efficacy analysis will be performed on the ITT Population. Unless otherwise specified, all other efficacy analyses also will be conducted on the ITT Population. Subject data for each Stage is included in ITT analyses based on the availability of randomization assignments. As efficacy results are also presented by Stage, an ITT Stage 1 population will be created (all randomized subjects) and an ITT Stage 2 population will be created (all randomized subjects entering Stage 2).
- **Modified Intent-To-Treat (mITT) Population:** The mITT Population will consist of all ITT subjects who received at least 2 weeks of study drug and had at least one post-dose measurement of CAPS-5 (CAPS-5 questionnaire must be complete.) Subjects in the mITT Population will be analyzed according to the treatment they are assigned at randomization. This analysis population will serve as sensitivity analysis for primary efficacy analysis. As efficacy results are also presented by Stage, a mITT Stage 1 population will be created (all mITT subjects) and a mITT Stage 2 population will be created (all mITT subjects entering Stage 2).
- **Per-Protocol Population (PP):** The PP Population will consist of all ITT Population subjects who do not incur a major protocol violation that would challenge the validity of their data (including compliance assessment). This population will be used to evaluate the sensitivity of the primary efficacy analysis. For the same reason as ITT population, a PP Stage 1 population (subjects from ITT without any major protocol deviation) and a PP Stage 2 population (subjects from ITT without any major protocol deviation entering Stage 2) will be created.

[redacted]

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last non-missing observation recorded prior to the first dose of study drug (NYX-783 or placebo) will be used as the baseline observation for all calculations of change from baseline for Stage 1 data. For purposes of safety evaluation, subjects that are re-randomized in Week 4, the last non-missing observation before Week 4 will be used as baseline for Stage 2 data, with exception of groups [4] and [7] as referenced in Figure 1. Changes from baseline for these groups will be based on the Stage 1 baseline given their study intervention remained unchanged.

For purposes of efficacy analyses, baseline values for Stage 2 data within all groups [4], [5], [6], [7], [8], [9], [10], and [11] will be based on the last assessment prior to first dose of study drug in Stage 2.

6.1.2. Adjustments for Covariates

The primary efficacy endpoint will be evaluated using the weighted combination of the estimated treatment effects from the Stage-specific mixed models for repeated measures (MMRM). The MMRM models will include variables for treatment group, visit, treatment-by-visit interaction term, baseline CAPS-5 score and baseline-by-visit interaction.

6.1.3. Handling of Dropouts or Missing Data

Missing efficacy data will be handled using MMRM's maximum likelihood method. No additional imputation is planned to be performed.

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the case report form (CRF) will be included in data listings that will accompany the clinical study report.

6.1.3.1. Handling of Missing Date Values

Partial or Missing Dates

The following conventions will be used to impute missing portions of dates for AEs. An AE with missing or incomplete start dates will be reported as treatment emergent for both Stages unless data provided clearly indicates an onset as occurring within a particular Stage (e.g. a month specific to Stage 1) or outside of the treatment-emergent period (e.g. year provided is prior to first dose of study drug) as defined in Section 6.1.4.

Partially available concomitant medication dates will be handled similarly with respect to identifying use as concomitant as defined in Section 9.7.

[redacted]

6.1.3.2. Imputation Methods and Sensitivity Analysis

Observed cases, without imputation, will be used for the majority of analyses.

If the relationship of an AE is missing, it will be considered possibly-related unless the event is not considered treatment-emergent as defined in Section 9.1. Missing AE severity will be coded as severe.

6.1.4. Derived Variables

- Actual treatment received: After unblinding, all blister cards dispensed will be unblinded. Actual treatment will be defined by stage as the higher dose received at least one time (one capsule) during the corresponding stage (50mg > 10mg > Placebo).
- CAPS-5 (Clinician Administered PTSD Scale for DSM-5) = The CAPS-5 is a 30-item structured interview for diagnosis and assessment of PTSD. CAPS-5 scores are derived at data-management level. CAPS-5 total symptom severity score is calculated by summing severity scores for the 20 DSM-5 PTSD symptoms. Similarly, CAPS-5 symptom cluster severity scores (subscores) are calculated by summing the individual item severity scores for symptoms corresponding to a given DSM-5 cluster: Criterion B, intrusions (items 1-5); Criterion C, avoidance (items 6-7); Criterion D, negative alterations in cognitions and mood (items 8-14); and, Criterion E, alterations in arousal and reactivity (items 15-20).
  The assessor combines information on frequency and intensity of an item into a single severity rating (0-4) for each of the 20 DSM-5 PTSD symptoms, with a maximum possible score of 80 points. A higher score corresponds to more severe PTSD.

- PCL-5 (PTSD Checklist for DSM-5) = The PCL-5 is a 20-item self-report measure that assesses PTSD symptoms experienced over the last week or month according to DSM-5 criteria. PCL-5 score is derived at data-management level. Items assess symptoms across 4 symptom clusters of PTSD (re-experiencing, negative mood, avoidance, and hyperarousal) on a 0-4 point Likert scale. Total scores range from 0-80. The "since last week" version should be used after screening. A higher score corresponds to more severe PTSD. PCL-5 response is defined as decrease (from baseline) of 10 points at the end of each stage (week 4/week 8) [6].If total sore is missing at one time point (Week4/Week8) then response will be set to missing. If patient early terminated and assessment at Week 4 or Week 8 missing then patient will be a non-responder. Baseline defined as in section 6.1.1.

- PSQI= The Pittsburgh Sleep Quality Index (PSQI) [8] is a questionnaire to assess sleep quality and disturbances over a 1-month time interval. The score and subscores on this scale are derived by biostatistics. A total of 19 items are self-rated, 15 objective (about frequency of sleep disturbances and subjective sleep quality) and 4 subjective (typical bedtime, wake-up time, sleep latency and sleep duration) items. These 19 items generate 7 component scores: subjective sleep quality, sleep

[redacted]

latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction, each of which ranges from 0: no difficulty to 3: severe difficulty. A global score >5 indicates significant sleep disturbance. The algorithm to calculate PSQI score is detailed in Appendix 1: PSQI Derivation. If response to any of these 19 items (except question 5J, if response to 5J is missing then it can be imputed to 0)) is missing, then PSQI score for that subject will be null.

- PSQIA= This is the addendum to the PSQI assessment assessing disruptive nocturnal behavior (DNB) in PTSD subjects based on 7 types of behaviors: 1) hot flashes, 2) general nervousness, 3) memories or nightmares of traumatic experience, 4) severe anxiety or panic, not related to traumatic memories, 5) bad dreams, not related to traumatic memories, 6) episodes of terror or screaming during sleep without fully awakening and 7) episodes of acting out dreams, such as kicking, punching, running, or screaming. Each DNB is rated on a scale of 0-3 (0: not in the past month, 1: less than once a week, 2: once or twice a week, and 3: three or more times a week), with a global score range of 0-21. Lower scores represent less disruptive behavior. PSQIA and is calculated by biostatistics in the following way:
    - Calculate number of non-missing monthly behavior scores responses. Call this count PSQIACNT. If PSQIACNT >=6 then PSQIA score = (PSQIASUM/PSQIACNT)*7 else set value to null. The score can range from 0 to 21.
- BAC Symbol Coding (Symbol Coding from the Brief Assessment of Cognition) = The Brief Assessment of Cognition (BACS) is a pen-and-paper cognitive assessment. BAC Symbol Coding is delivered on a Pathway tablet and offers a sensitive measure of processing speed. Participants are provided a key and asked to fill in the corresponding numbers beneath a series of symbols as quickly as possible within 90 seconds. The assessment takes approximately 3-5 minutes to complete, including instructions and practice. The measure represents the correct number of numerals (0-110); a higher count reflects a higher function.
- CGI-S (Clinical Global Impressions-Severity) = The CGI-S scale assesses the global severity of illness and change in clinical condition over time, and subjects are rated from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects).
- HADS (Hospital and Anxiety Depression Scale) =The HADS is a self-assessment tool consisting of two subscales, one for anxiety (HADS-A) and one for depression (HADS-D). Each subscale consists of 7 items that are scored from 0-3, for a maximum score of 21 for either anxiety or depression; higher scores represent more severe anxiety or depression. HADS score are derived by biostatistics. HADS-A and HADS-D total scores will be computed only if the 7 items in each subscale are complete.

[redacted]

- [redacted]

- DES-II (Dissociative Experiences Scale-II) =The Dissociative Experiences Scale-II (DES-II) is a 28 item, self-report questionnaire that measures a wide variety of dissociative experiences, from normal (e.g., day-dreaming) to pathological (depersonalization). The DES-II score is derived by data-management. Subjects rate the percentage of time they have the experience, from 0% to 100% (in increments of 10), the score is the sum of the individual items divided by 28. DES-II total score will be computed only if all the 28 individual questions are non-missing.

- [redacted]

- Sheehan Suicidality Tracking Scale (S-STS) = The standard version of the S-STS is a 16-item scale that assesses the seriousness of suicidality phenomena on a Likert-type scale (0 to 4) ranging from 0 = “not at all” to 4 = “extremely.” The S-STS score will be derived by data-management. The S-STS accommodates a wide range of timeframes. In clinical trials, the frequently used variants are “in the past week”, “in the past month”, “since the last visit”, “lifetime look back”, and “in the past day.” In this study, during screening, "in the past month" version is used. For all the other visits "since the last visit" version of the S-STS is used.

- Subjects with high S-STS scores- Subjects with a score of 3 or 4 on any questions 2, 3, 4, 5, 6, 7, 8 or 13 in the S-STS questionnaire will be flagged.

- Placebo Non-responder = A Placebo Non-responder must satisfy the following criteria.
    - Randomized to placebo in Stage 1 of the study
    - Week 4 whose CAPS-5 total score reduction from baseline [Day 1] ≤35% and Week 4 CAPS-5 total score is ≥ 26
- Change from baseline = value at current visit– value at baseline (as defined in Section 6.1.1).
- TEAE = this is any adverse event with an onset date on or after first dose of study drug through 7 days after last dose of study drug. The Stage in which an event is considered treatment emergent will also be determined based on the relative onset timing against the first dose of Stage-specific study drug. Adverse Events with an onset during the 7 days after end of Stage 2 will be part of Stage 2.
- Duration of reported treatment period (years): For displays of TEAEs, it may be necessary to standardize rates of events due to variable treatment reporting periods. For Stage-specific reporting, durations are computed based on (the date of the last dose of study drug - the date of the first dose of Stage-specific study drug + 1).
- Treatment Related AEs= For each reported AE/SAE, the investigator assesses the relationship to study drug and categorize them into the following categories: Not Related = Unrelated and Unlikely Related, Related = Possibly Related and Probably Related). If an assessment is missing, then it will be treated as Related.
- Sexual Abuse= this is used to flag subjects who were victims of sexual abuse. If the medical history term preferred term is 'Sexual Abuse' or 'Victim of Sexual Abuse' then those subjects will be flagged as victim of sexual abuse.
- Time since start of Trauma (months) = date of randomization - date of index traumatic event (from medical history mhterm equals PTSD or POST TRAUMATIC STRESS DISORDER)
- High Avoidance Scores= Subjects with scores >=3 in Q6 or Q7 or Q13, avoidance related questions in CAPS-5 questionniare will be flagged. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All *P* values will be displayed in four decimals and rounded using standard scientific notation (e.g., 0.XXXX). If a p value less than 0.0001 occurs it will be shown in tables as <0.0001.

[redacted]

Adverse events will be coded using the MedDRA version 21.1 thesaurus.

7. Study Patients/Subjects and Demographics

Unless specified otherwise, summaries defined in this section will be presented by Stage based on treatment groups defined in Section 4.1 and in total within each reporting period.

7.1. Disposition of Patients/Subjects and Withdrawals

The summary of subject enrollment and disposition will display the number of subjects who are screen failures (Stage 1), the number and percentage of subjects randomized, treated, completed and discontinued in each Stage. Specific reasons for discontinuation will be summarized according to the reasons listed on the eCRF. Percentages will be calculated based on randomized subjects in each Stage and overall.

The number of subjects enrolled, screen failures, randomized, treated and entering Stage 2 will be also tabulated by site. This summary will be reproduced Over All Stages.

For each stage and overall, each analysis population will be described.

All subject disposition data and analysis population details will be presented in data listings. Screen failure data will also be listed.

7.2. Protocol Violations and Deviations

Prior to database lock, the protocol deviations will be reviewed for the following reasons:

- Standard study terminology deviation categories assigned
- Severity (major versus minor) assigned
- If a subject should be excluded from the PP population

Documentation will be put into place around the determination of patient population prior to lock and unblinding.

After database lock it may be determined that additional protocol deviations occurred, but could not be known prior to database lock. For example, a subject receiving study drug for the wrong treatment arm (i.e., a treatment arm other than the one they were randomized to). As a result, any additional protocol deviations found after database lock will be included with previous protocol deviations and documented separately to ensure timing of deviation is identified.

A subject listing will include the planned treatment arm, deviation category, protocol deviation, occurrence date with the corresponding study day, severity (major versus minor), and if the protocol deviation resulted in excluding a subject from the PP population. A frequency distribution table will be created to summarize only major protocol deviations by the assigned deviation categories.

[redacted]

7.3. Demographics and Other Baseline Characteristics

Demographic and other baseline characteristic data including gender, age, height, weight and BMI will be summarized using descriptive statistics. For the continuous variables, the number of non-missing values and the mean, standard deviation, minimum, median and maximum will be tabulated.

Categorical data for age group, race, sex, ethnicity, family status, education and employment will be summarized by counts and percentages.

Time since start of PTSD (months) will be summarized. Similar descriptive statistics will be used to summarize the baseline clinical measures such as CAPS-5, PCL-5, HADS, CGI-S, PSQI and PSQI-A.

Treatment differences in subject characteristics at baseline (based on Stage 1 treatment groups), will be assessed using Chi-square test (or Fisher's exact test in case Chi-square does not fit the data) for categorical variables and Type III sums of squares analysis of variance (ANOVA) for continuous variables. For continuous variables, in case normality is not assessed a Kruskall-Wallis test will be performed.

These analyses will be performed on both the ITT Population using assigned treatment and SAF Population using actual treatment received for Stage 1 and Stage 2. For SAF Stage 1 analysis, actual treatment received during Stage 1 will be used for treatment group. For SAF Stage 2 analysis, actual treatment received during Stage 2 will be used for treatment group and placebo will be splitted in Placebo Only and Placebo Stage 2.

The number and percentage of subjects reporting types of medical histories will be tabulated by MedDRA system organ class and preferred term (coded using MedDRA v.21.1). This analysis will be conducted by Stage 1 treatment groups for the SAF.

All baseline characteristics data, including medical and disease history, as well as diagnosis information, will be reported in data listings.

7.4. Exposure and Compliance

The first dose of study drug in Stage 1 will be administered orally at the investigative site. Subsequent study drug administration will be conducted on an outpatient basis. Stage 2 dosing begins the day after the Week 4 visit. Subjects will be instructed to take 1 capsule per day with water. A digital video dosing verification system for self-administration of investigational product (AiCure) was used to track capsule ingestion, and day and time of self-administration. This system is independent from EDC so a spreadsheet containing its information will be included in the statistical analysis of compliance. Cumulative counts for the total number of capsules dispensed; taken; returned and lost; subject compliance; as well as the duration of treatment will be summarized by actual treatment received (placebo [regardless of Stage 1 assignment], NYX-783 10 QD, and NYX-783 50 QD. The percentage of subjects who were compliant in each Stage will also be presented based on the SAF population. A subject will be considered compliant if between 80% and 120% of their expected dose had been taken.

Exposure and compliance data will be listed.

[redacted]

8. Efficacy Analysis

Unless specified otherwise, all efficacy analyses will be based on the ITT Population by treatment group (Placebo, NYX-783 50 mg and NYX-783 10 mg).

8.1. Primary Efficacy Analysis

The sequential parallel comparison design (SPCD) is an adaptive design that allows for re-randomization of placebo subjects (both "non-responders" and “responders”) from an initial stage of the study to placebo or active treatment in a subsequent stage of the trial. In this study, data from the “all-comers” population of Stage 1 arms [1 = placebo], [2 = NYX-783 50 mg QD], [3 = NYX 783 10 mg QD] and the subpopulations of “placebo non-responders” in Stage 2 arms [7 = placebo], [8 = NYX-783 50 mg QD], [9 = NYX 783 10 mg QD] are pooled to yield a single p-value for treatment comparison.

8.1.1. CAPS-5

The primary efficacy endpoint is change in CAPS-5 total score and subscores following 4 weeks of treatment in each respective Stage (Stage 1 [baseline to Week 4] and Stage 2 [Week 4 to Week 8]). Changes from baseline for specific visits and treatment groups will be used for the comparison of NYX-783 to placebo as described in Section 6 (for specification of visit alignment) and Section 6.1.1 (for information on baseline derivations). Modeled data will consist of change from baseline data through Week 4 for all of those randomized to treatment arms 1, 2 or 3 for Stage 1; and change from Week 4 assessment data for subjects randomized to arms 7, 8, or 9 for Stage 2.
The primary efficacy endpoint will be evaluated using the weighted combination of the estimated treatment effects from the Stage-specific mixed models for repeated measures (MMRM). The MMRM models will include variables for treatment group, visit, treatment-by-visit interaction term, baseline CAPS-5 score as covariate, and baseline-by-visit interaction. An unstructured covariance matrix will be used. If the model fails to converge with an unstructured covariance matrix other structures will be tried and the structure with the lowest corrected Akaike information criterion (AICC) will be used for the analysis. Full details will be included in the CSR. The Kenward-Roger approximation will be used to adjust the denominator degrees of freedom.

The treatment effect will be assessed as the differences in least-squares mean (LS mean) changes from baseline to Week 4 (Stage 1) and from Week 4 to Week 8 (Stage 2) for the NYX-783 50 mg QD, NYX-783 10 mg QD, and placebo groups defined in Section 8.1. A pairwise comparison will be made between each of the NYX-783 arms and placebo.
The treatment effect will be pooled across Stages 1 and 2 using pre-specified 0.6/0.4 weighting for Stage 1/Stage 2.

Combined inference is computed using the weighted linear combination of stage-wise test statistics[4]:

[redacted]

$$Z_{Combined} = \frac{0.6\widehat{\delta_1} + 0.4\widehat{\delta_2}}{\sqrt{0.6^2 Var(\widehat{\delta_1}) + 0.4^2 Var(\widehat{\delta_2})}}$$

Where, $\widehat{\delta_1}$ is the estimated Stage 1 treatment effect and $\widehat{\delta_2}$ is the estimated Stage 2 treatment effect. The combined test statistic $Z_{combined}$ is used to compute the overall one sided treatment effect p-value.

LS means, 80% CIs (the interpretation of which is equivalent to a one-sided 90% CI when restricted to a single bound), and SEs for the mean CAPS-5 scores by visit and treatment group within each Stage will be estimated based on the separate MMRM models. This inferential analysis will also be performed for estimation of the following mean CAPS-5 treatment differences within each Stage:

- placebo vs NYX-783 10mg QD
- placebo vs NYX-783 50mg QD
- placebo vs NYX-783 10mg QD + NYX-783 50mg QD

One-sided P-values for these Stage-specific differences will be reported based on individual t-tests but no formal statistical inferences are planned for these results.

These analyses will be repeated for each subscore.

Descriptive statistics for observed CAPS-5 total score, subscores and their relative changes from baseline will also be tabulated by study visit and treatment group as described in Section 4.1 for the groups specified in Section 8.1.

CAPS-5 scores will also be presented graphically by treatment at each visit based on mean plots.

The following pseudo SAS code will be used to implement the MMRM analyses

```
proc mixed data=xxx ;
 class trt avisit subjid;
 model change = trt avisit trt*avisit caps5b caps5b*avisit
/ s ddfm=kenwardroger
 repeated avisit /subject = subjid type=un;
 lsmeans avisit * trt / diff=all cl alpha=0.2
run;
```

8.1.2. Primary Efficacy- Sensitivity Analysis

The following sensitivity analyses will be performed to assess the robustness of the results of the primary analyses and to test the assumptions of the MMRM model:

- The primary efficacy analyses will be repeated using the PP Population.

[redacted]

- The primary efficacy analyses will be repeated using the mITT Population.
- The treatment effect will be pooled across Stages 1 and 2 using 0.5/0.5 weighting for Stage 1/Stage 2.

8.2. Secondary Efficacy Analysis

PCL-5 total score, PSQI score, PSQI-A score, BAC symbol coding, CGI-S scale, HADS-A scale, and HADS-D scale, will be analyzed based on the methods described in Section 8.1.1, using the endpoint appropriate baseline covariate.

8.3. Exploratory Efficacy Analyses

[redacted]

8.3.5. Subgroup Analyses

The primary efficacy endpoint will be described on the following subgroups

1. Gender
2. Race (White, Non-white)
3. Time Since Trauma (≤ median and > median) , date of trauma from medical

history where mhterm equals PTSD, POST TRAUMATIC STRESS DISORDER
4. Marital Status (Married, Not Married)
5. Trauma type(Sexual Abuse (from medical history where preferred term in "Sexual Abuse"," Victim of Sexual Abuse) vs. other)
6. Taken Pain Medication during study () at any point in the study (Yes, No). The list of concomitant medications will be reviewed prior to database lock and pain medications of interest will be identified for this analysis.
7. PSQI Sleeping Status (Good Sleeper total score <=5, Poor Sleeper total score >5) at baseline (Day 1 only)
8. HADS-A and HADS-D Score categories (normal (0-7), borderline abnormal (8-10) and abnormal (>=11))
9. Subjects with and without AEs of interest at any point during the study (Yes, No)
10. Subjects with high avoidance scores- Subjects with score 3,4 in avoidance categories of CAPS5 Q6,7 or distant from other people, Q13.

9. Safety and Tolerability Analysis

Safety will be evaluated from reported AEs, changes in clinical laboratory values, changes in vital signs, electrocardiogram (ECG) and physical examination results. Safety data will be summarized by stage and group as described in Section 4.1.

All safety analyses will be performed on the SAF.

9.1. Adverse Events

The number, percentage and incidence rate of subjects reporting treatment emergent AEs (TEAEs), grouped by MedDRA system organ class (SOC) and preferred term (PT) (coded using MedDRA v21.1), will be tabulated by Stage, and treatment group. In the case of multiple occurrences of the same TEAE within the same subject and Stage, a subject will only be counted once for each PT or SOC. Similar methods will be used to provide summaries further reported by severity and relationship. In the summaries reporting severity and relationship to study medication the event with the maximum severity and strongest relationship will be reported, respectively. For these analyses, missing severity and relationship will be imputed as described in Section 6.1.3.2.

The frequency, percentage, and incidence rate of subjects reporting TEAEs, will be reported as described for the following summaries:

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and maximum severity
- Treatment-related TEAEs by SOC and PT
- Treatment-related TEAEs by SOC, PT, and maximum severity

An overall summary of TEAEs, TEAEs leading to discontinuation of study, serious TEAEs, Severe or life-threatening TEAEs, and fatal AEs will be reported. This summary will also be reported for treatment-related TEAEs. Overall summaries for TEAEs and

treatment-related TEAEs by maximum severity will also be provided. The number of total events at each level of TEAE reporting will also be used in the calculation of incidence rate per subject-years of study participation given the specified Stage and reporting treatment period (total events/total patient-years included in the reported treatment period). In general, the duration of the reported treatment period is based on the amount of time a subject has taken the assigned drug within each Stage of reporting for a specified treatment; this is described in more detail in Section 6.1.4.

Missing and partially missing AE start and/or stop dates will be used to determine TEAE status for reporting, according to the specifications described in Section 6.1.5.

In the AE data listings, all AEs will be displayed. AEs that are not treatment-emergent will be flagged.

9.2. Adverse Events of Interest

The following are AEs of interest.

- Suicidality (ideation or attempt)
- Abuse and/or dependency events (drug & alcohol)
- Dissociative experience events
- Depression (or worsening depression)

The following AEs are also of potential clinical interest

- Eating disorder
- Nightmares (or worsening nightmares)
- Anxiety (or worsening anxiety)
- Panic attack
- Self-injurious behavior
- Aggressive behavior toward others
- Negative social events (e.g. loss of job, separation from significant other)

A summary of incidence rates (frequencies and percentages) by SOC, and preferred term will be prepared for all adverse event of interest listed above. The summary will be presented for each Stage as described in Section 9.1.

9.2.1. Adverse Events Leading to Discontinuation of Study

A summary of incidence rates (frequencies and percentages) of TEAEs leading to discontinuation of study, by SOC, and preferred term will be prepared. The summary will be presented by each Stage, as described in Section 9.1. No inferential statistical tests will be performed.

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

[redacted]

9.2.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious adverse events will be listed and tabulated by SOC and PT; the summary will be presented by each Stage, as described in Section 9.1. A summary of fatal TEAEs will also be provided.

9.3. S-STS

Data collected for S-STS will be summarized using descriptive statistics. Change from baseline will also be calculated and summarized in the same manner. All S-STS data will be provided in the data listings.

A summary of subjects with a score of 3 or 4 on questions 2 to 8 and 13 will be presented by stage and treatment group.

9.4. Clinical Laboratory Evaluations

Laboratory test results from hematology, serum chemistry, and urinalysis will be summarized descriptively (counts and percentages for categorical parameters) by treatment group, Stage and time point as both observed values and change from baseline values. Proportion of subjects with values < LLN and >ULN by treatment group, Stage and time point will be presented in summary tables.

The number of subjects with clinical laboratory values below, within, or above the normal range in relation to baseline will be tabulated for each clinical laboratory analyte by Stage and treatment group (bi-directional shift table) and visit. For those shift table, the most extreme post-baseline value will be used.

Urine drug screen, alcohol test and urine pregnancy test results will be presented in listings.

Potentially Clinically Significant (PCS) Laboratory Tests are defined as below

Table 2 PCS criteria for lab tests

Serum Chemistry	Alkaline Phosphatase (ALP)	> 2 x ULN
Serum Chemistry	Alanine Aminotransferase (ALT)	> 3 x ULN
Serum Chemistry	Aspartate Aminotransferase (AST)	> 3 x ULN
Serum Chemistry	Blood Urea Nitrogen (BUN)	> 1.5 x ULN
Serum Chemistry	Creatinine	>1.5 x Baseline or > 1.5 x ULN
Serum Chemistry	Gamma-Glutamyl Transferase (GGT)	> 3 x ULN
Serum Chemistry	Lactate Dehydrogenase (LDH)	> 3 x ULN

[redacted]

Serum Chemistry	Total Bilirubin	> 2 x ULN
Hematology	White Blood Cell Count	≤ 2.8 10^9/L
Hematology	Absolute Neutrophils Count	<1.5 10^9/L

Frequency distributions of the clinical laboratory tests of interest listed above will summarized for PCS values at any post-baseline visit.

Evaluation of potential Drug-Induced Serious Hepatotoxicity (eDISH) will also be done by plot.

9.5. Vital Signs and Physical Examination

Descriptive summaries of actual values and changes from baseline will be calculated for supine systolic blood pressure, supine diastolic blood pressure, heart rate, respiratory rate, oral body temperature and weight by dose treatment group and visit/time point.

:

PCS criteria for vital signs are listed below

Table 3 PCS criteria for vital signs

Supine Systolic Blood Pressure	≤90 and decrease ≥20 mm Hg; ≥180 and increase ≥20 mm Hg
Supine Diastolic Blood Pressure	≤50 and decrease ≥15 mm Hg; ≥105 and increase ≥15 mm Hg
Supine Heart Rate	≤50 and decrease ≥15 bpm; ≥120 and increase ≥15 bpm
Body Weight	Change(increase or decrease) from Baseline ≥7%
Respiratory Rate	<12 and >20 per minute

Frequency distributions of the vital signs of interest listed above will summarized for PCS values at any post-baseline visit.

Physical Examinations will be listed.

[redacted]

9.6. Electrocardiograms

Descriptive summaries will be presented for ECG measures of PR interval, QRS interval, QT interval, QTc interval (both correction methods), and HR. These summaries will be presented by treatment group, Stage and visit.

The number and percentage of patients/subjects with normal and abnormal investigator reported ECG results will be summarized by visit and treatment group. An outlier analysis using QTcF will also be done based on these standard criteria. If the change from baseline QTcF values are > 30 or 60 msec, or if QTcF post baseline values are >450, 470 or 500. This will be done by Stage and Over All. Shift tables for results (normal, abnormal CS, abnormal NCS) from baseline to post-baseline visits will be presented by body system, treatment group, Stage and visit.

Bazett's correction (QTcB) and Fridericia's correction (QTcF) will be derived as follows:

Bazett's Correction (QTcb)	$QTc_b = \frac{QT_{msec}}{\sqrt{RR}}$
Fridericia's Correction (QTcf)	$QTc_f = \frac{QT_{msec}}{\sqrt[3]{RR}}$

Where: Relative Rate: RR = 60 / HR

HR = Heart Rate obtained from the ECG.

9.7. Concomitant Medication

The number and percentage of subjects using prior and concomitant medications will be grouped by ATC Level 4 and preferred name (coded based on Sept 2018 version of World Health Organization Drug Coding Dictionary [WHODD], and tabulated by stage and treatment group. In the case of multiple uses of the same medication within the same subject, each subject will only be counted once for each preferred name. Prior medications will be presented separately from concomitant medications. Medications that started prior to the first dose of study drug (Stage 1) will be considered prior medications whether or not they were stopped prior to the first dose of study drug. If a medication starts prior to the first dose and continues after the first dose of study drug, it will be considered both prior and concomitant. A medication will be determined as concomitant for each Stage if taken at any time during the reported timeframe.

Prior medications will be reported by Stage 1 treatment groups only. Concomitant medications will be reported for each Stage. If the use of concomitant medication starts in Stage 1 and ends after Stage 2 dose administration start date, it will be reported in Stage 1 and Stage 2 summary tables. Incidences will be displayed by treatment group. For

[redacted]

reporting in each Stage, subjects will be reported by the treatment received in their respective Stage.

10. Other Planned Analysis

[redacted]

10.2. COVID-19 Assessment Impact

To address the impact of COVID-19 on evaluating the efficacy of the trial, the following approach will be implemented:

- First describing the population : randomized date, visits missed, visits done remotely, restriction due to COVID-19 by visit.Restriction due to COVID-19 is defined as first day to stay at home, it will be defined by state.
- Second a sensivity analysis on efficacy endpoints CAPS-5, PCL-5, PSQI score, HADS will be run. The main MMRM model will be run adding the COVID-19 restriction variable to evaluate impact of this covariate on treatment difference estimates. This covariate will be a time-varying covariate.
- A listings of all patient impacted by COVID-19 will be produced.

11. Changes from Protocol Planned Analysis

[redacted]

- Add mITT population for sensitivity analysis of primary efficacy.
- Add responder analysis for PCL-5.
- Add analysis for several subgroups
- Comparison of active treatment groups together is not relevant in this exploratory analysis without having any results on the comparison versus Placebo.
- Add COVID-19 Assessment Impact Analysis

[redacted]

12. References

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2. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.
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4. Chen Y, Yang Y, Hung HM, Wang S. Evaluation of performance of some enrichment designs dealing with high placebo response in psychiatric clinical trials. Contemp Clin Trials. 2011;32:592-604.
5. Fava M, Evins A, E, Dorer D, J, Schoenfeld D, A: The Problem of the Placebo Response in Clinical Trials for Psychiatric Disorders: Culprits, Possible Remedies, and a Novel Study Design Approach. Psychother Psychosom 2003;72:115-127.
6. Weathers, F.W., Litz, B.T., Keane, T.M., Palmieri, P.A., Marx, B.P., & Schnurr, P.P. (2013). The PTSD Checklist for DSM-5 (PCL-5). Scale available from the National Center for PTSD at www.ptsd.va.gov.
7. [redacted]
8. Buysse, Daniel J., et al. "The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research." Psychiatry res28.2 (1989): 193-213.

[redacted]

13. Tables, Listings, and Figures

All listings, tables and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (CRF page or listing number).

In general, one listing will be produced per CRF domain. All listings will be sorted by treatment, site, and subject number. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line (e.g., repetition of subject number), then only the first occurrence will be displayed.

In data listings, the information for one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

All tables, listings are described in the NYX-783-2004 SAP Shells latest document.

[redacted]

14. Appendix 1: PSQI Derivation

In order to calculate the PSQI total score first the following 7 variables need to be derived

PSQIDURAT, PSQIDISTB, PSQILATEN, PSQIDAYDYS, PSQIHSE, PSQISLPQUAL, PSQIMEDS (noted as Q1A-Q1G in Section 6.1.4). All of them are added to give PSQI total score.

PSQIDURAT- DURATION OF SLEEP

IF Q4 ≥ 7, THEN set value to 0

IF Q4 < 7 and ≥ 6, THEN set value to 1

IF Q4 < 6 and ≥ 5, THEN set value to 2

IF Q4 < 5, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIDISTB - SLEEP DISTURBANCE

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) = 0, THEN set value to 0

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) ≥ 1 and ≤ 9, THEN set value to 1

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 9 and ≤ 18, THEN set value to 2

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 18, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQILATEN - SLEEP LATENCY

First, recode Q2 into Q2new thusly:

IF Q2 ≥ 0 and ≤ 15, THEN set value of Q2new to 0

IF Q2 > 15 and ≤ 30, THEN set value of Q2new to 1

IF Q2 > 30 and ≤ 60, THEN set value of Q2new to 2

IF Q2 > 60, THEN set value of Q2new to 3

Next

IF Q5a + Q2new = 0, THEN set value to 0

IF Q5a + Q2new ≥ 1 and ≤ 2, THEN set value to 1

IF Q5a + Q2new ≥ 3 and ≤ 4, THEN set value to 2

IF Q5a + Q2new ≥ 5 and ≤ 6, THEN set value to 3

[redacted]

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIDAYDYS- DAY DYSFUNCTION DUE TO SLEEPINESS

IF Q8 + Q9 = 0, THEN set value to 0

IF Q8 + Q9 ≥ 1 and ≤ 2, THEN set value to 1

IF Q8 + Q9 ≥ 3 and ≤ 4, THEN set value to 2

IF Q8 + Q9 ≥ 5 and ≤ 6, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIHSE- SLEEP EFFICIENCY

Diffsec = Difference in seconds between day and time of day Q1 and day Q3

Diffhour = Absolute value of diffsec / 3600

newtib =IF diffhour > 24, then newtib = diffhour – 24

IF diffhour ≤ 24, THEN newtib = diffhour

(NOTE, THE ABOVE JUST CALCULATES THE HOURS BETWEEN GNT (Q1) AND GMT (Q3))

tmphse = (Q4 / newtib) * 100

IF tmphse ≥ 85, THEN set value to 0

IF tmphse < 85 and ≥ 75, THEN set value to 1

IF tmphse < 75 and ≥ 65, THEN set value to 2

IF tmphse < 65, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQISLPQUAL- OVERALL SLEEP QUALITY

Q6

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIMEDS- NEED MEDS TO SLEEP

Q7

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQI TOTAL

PSQIDURAT + PSQIDISTB + PSQILATEN + PSQIDAYDYS + PSQIHSE + PSQISLPQUAL + PSQIMEDS

Minimum Score = 0 (better); Maximum Score = 21 (worse)

Interpretation: TOTAL ≤ 5 associated with good sleep quality

TOTAL > 5 associated with poor sleep quality