STATISTICAL ANALYSIS PLAN

PROTOCOL NEP-MDD-201

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP EFFICACY AND SAFETY STUDY OF BTRX-246040 ADMINISTERED ONCE DAILY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER WITH OR WITHOUT ANHEDONIA

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
0.1		John Bauman	First Draft
0.2		John Bauman	Second Draft – Updates based on BlackThorn Review and Dry Run findings
0.3		Arane Thava	Third Draft – Updates based on BlackThorn Review and Dry Run findings
1.0		Sabina Rich	Final Draft – updates based on DR2 and client updates

Contents

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol NEP-MDD-201. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 6.0, dated 20 November 2018.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to evaluate the effects of BTRX-246040 on symptoms of depression in adult patients with Major Depressive Disorder after 8 weeks of double-blind treatment.

2.2. SECONDARY OBJECTIVES

The secondary objectives are as follows.

- To evaluate the effects of BTRX-246040 on anhedonia in adult patients with MDD.
- To evaluate the safety and tolerability of BTRX-246040 in adult patients with MDD.
- To evaluate the effects of BTRX-246040 on the performance of tasks as measured by the Facial Expression Recognition Task (FERT), Probabilistic Reward Task (PRT), and Effort Expenditure for Reward Task (EEfRT) in adult patients with MDD.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are as follows.

- To evaluate the effects of BTRX-246040 on anxiety-related symptoms in adult patients with MDD.
- To evaluate the effects of BTRX-246040 on pain-related symptoms in adult patients with MDD.
- To evaluate the effects of BTRX-246040 as measured by biomarkers in adult patients with MDD.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

Study NEP-MDD-201 is an 8-week, randomized, double-blind, placebo-controlled, parallel group, multicenter study. There will be a 28-day screening period, 8-week active treatment period (during which patients will receive either BTRX-246040 or placebo), and an approximate 1- to 2-week off-drug safety follow-up period (Figure 1).

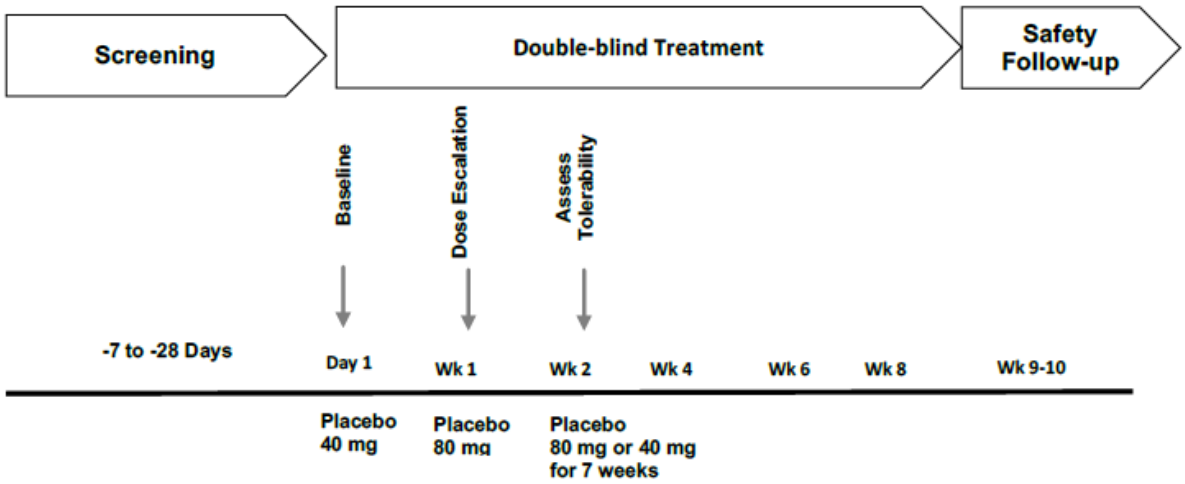

Figure 1: Study Design

Patients will be consented and screened for the study until approximately 100 patients are randomized. Randomization will be performed at Visit 2 (baseline) in a 1:1 ratio to one of two treatment arms (placebo or BTRX-246040 QD) after meeting disease diagnostic criteria for MDD and study inclusion (see section 8). Randomization will be stratified by anhedonia symptom severity, as indicated by a SHAPS total score ≤ 4 and > 4.

3.2. SCHEDULE OF ASSESSMENTS

The schedule of assessments can be found in Table 1 in Section 9.8 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

There are no planned changes from the protocol.

4. PLANNED ANALYSES

There are no analyses for data monitoring committees or interim analyses planned for this study. Thus, the only analysis planned for this study is the final analysis following database lock.

4.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC for this study.

4.2. INTERIM ANALYSIS

There will be no interim analysis for this study.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following sponsor authorization of this statistical analysis plan, database lock, sponsor authorization of analysis sets and unblinding of treatment groups.

5. ANALYSIS SETS

Agreement and authorization of patients included/excluded from each analysis set will be conducted prior to the unblinding of the study. The analysis for the Full-Analysis Set population defined in section 5.3 will be performed according to the treatment patients were randomized to. All other analyses will be performed according to the treatment the patient received.

5.1. ALL PATIENTS ENROLLED SET [ENR]

The all patients enrolled (ENR) set will contain all patients who provide informed consent for this study.

5.2. ALL PATIENTS RANDOMIZED SET [RND]

The all patients randomized (RND) set will contain all patients in the ENR set who were randomized to study medication.

5.3. FULL ANALYSIS SET [FAS]

The full analysis set (FAS) will contain all patients in the RND set who received at least one dose of study medication and have at least one post-dose efficacy assessment. The intent-to-treat principle is preserved, despite the exclusion of patients randomized who did not take the study medication or do not have post-baseline efficacy data, because the decision of whether or not to begin the treatment could not be influenced by knowledge of the assigned treatment due to the study blinding.

5.4. PER PROTOCOL ANALYSIS SET [PPAS]

The per-protocol analysis set (PPAS) will contain all patients in the FAS who did not experience any major protocol deviations which impact the efficacy conclusions of the study. Examples of major protocol deviations which may affect inclusion in the PPAS include:

- Treatment compliance of <80% or ≥120% of the prescribed dosage.
- Clinically significant discrepancies between planned and actual treatment.
- Receipt of prohibited medications.
- Violations of the entry criteria.

5.5. SAFETY ANALYSIS SET [SAF]

The safety analysis set (SAF) will contain all patients in the RND set who receive at least one dose of study drug.

If there is any doubt whether a patient was treated or not, they will be assumed treated for the purposes of analysis.

5.6. PHARMACOKINETIC ANALYSIS SET [PK]

The pharmacokinetic analysis set (PK) will include all patients in the RND with at least one valid PK measurement.

5.7. COMPLETERS ANALYSIS SET [CAS]

The completers analysis set (CAS) will contain all patients in the FAS who completed the full treatment period, as recorded in treatment disposition page of the eCRF.

5.8. MADRS NON-RESPONDERS ANALYSIS SET [MNRAS]

The MADRS non-responders analysis set (MNRAS) will contain all patients in the FAS who have a Week 2 investigator-administered MADRS total score that is >50% of the baseline MADRS total score. This determination will be made programmatically using the Baseline and Week 2 MADRS total scores.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication (Day 1).

- If the date of the event is on or after the reference date then:

  Study Day = (date of event – reference start date) + 1.

- If the date of the event is prior to the reference date then:

  Study Day = (date of event – reference start date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix 2; Partial Date Conventions.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). For this study, the reference date will be the date of first study drug dosing. In the case where the last non-missing measurement and the reference start date coincide, collection time, where available, will be compared with first dose time to determine whether the measurement is pre-baseline or post-baseline. If time is not available the measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded closest to the nominal visit day will be presented. Section 6.4 includes more details regarding visit windowing conventions and data handling for by-visit summaries.

Early termination data will be considered when assigning values to a visit window.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. WINDOWING CONVENTIONS

For each visit, a window will be defined such that the lower and upper bounds of each window is generally the midpoint between 2 consecutive study visits.

Visit Analysis Windows for Efficacy and Safety Variables Evaluated by Visit

	Baseline	Week 1	Week 2	Week 4	Week 6	Week 8
Scheduled Visit Day[a]	1	8	15	29	43	57
MADRS and other tests scheduled at each visit	≤1	2 – 11	12 – 22	23 – 36	37 – 50	≥51
HAM-A, PK, ECGs, and other tests scheduled at similar visits	≤1			2 – 43		≥44
Pain Questionnaire	≤1		2 – 22	23 – 36	37 – 50	≥51
SHAPS	≤1	2 – 11	12 – 22	23 – 43		≥44
FERT	≤1	2 – 11	12 – 22			
Urine Drug and Alcohol Screen	1	8		29	43	57

[a] Days are relative to the first dose of study medication.

Note: Any value collected after the administration of first dose on Day 1 will be grouped under Day 2.

Visit windowing will be applied to remap early termination visit data only. Thus, more than one result for a parameter may be obtained in a visit window. In such an event, the result from the scheduled visit will be used over the early termination visit.

The study window convention will not be applied to the eCRF data listings. The data listings for eCRF data will display the raw data as collected and entered in the eCRF.

Windowing will be applied to the data prior to any missing data calculations.

6.5. STATISTICAL TESTS

Confidence intervals will be reported at the 95% level and all tests will be two-sided, unless otherwise specified in the description of the analyses. P-values will be presented to identify trends in the study. That is, statistical tests that are significant at the 10% level will be considered as demonstrating a trend

and statistical tests that are significant at the 5% level will be considered as demonstrating a strong trend.

6.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

6.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates and factors are used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Baseline score (continuous variable)
- Treatment group (BTRX-246040 or placebo)
- Pooled Investigative Site
- Study visit (Weeks 1 – 8)
- Treatment-by-visit Interaction

If over parameterization means analyses cannot be performed pooling of investigative sites will be considered, if an appropriate pooling is possible, otherwise investigative site will be removed from the analysis.

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers within the United States. Randomization to treatment arms is not stratified by center.

7.3. MISSING DATA

In general, missing data will not be imputed. However, partial dates will contribute to analyses as

described in Appendix 2. All available data will be included in the safety analysis.

Details for the imputation algorithm for the missing endpoint values for the sensitivity analyses are described in Section 15.1.4 of this analysis plan.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

The nature of this study is to establish trends and is powered with that intent. Thus, no adjustments will be made for multiple comparisons.

7.5. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in the exploratory analysis sections. It should be noted that the study was not designed to detect treatment differences with high statistical power within subgroups.

The following subgroups will be assessed and described within the exploratory analysis sections:

- Gender.
- Baseline severity of anhedonia symptoms (SHAPS) score (≤4, >4).
- Baseline severity of anhedonia symptoms (SHAPS) score (≤7, >7).
- Baseline anxiety, as assessed by the Hamilton Anxiety Rating Scale (HAMA-A) score (<20, ≥20)

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The shell templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings (TFLs) that will be provided by IQVIA Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study.

Patient disposition, withdrawals and reasons for withdrawal will be presented for the ENR set by treatment group, investigative site and overall.

The number and percentage of patients completing the treatment period will be provided by treatment group and overall. Reasons for discontinuation from the treatment period will be summarized. The proportion of subjects that discontinue early will be compared between treatment groups using Fisher's exact test. The number of subjects that complete and reasons for failing to complete the follow-up visit will be presented for each treatment group. These analyses will be conducted on all patients enrolled,

the full Analysis Set and the Safety Analysis Set.

In addition, major protocol deviations which lead to exclusion for the PPAS will be summarized by treatment group and protocol violation category for the FAS. Inclusion in all analysis sets will be summarized by treatment group and overall for the RND set.

Listings will be produced to display the information collected in the eCRF regarding patient disposition. Listings will also be generated to show patient randomization assignment, analysis set assignment and all key protocol violations.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented by treatment group and overall.

The following variables will be summarized:

- Age at screening (years) - calculated relative to date of consent
- Sex
- Race
- Ethnicity
- Childbearing potential (females only)
- Height at Screening (cm)
- Weight as Baseline (kg)
- BMI at Baseline (kg/m2)
- Alcohol consumption status (occurrence, average number of drinks per week)
- Smoking status (occurrence, average number of packs per week)
- Hand Dominance
- Glasses Usage

Categorical variables like sex and ethnicity will be compared between treatment groups using Fisher's exact test for categorical data and continuous variables like age and height will be compared using an ANOVA model with treatment and investigative site as covariates. This analysis will be performed for the FAS, SAF PPAS, CAS and MNRAS sets. Similar comparisons will be conducted for alcohol consumption and smoking status, but only using the SAF set.

All demographic data collected within the eCRF will be listed.

10.1. DERIVATIONS

BMI (kg/ m2) = weight (kg)/ height (m)2

11. MEDICAL AND PSYCHIATRIC HISTORY

Medical and psychiatric history information will be presented for the SAF set. Medical and psychiatric history conditions are defined as those conditions which stop prior to or at Screening. Conditions will be coded using MedDRA version 20.0 and presented by treatment group, SOC and PT.

Data collected from the Structured Clinical Interview for DSM Disorders-Clinical Trials (SCID-CT) including personal history of traumatic events and Lifetime Illness Characteristics Questionnaire (LICQ) at screening will be presented in listings.

12. CONCOMITANT ILLNESSES

Concomitant medical and psychiatric information will be presented for the SAF set. Concomitant illnesses are defined as those conditions which start prior to or at Screening and are ongoing at the date of screening. Concomitant illnesses will be coded using MedDRA version 20.0 and presented by treatment group, SOC and PT.

Information regarding all concomitant illnesses will be listed alongside information for historical medical and psychiatric conditions

13. MEDICATIONS

Prior and concomitant medications will be presented using the SAF set and coded using WHO Drug Dictionary (WHODD) 05 June 2017. Summaries will be presented by treatment group, Anatomical, Therapeutic, or Chemical (ATC) level 5 and preferred drug name for prior and concomitant medications separately.

See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e. concomitant.

- 'Prior' medications are medications which started and stopped prior to the first dose of study drug.
- 'Concomitant' medications are medications which:
    - started prior to, on or after the first dose of study drug
    - AND ended on or after the date of first dose of study drug or were ongoing at the end of the study.

All information recorded in the eCRF with regards to medications will be listed.

13.1. NON-PHARMACOLOGICAL THERAPIES

Use of Cognitive Behavioral Therapy (CBT) will be summarized by treatment group, including a summary of the number of patients who started or stopped CBT whilst receiving study medication.

All Non-pharmacological therapies will be listed.

14. STUDY MEDICATION EXPOSURE AND COMPLIANCE

The proportion of patients compliant to study medication will be presented for the SAF, FAS and MNRAS analysis sets. A patient will be considered compliant if they received ≥80% and <120% of the expected number of doses during the study. In addition, the proportion of patients who have a dose reduction during week 2 from 80mg to 40mg as permitted in the protocol will be displayed. Compliance and exposure to study drug will also be summarized through descriptive statistics.

14.1. DERIVATIONS

Compliance will be calculated according to the following formula:

$$\text{Compliance } (\%) = \left(\frac{\sum \text{Doses received } (\text{mg})}{\sum \text{Expected doses } (\text{mg})} \right) \times 100$$

The expected dosage is 7 daily doses at 40mg followed by 49 daily doses at 80mg. Therefore, the sum of all expected doses for a patient who completes the trial is 7 x 40mg + 49 x 80mg = 4200mg.

If a patient discontinues the study early, the sum of all planned doses will be adjusted accordingly so the compliance calculation is not influenced by the time on treatment. The calculation will use the last dose date recorded on the patient disposition page of the eCRF. E.g. if a patient takes their final dose on day 28 the sum of all expected doses will be calculated as the following: 7 x 40mg + 21 x 80mg = 1960mg.

In addition, as the protocol allows for a dose reduction during week 2 this will also be accounted for in the compliance calculation. For example, if a patient decides to reduce the daily dosage to 40mg on day 10 and then went on to complete the treatment period, the sum of all expected doses would be calculated as the following: 7 x 40mg + 2 x 80mg + 47 x 40mg = 2320mg. Any dose reductions after week 2 would be considered a protocol violation and therefore the compliance calculation would not be adjusted.

The sum of all doses received will be calculated using drug accountability data collected on site. The number of capsules dispensed (calculated as the number of bottles dispensed x 16), the number of capsules returned will be recorded. Each capsule is 40mg, therefore the sum of all doses received will be calculated as:

$$\sum \text{Doses received (mg)} = \left(\sum \text{Capsules dispensed} - \sum \text{Capsules returned} \right) \times 40$$

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy variable is the change from Baseline in investigator-administered Montgomery-Asberg Depression Rating Scale (MADRS) total score at Week 8. The MADRS is a 10-item rating scale for the evaluation of depressive symptoms. Each item is rated on a 0 to 6 scale with higher scores indicating higher levels of depressive symptoms. Thus, the total score can range from 0 to 60. The MADRS total score will be taken as recorded by the Investigator (i.e., not altered or adjusted) from the vendor dataset provided by Data Management. Change from baseline values will be computed as the MADRS total score at Week 8 – the MADRS total score at Baseline.

15.1.2. MISSING DATA METHODS FOR THE PRIMARY EFFICACY VARIABLE

No missing data imputation is required for the primary analysis, LS means estimates will be adjusted for missing data through the mixed model for repeated measures (MMRM) methods used in the analysis. If data is missing at Week 8 for a patient then they will not be included in the analysis. However, a sensitivity analysis will be conducted with imputed data as described in section 15.1.4.

15.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary objective of this study is to evaluate the effects of BTRX-246040 on symptoms of depression in adult patients with Major Depressive Disorder after 8 weeks of double-blind treatment. To meet this objective the hypothesis that BTRX-246040 is superior to placebo will be tested as follows:

$$H_0: \mu_{BTRX\text{-}246040} = \mu_{placebo} \text{ vs. } H_a: \mu_{BTRX\text{-}246040} \neq \mu_{placebo}$$

Where μ is the change from baseline in investigator-administered MADRS total score at week 8.

The primary efficacy analysis will be performed for the full analysis set (FAS).

The primary analysis will be a MMRM. A repeated measures analysis refers to a restricted-maximum-likelihood- (REML-) based, MMRM analysis using all the longitudinal observations at each post-baseline visit. The model for this analysis will include the fixed class effects of treatment, investigative site, visit, and the treatment-by-visit interaction as well as the continuous covariate of baseline investigator-administered MADRS total score. An unstructured covariance structure will be used to model the within-patient errors. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous autoregressive variance-covariance structure will be used. The difference in least square means (LS Means) between BTRX-246040 and placebo at Week 8, with corresponding 2-sided 95% confidence intervals and estimated P-values will be presented.

15.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The following sensitivity analyses will be conducted on the change from baseline in investigator-administered MADRS total score to ensure robustness of the primary efficacy analysis. The FAS will be used for all sensitivity analyses unless otherwise specified.

- The primary efficacy analysis will be repeated on the PPAS, CAS, and MNRAS analysis sets.
- The MMRM model used for the primary efficacy analysis will be used to analyze the change from Baseline in investigator-administered MADRS total score at each post-Baseline visit. For each visit the difference in LS Means between BTRX-246040 and placebo will be presented alongside the 2-sided 95% confidence interval and P-value.
- ANCOVA will be used to analyze the change in investigator-administered MADRS total score from baseline to week 8, with missing data imputed. The ANCOVA model will include treatment group, investigative site as fixed effects and baseline investigator-administered MADRS total score as a covariate. Only the MADRS total score will be imputed where missing, the individual component scores will not be imputed. Imputation will be performed following visit window remapping. The following two methods of data imputation will be used:
  - Multiple imputation using Rubin's rules with SAS Proc MI and MIANALYSIS.
  - Single imputation by last observation carried forward (LOCF).
- Finally, the change from baseline in the computer-administered MADRS total score will be analyzed using the same method as the primary efficacy analysis.

Forest plots of the treatment difference and confidence intervals will be created for the primary analysis and each of the efficacy analyses.

15.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed for the FAS unless otherwise specified.

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

15.2.1.1. MADRS Total Score

The derivation of the MADRS total score is defined in section 15.1.1.

15.2.1.2. MADRS-6 Subscale

The MADRS-6 subscale focuses on the core symptoms of depression and is the sum of items about the following symptoms: apparent sadness, reported sadness, inner tension, lassitude, inability to feel, and pessimistic thoughts. Overall score ranges from 0 to 36.

15.2.1.3. MADRS Individual Item Scores

The MADRS individual item scores refer to the 10 items, on a scale 0 – 6 which comprise the MADRS total score.

15.2.1.4. Hospital Anxiety and Depression Scale subscales

The Hospital Anxiety and Depression Scale (HADS) subscales comprises of 7 questions regarding Depression and 7 questions regarding Anxiety. Each question is rated on a scale from 0 – 3. The outcome of the HADS questionnaire is two total scores, the HADS-A (for anxiety) and the HADS-D (for depression). Both total scores are graded on a scale of 0 – 21 and can be categorized as Normal (0 – 7), Borderline Abnormal (8 – 10) and Abnormal (11 – 21). Higher scores indicate higher levels of anxiety and depression.

15.2.1.5. Dimensional Anhedonia Rating Scale

The Dimensional Anhedonia Rating Scale (DARS) is a 17-item questionnaire with each answer between 0 and 4 on a Likert scale grading (0=Not at all, 1=Slightly, 2=Moderately, 3=Mostly, 4=Very Much). Therefore, the DARS total score is on a scale of 0 – 68. The DARS Total score is broken down into four dimensions; Hobbies, Food/Drink, Social Activities and Sensory Experience.

15.2.1.6. Snaith Hamilton Pleasure Scale

The Snaith Hamilton Pleasure Scale (SHAPS) is a 14-item questionnaire. The SHAPS is scored two different ways. Under the original scoring method, each question has 4 responses, 2 of which imply agreement (Definitely Agree, Agree; each scored as 0) and 2 which imply disagreement (Disagree, Strongly Disagree; each scored as 1). Therefore, the SHAPS total score ranges 0 – 14. In this study, in addition to the traditional scoring method, an alternative scoring method will assign 1 - Strongly Agree, 2 - Agree, 3 – Disagree, and 4 – Strongly Disagree. Using this alternative scoring method, the total score ranges 14-56. In both scoring systems, higher scores indicate greater anhedonia.

15.2.1.7. Response

Response will be defined in the following three ways:

- **Clinical response** will be defined as a reduction in the investigator-administered MADRS total score of 50% between baseline and week 8.
- **Remission** will be defined as an investigator-administered MADRS total score of ≤10 at week 8.
- **Improvement** will be defined as a Clinical Global Impression Scale – Improvement (CGI-I) score of 1 or 2 at week 8. The CGI-I is a 7-point scale that relates to an improvement in patients symptoms when compared to the Clinical Global Impression Scale – Severity (CGI-S), which is also measured on a 7-point scale.

15.2.1.8. The Facial Expression Recognition Task

The FERT is a computer test used to assess attention to, and perception of, social cues and affective

information. Faces with 6 different basic emotions (happiness, fear, anger, disgust, sadness, surprise) are displayed on the screen and the patient is required to indicate the expression of the face via a button-press. Different intensity levels (10) of each emotion are presented, which increases the ambiguity of the facial expression and the sensitivity of the task (Harmer et al, 2009). In addition, neutral faces will be displayed on screen during the task and is a button-press option. Intensity levels do not apply to the neutral face but the 5 outcome measures will be reported for neutral faces as well.

There are 5 outcome measures from the FERT for each emotion. They are:

- Accuracy (%)
- Misclassification (%)
- Average reaction time (ms)
- Target sensitivity
- Response bias

These measures, along with the accuracy response for each intensity level, for each emotion will be provided by the vendor data and will be used in the analysis described in section 15.2.3.8.

15.2.1.9. Probabilistic Reward Task

The PRT is a measure of reward learning consisting of trials in which patients are asked to respond to two hardly distinguishable cues, of which one is more frequently rewarded. Patients complete a total 300 trials in 3 blocks of 100. Response bias for the rewarded category is the main outcome of interest (Pizzagalli, et al, 2008). In addition, the following outcome measures will be provided:

- Discriminability (subject's ability to differentiate between the two cues)
- Reaction time
- Accuracy (hit rates)

All measures will be computed and provided by the vendor in the source data for each block and as an overall total. The response bias and discriminability measures will also have log-linear adjusted values provided. The adjusted values for response bias and discriminability and original values for reaction time and hit rates at each block will be utilized in the analyses.

Additionally, there will be a series of checks on the data to insure validity of the data used in the analysis. Only subjects with data meeting the following criteria will be used in the analysis.

- The number of valid trials is >80% for each block
- Reward ratio of rich:lean is greater than 25:10 (ratio: 2.5) in each block.
- The number of rich rewards is between 24 and 30, inclusively.
- The number of lean rewards is between 7 and 10, inclusively.
- The lean accuracy in each block is greater than or equal to 40%.
- The rich accuracy in each block is greater than or equal to 40%.
- For combination of blocks e.g. Main, Total: If one block is not usable, then the combo is not usable (i.e. if block 2 is not usable, then total is not usable).

15.2.1.10. Effort Expenditure for Reward Task

The EEfRT task is a multi-trial game in which participants are given an opportunity on each trial to choose between two different task difficulty levels in order to obtain monetary rewards. Patients are required to complete the task with a specific number of button responses within a constrained period of time in order to obtain a monetary reward. The outcome measures of the EEfRT are:

- Preference (hard or easy task)
- Completion rates

These measures will be provided by the vendor data and will be used in the analysis described below.

Additionally, there will be a series of checks on the data to insure validity of the data used in the analysis. Only subjects with data meeting the following criteria will be used in the analysis.

- Proportion of completed tasks > 75%.
- No more than 10 failed tasks in a row, which would suggest the subject 'took a break'.
- The subject does not time out on >10% of trials
- Average reaction times of ≥500ms (0.5s).

15.2.2. Missing Data Methods for Secondary Efficacy Variable(s)

No missing data imputation will be used for the secondary efficacy variables.

15.2.3. Analysis of Secondary Efficacy Variables

15.2.3.1. MADRS Total Score

The following analyses will be produced for both the investigator-administered MADRS assessment and the computer-administered MADRS assessment in addition to the analyses described above.

The MADRS total score and change from baseline in MADRS total score will be summarized through descriptive statistics (mean, standard deviation, median, and range) by treatment group and visit. The MADRS total score will also be summarized as a categorical variable by classifying the MADRS total score as Normal (0 – 6), Mild Depression (7 – 19), Moderate Depression (20 – 34) or Severe Depression (35 – 60) for each treatment group and visit.

In addition, the difference for each patient between the investigator-administered MADRS total score and the computer-administered MADRS total score will be summarized for each treatment group and visit alongside the 95% confidence interval p-value from a paired t-test.

15.2.3.2. MADRS-6 Subscale

The change from baseline in the investigator-administered MADRS-6 subscale to week 8 will be analyzed using the same method as the primary efficacy endpoint, substituting the baseline MADRS-6 subscale as the covariate in place of the MADRS total score. In addition, the MADRS-6 subscale and the change from baseline in investigator-administered MADRS-6 subscale will be summarized through

descriptive statistics by treatment group and visit.

15.2.3.3. MADRS Individual Item Scores

The change from baseline for each individual item comprising the investigator-administered MADRS total score to week 8 will be analyzed using the same method as the primary efficacy endpoint, substituting each individual item as covariates in place of the MADRS total score. The investigator-administered MADRS individual item scores and their change from baseline will also be summarized through descriptive statistics by treatment group and visit.

The MADRS individual item scores, total scores and MADRS-6 total scores will be listed for all patients and visits.

15.2.3.4. Hospital Anxiety and Depression Scale subscales

The change from baseline for both the HADS-A total score and HADS-D total score to week 8 will be analyzed using the same method as the primary efficacy endpoint, substituting the baseline HADS-A and HADS-D total score as appropriate as the covariate in place of the MADRS total score. The HADS-A total score and HADS-D total score and change from baseline in HADS-A total score and HADS-D total score will be summarized through descriptive statistics by treatment group and visit. The HADS-A total score and the HADS-D total score will also be summarized as categorical variables using the classification of Normal/Borderline Abnormal/Abnormal described above by treatment group and visit. Finally, the number and percentage of patients within each result category will be presented by treatment group, item and visit.

All HADS-A and HADS-D total scores and individual item scores will be listed.

15.2.3.5. Dimensional Anhedonia Rating Scale

The change from baseline for the DARS total score to week 8 will be analyzed using the same method as the primary efficacy endpoint, substituting the baseline DARS total score as the covariate in place of the MADRS total score. The DARS total score and change from baseline in DARS total score will be summarized through descriptive statistics by treatment group and visit. In addition, the number and percentage of patients within each result category will be presented by treatment group, item and visit. Each DARS dimensions score (Hobbies, Food/Drink, Social Activities, Sensory Experience) and change from baseline in DARS dimensions score will be summarized through descriptive statistics by treatment group and visit.

All DARS individual item scores and total scores will be listed.

15.2.3.6. Snaith Hamilton Pleasure Scale

The change from baseline for the SHAPS total score to week 8 will be analyzed using the same method as the primary efficacy endpoint, substituting the baseline SHAPS total score as the covariate in place of the MADRS total score. The SHAPS total score and change from baseline in SHAPS total score will be summarized through descriptive statistics by treatment group and visit. In addition, the number and percentage of patients who agree or disagree to each question will be presented by treatment group, item and visit.

All SHAPS individual item scores and total scores will be listed.

15.2.3.7. Response

The difference in the proportion of responders at week 8 between each treatment group will be estimated for each response variable using a logistic regression model with treatment and investigator site as a fixed effect and baseline investigator-administered MADRS total score as a continuous covariate, using Firth's Penalized Likelihood with CI and p-values based on individual Wald tests.

In addition, the number and percentage of patients within each CGI-S and CGI-I result category will be presented by treatment group and visit. Both CGI-S and CGI-I results will be available at the baseline visit, the CGI-I at baseline will refer to the CGI-S assessment at screening. All subsequent CGI-I assessments will refer to the baseline CGI-S assessment.

Results of each response category at week 8 will be listed for all randomized patients. In addition, all CGI-S and CGI-I results will also be listed.

15.2.3.8. The Facial Expression Recognition Task

For each emotion of the FERT, each outcome measure will be summarized (mean, standard deviation, median, and range) by treatment group at each visit. Line plots of means (+/-SD) will also be presented by treatment group and visit. Additionally, accuracy will be summarized by intensity level for each emotion and plotted versus intensity level in scatterplots.

At each scheduled visit, an ANOVA model with a term for treatment will be used to analyze treatment differences. LS Means and standard errors (SEs) will be presented for each treatment group. A second ANOVA model will be fit with additional factors of gender, baseline MADRS total score, and baseline FERT outcome measure. The difference in LS Means with corresponding SEs, 95% confidence intervals for differences, and p-values will also be presented. No adjustments will be made for multiple comparisons.

All data, including the accuracy response for each intensity level, will be listed by treatment and patient.

15.2.3.9. Probabilistic Reward Task

Each outcome measure of the PRT will be summarized (mean, standard deviation, median, and range) at each visit. Response bias and discriminability will be summarized by block and treatment. Reaction time and hit rates will be summarized by stimulus (rich vs. lean), block and treatment. Line plots of means (+/-SD) will also be presented by treatment group and visit.

At each scheduled visit, an ANOVA model will be used to compare treatment groups. The models for response bias and discriminability will include terms for treatment, block, and treatment-by-block will be used to analyze treatment differences. The models for reaction time and hit rates will include terms for treatment, block, stimulus, and treatment-by-block will be used to analyze treatment differences. The models LS Means and standard errors (SEs) will be presented for each treatment group. The difference in LS Means with corresponding SEs, 95% confidence intervals for differences, and p-values will also be presented. No adjustments will be made for multiple comparisons.

All data, including the overall total scores, will be listed by treatment and patient.

15.2.3.10. Effort Expenditure for Reward Task

Each outcome measure of the EEfRT will be summarized (mean, standard deviation, median, and

range) by treatment group at each visit. Line plots of means (+/-SD) will also be presented by treatment group and visit.

The analysis of completion rates will use an ANOVA model with a term for treatment to analyze treatment differences at each scheduled visit. The models LS Means and standard errors (SEs) will be presented for each treatment group. The difference in LS Means with corresponding SEs, 95% confidence intervals for differences, and p-values will also be presented. No adjustments will be made for multiple comparisons.

The analysis of preference will be completed utilizing Generalized Estimating Equation (GEE) models. A binary logistic distribution will be used to model the dichotomous outcome of preference at each scheduled visit. At each visit a series of models using a variety of factors will be fit. All models in the series will include explanatory variables reward magnitude, reward probability, and expected value (reward magnitude X probability) as a base. For each series, four models will be fit. The first will include the base variables with the additional variable of interest with no interactions. The next three models will include the same but with an interaction term between the variable of interest and each base variable in order. The variables of interest that will be explored include:

- Age
- Sex
- Treatment
- MADRS Total Score
- SHAPS Score (0 – 14 scoring method)
- DARS Total Score

The parameter estimates, standard error, 95% confidence interval, degrees of freedom and p-values will be presented to for each model.

All data will be listed by treatment and patient.

15.3. EXPLORATORY EFFICACY

15.3.1. EXPLORATORY EFFICACY VARIABLES & DERIVATIONS

15.3.1.1. Hamilton Anxiety Rating Scale

The Hamilton Anxiety Rating Scale (HAM-A) consists of 14 items. Each item is rated on a scale of 0 (feeling not present) to 4 (very severe prevalence of the feeling). The HAM-A total score is the sum of the 14 items and the score ranges from 0 to 56.

15.3.1.2. Pain Question

The Pain question is a single item which assesses the average pain over the last 24 hours. The response is scored from 0 (no pain) to 10 (pain as severe as you can imagine).

15.3.1.3. Nonpharmacogenetic Biomarkers

Results for the following nonpharmacogenetic biomarkers will be available: plasma nociception, serum IL-1ß, IL-2, IL-6, IL-10, TNFα, IFNγ and CRP. If applicable biomarker results below the limit of quantification (BLOQ) will be imputed as BLOQ/2 and biomarker results above the limit of quantification (ALOQ) will be imputed as the ALOQ for the purpose of change from baseline calculations.

15.3.2. Missing Data Methods for Exploratory Efficacy Variable(s)

No missing data imputation will be used for the exploratory efficacy variables.

15.3.3. Analysis of Exploratory Efficacy Variables

15.3.3.1. Hamilton Anxiety Rating Scale

The change from baseline for the HAM-A total score to week 8 will be analyzed using the same method as the primary efficacy endpoint, substituting the baseline HAM-A total score as the covariate in place of the MADRS total score. Using the same model, the difference in between treatment groups will also be presented for the change from baseline to week 4. The HAM-A total score and change from baseline in HAM-A total score will be summarized through descriptive statistics by treatment group and visit.

15.3.3.2. Pain Question

The change from baseline for the Pain score to week 8 will be analyzed using the same method as the primary efficacy endpoint, substituting the baseline Pain score as the covariate in place of the MADRS total score. The Pain score and change from baseline in Pain score will be summarized through descriptive statistics by treatment group and visit.

15.3.3.3. Nonpharmacogenetic Biomarkers

The change from baseline to week 8 for each nonpharmacogenetic biomarker will be analyzed using an ANCOVA model with treatment group and investigative site as fixed effects and baseline biomarker result as a continuous covariate. The change from baseline in nonpharmacogenetic biomarker result will be summarized through descriptive statistics by biomarker, treatment group and visit. The number and percentage of BLOQ/ALOQ results at each visit will also be presented. In addition, panel plots displaying the correlation of the change from baseline to week 8 in biomarker level with the change from baseline to week 8 in MADRS total score and total treatment exposure will be presented.

15.3.4. Subgroup Analysis

Analysis by the subgroups defined in section 7.5 will be performed on efficacy endpoints according to the following table. The change from baseline to week 8 for each endpoint will be analyzed using the same method as the endpoint in the main analysis. For the anhedonia severity subgroup analysis, that term will be dropped from the model.

Subgroup Analyses for Efficacy Endpoints

Efficacy Endpoint	Subgroup			
	Gender	Anhedonia Severity (SHAPS)		Baseline HAM-A (<20, >=20)
		(<=4, >4)	(<=7, >7)	
MADRS total score	X	X	X	X
PRT			X	
EEfRT			X	

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

16.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 20.0.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication.

See APPENDIX 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

An overall summary of number of patients within each of the categories described in the sub-section below will be provided as specified in the templates.

Listings will include TEAEs and Non-TEAEs.

16.1.1. ALL TEAES

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity and relationship to study medication.

16.1.1.1. Severity

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If a patient reports a TEAE more

than once within that SOC/ PT, the AE with the worst case severity will be used in the corresponding severity summaries.

16.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as ”not related”, “unlikely related”, “possibly related”, and “related” (increasing severity of relationship). A ”related” TEAE is defined as a TEAE with a relationship to study medication as ”possibly related” or ”related” to study medication. TEAEs with a missing relationship to study medication will be regarded as related to study medication. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

16.1.2. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified from the Adverse Event eCRF page where the action taken with the study treatment was selected as “Drug withdrawn”.

For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

16.1.3. TEAE’s Leading to Early Study Discontinuation

TEAEs leading to early study discontinuation will be identified from the relevant question in the Adverse Event eCRF page.

For TEAEs leading to early study discontinuation, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

16.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as ”Serious” on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared.

16.1.5. Adverse Events Associated with Self-harm Episodes

TEAEs associated with self-harm episodes will be identified from the relevant question in the Adverse Event eCRF page.

For TEAEs associated with self-harm episodes, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

16.2. Deaths

If any patients die during the study, as recorded on the ”death details” page of the eCRF , the

information will be presented in a data listing.

16.3. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for Hematology, Clinical Chemistry (including Amylase and total Lipase) and Urinalysis. A list of laboratory assessments to be included in the outputs is included in the protocol, Section 11.4.

Presentations will use SI Units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification, or "> X", i.e. above the upper limit of quantification, will be converted to X/2 or X respectively for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings, where X has been converted into the SI unit.

The following summaries will be provided for laboratory data:

- Summary tables of actual and change from baseline by visit (for quantitative measurements)
- Shift from baseline to each post-baseline assessment according to normal range criteria (for quantitative measurements and categorical measurements)
- Listing of patients meeting abnormal criteria

Laboratory tests related to patient screening, such as, urine drug screening, hepatitis screening and thyroid function, if available, will be listed only. Results from serum and urine Pregnancy tests will be listed.

16.3.1. LABORATORY REFERENCE RANGES AND ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

16.4. ECG EVALUATIONS

Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study.

The following ECG parameters will be reported for this study:

- PR Interval (msec)
- RR Interval (msec)

- QRS Duration (msec)
- QT Interval (msec)
- QTcF Interval (msec)
- QTcB Interval (msec)
- Heart Rate (bpm)
- Axis and Voltage (deg)
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant (ANCS)
    - Abnormal, Clinically Significant (ACS)

Summary tables and boxplots of actual and change from baseline results for all quantitative ECG parameters will be presented.

16.4.1. ECG MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria:

- Absolute values for QT interval, QTc interval, QTcB interval and QTcF will be classified as:
    - > 450 msec
    - > 480 msec
    - > 500 msec
- Change from Baseline for QT interval, QTc interval, QTcB interval and QTcF will be classified as:
    - >30 msec increase from baseline
    - >60 msec increase from baseline

Results which meet the above criteria will be flagged in the listing.

16.5. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Standing/ Supine Systolic Blood Pressure (mmHg)
- Standing/ Supine Diastolic Blood Pressure (mmHg)
- Standing/ Supine Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (^{o}C)

- Weight (kg)
- BMI (kg/m2)

Summary tables and boxplots of actual and change from baseline results for all quantitative ECG parameters will be presented.

16.5.1. VITAL SIGNS ABNORMAL CRITERIA

Abnormal quantitative vital signs measurements will be identified in accordance with the following predefined abnormal criteria:

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg OR change from baseline ≤ -20 mmHg OR difference between supine and standing (standing – supine) ≤ -20 mmHg	≥ 160 mmHg OR change from baseline ≥ 20 mmHg OR difference between supine and standing (standing – supine) ≥ 20 mmHg
DBP	mmHg	≤ 50 mmHg OR change from ≤ -10 mmHg OR difference between supine and standing (standing – supine) ≤ -10 mmHg	≥ 100 mmHg OR change from baseline ≥ 10 mmHg OR difference between supine and standing (standing – supine) ≥ 10 mmHg
Pulse rate	Bpm	≤ 50 bpm OR change from baseline ≤ -15 bpm OR difference between supine and standing (standing – supine) ≤ -15 mmHg	≥ 120 bpm OR change from baseline ≥ 15 bpm OR difference between supine and standing (standing – supine) ≥ 15 mmHg
Body temperature	˚C	NA	≥ 38.3 ˚C OR change from baseline ≥ 1.1 ˚C
Weight	Kg	percentage change from baseline ≤ -7.0 %	percentage change from baseline ≥ 7.0 %

Results which meet the above criteria will be flagged in the listing.

16.6. SUICIDE IDEATION/SUICIDALITY

The assessment of suicidality is based on changes from baseline in the incidence rates of suicidal behavior and suicidal ideation as measured by the Columbia Suicide Severity Rating (C-SSRS). The post-baseline C-SSRS assesses the occurrence of suicidal behavior and suicidal ideation since the last visit. The occurrence of suicidal behavior and suicidal ideation are determined as follows.

- Suicidal behavior: having answered "yes" to at least one of the following four suicidal behavior items (Items 12, 14, 15, and 16 — actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior, respectively) at any post-baseline evaluation;
- Suicidal ideation: having answered "yes" to at least one of the following two suicidal ideation items (Items 1 and 2—wish to be dead and non-specific active suicidal thoughts, respectively.

The number and percentage of patients who indicate suicidal behavior or suicidal ideation at any post-baseline visit will be summarized.

The number of discrete events of suicidal behavior, possible suicidal behavior, and non-suicidal self-injurious behavior will be captured in the Self-Harm Supplement Form (SHSF). The number of events will also be summarized at each visit. The details of each episode are captured on the Self-Harm Follow-up Form (SHFU). The information captured in the SHFU will be listed.

16.7. PHYSICAL AND NEUROLOGICAL EXAMINATION

Listings will be generated for the physical and neurological examination data.

17. DIGITAL ASSESSMENTS

Vocal and/or behavioral digital assessments will be conducted with HIPAA compliant digital application that have been downloaded one the patient's smartphone with an iOS or Android operating system. The applications will be used for active collection of brief vocal samples for subsequent analysis of acoustic features that are associated with affective states and for passive acquisition of metadata to assess behavioral pattern that are associated with affective or cognitive states. The data will be reported in a separate protocol.

18. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

A summary table of concentrations by visit for patients randomized to BTRX-246040 including number of patients who are below the limit of quantification (BLQ) and will be presented. Pharmacokinetic data collected in this study will be listed for the Pharmacokinetic Analysis Set.

Population PK analysis of the plasma concentrations in this study will be reported separately.

Other exploratory analyses, such as the relationship between BTRX-246040 exposure and efficacy measures or AEs or other safety endpoints, may be undertaken as deemed appropriate.

19. PHARMACOGENETIC ANALYSIS

Information regarding the collection of pharmacogenetic sample will be listed. Any analysis of pharmacogenetic sample will be reported separately.

20. REFERENCES

None

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to IQVIA's Global Biostatistics Standard Output Conventions.

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

- BTRX-246040
- Placebo

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Baseline	BL
Week 1	W1
Week 2	W2
Week 4	W4
Week 6	W6
Week 8	W8
Safety Follow Up	SFU

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- randomized treatment group, first by BTRX-246040 and then placebo,
- center-subject ID,
- date (where applicable),
- For listings where non-randomized patients are included, these will appear in a category after the randomized treatment groups labeled 'Not Randomized'.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE

START DATE	STOP DATE	ACTION
		If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant

START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Missing	Assign as concomitant