Official Title: A Phase 2, Multicenter, Randomized, Double-blind, Active- and Placebo-controlled Trial of the Safety and Efficacy of OPC-64005 in the Treatment of Adult Attention-deficit/Hyperactivity Disorder

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Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational New Drug

OPC-64005

Protocol No. 277-201-00001
IND No. 108,077

A Phase 2, Multicenter, Randomized, Double-blind, Active- and Placebo-controlled Trial of the Safety and Efficacy of OPC-64005 in the Treatment of Adult Attention-deficit/Hyperactivity Disorder

Statistical Analysis Plan

Phase 2
Version Final 1.0
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Date of Amendment 2: 28 August 2017

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1 Introduction

This statistical analysis plan (SAP) documents the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of safety and Pharmacokinetic data of Trial 277-201-00001.

This SAP is prepared based on the protocol version 1, dated February 27, 2017, Amendment 1, dated June 29, 2017 and Amendment 2, dated August 28, 2017.

2 Trial Objectives

Primary objective

The primary objective of this trial is to assess the efficacy of OPC-64005 (20 - 30 mg/day) relative to atomoxetine (40 - 80 mg/day) in adult subjects with attention-deficit/hyperactivity disorder (ADHD).

Other Objectives

- To estimate the difference in effect between OPC-64005 (20 - 30 mg/day) and placebo and its variability in adult subjects with ADHD in order to plan for the next trial.
- To assess the safety and tolerability of OPC-64005 (20 - 30 mg/day) in adult subjects with ADHD compared with both control arms.

3 Trial Design

3.1 Type/Design of Trial

This is a multicenter, randomized, double-blind, active- and placebo-controlled trial designed to evaluate the efficacy and safety of OPC-64005 in the treatment of adult subjects with attention-deficit/hyperactivity disorder.

Approximately 201 adult subjects with ADHD are randomized (1:1:1) to be administered OPC-64005, atomoxetine, or placebo to provide for 150 subjects who complete the trial (50 per arm). The trial includes a Screening Period (≤ 28 days), a 4-day titration period, a 52-day treatment period, a follow-up telephone contact to occur at 3 (± 1) days after the last dose, and a follow-up telephone contact to occur 30 (+ 2) days after the last dose. A schematic of the trial design is provided in Figure 3.1-1.

Screening Period: The Screening Period will last up to 28 days and will begin when informed consent is signed. The purpose of the Screening Period is to assess eligibility criteria at 1 or more visits (as necessary to complete screening assessments) and to wash

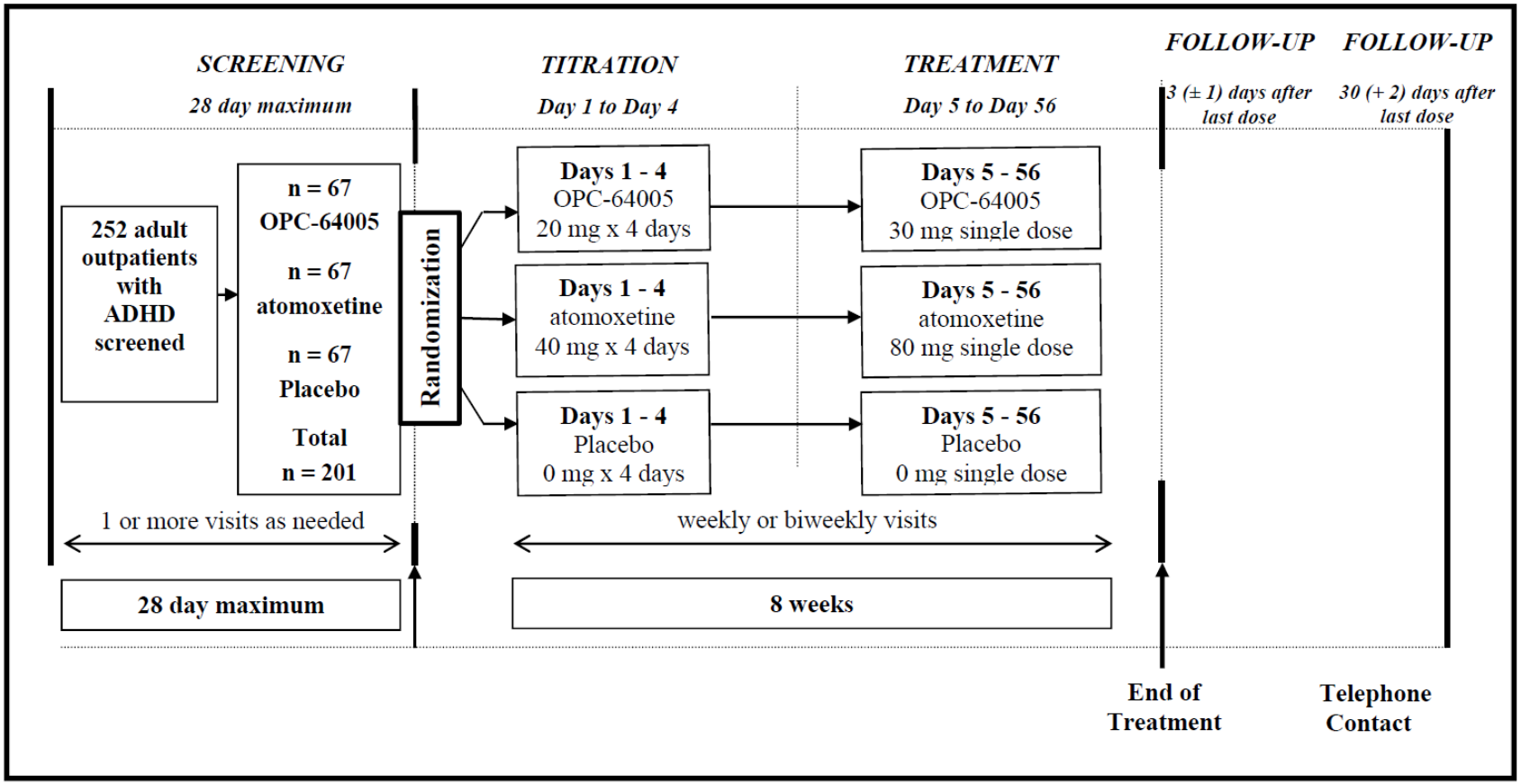
out prohibited concomitant pharmacotherapy, including current ADHD therapies, if applicable.

Titration Period: At the end of the Screening Period, the subjects will be randomized (1:1:1) to receive OPC-64005, atomoxetine, or placebo during the Titration Period (Days 1 - 4).

Treatment Period: During the Treatment Period (Days 5 - 56), subjects who are randomized to the OPC-64005 arm for Titration will continue in the OPC-64005 arm for Treatment. Subjects randomized to the atomoxetine arm for Titration will continue in the atomoxetine arm for Treatment. Subjects randomized to the placebo arm for Titration will continue in the placebo arm for Treatment. During the 8-week Titration/Treatment Period, subjects will have weekly or biweekly visits to the clinical site. On scheduled visit days (Days 7, 14, 21, 28, 42, and 56), dosing should be held until the subject is in the clinic; subjects will be dosed from a newly dispensed blister card.

The total duration of this trial for each subject is estimated to be up to 16 weeks (Screening Period of up to 28 days, 56 days of dosing, a 3 [± 1]-day safety follow-up phone call, and a 30 [+ 2]-day safety follow-up phone call).

Figure 3.1-1 Trial Design Schematic



3.2 Trial Treatments

OPC-64005 is provided as 10-mg tablets, atomoxetine is provided as 40-mg capsules, and placebo is provided as both tablets (matching the OPC-64005 tablets) and as capsules (matching the atomoxetine capsules). Details of the dosing schedule and formulations to be administered are shown in Table 3.2-1.

Table 3.2-1 Dosing Schedule

Trial Days	Time	Dose
1 - 4[a] (Titration Period)	AM dosing	20 mg OPC-64005: two 10-mg tablets and one placebo tablet of OPC-64005 and two atomoxetine placebo capsules QD or 40 mg atomoxetine: one 40-mg capsule and one placebo capsule of atomoxetine and three OPC-64005 placebo tablets QD or Placebo: three OPC-64005 placebo tablets and two atomoxetine placebo capsules QD
5 - 56[a] (Treatment Period)	AM dosing	30 mg OPC-64005[b]: three 10-mg tablets of OPC-64005 and two atomoxetine placebo capsules QD Or 80 mg atomoxetine[c]: two 40-mg capsules of atomoxetine and three OPC-64005 placebo tablets QD or Placebo: three OPC-64005 placebo tablets and two atomoxetine placebo capsules

QD = daily.

[a]Blood samples for PK analyses will be collected predose and at 1 and 3 hours postdose at the Baseline (Day 1) Visit, predose and at 2 hours postdose at the Day 7 (± 1 day) Visit, predose and at 3 hours postdose at the Day 14 (± 1 day) Visit, and predose at the Day 21 (± 1 day) Visit.

[b]May be reduced to 20 mg if the 30 mg dose is not tolerable. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005) during the trial. When a subject is titrated down to a lower dose, they should be maintained on that low dose for a minimum of 4 days before being titrated back up to the higher dose.

[c]May be reduced to 40 mg if the 80 mg dose is not tolerable. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 80 mg for atomoxetine) during the trial. When a subject is titrated down to a lower dose, they should be maintained on that low dose for a minimum of 4 days before being titrated back up to the higher dose.

3.3 Trial Population

Approximately 201 adult male and female subjects with ADHD will be randomized (1:1:1) to be administered OPC-64005, atomoxetine, or placebo (50 completers per arm).

3.4 Trial Visit Window

Trial Day/Week is derived by mapping Trial Day into corresponding time windows as specified in Table 3.4-1. Trial Day is derived as: Trial Day = Date of assessment - Date of IMP dosing + 1. If there are multiple observations within the same time interval, only the last observation within that time interval is used for the summary tables. The time

window mapping rules are applicable to all data that are reported by scheduled day/week unless otherwise stated.

Table 3.4-1 Trial Day and Visit Windows

Trial Day/Week	Target Day	Trial Day Interval for Assessments on Day 1, 7, 14, 21, 28, 42 and 56	Trial Day Interval for Assessments Only on Day 1, 28 and 56
Baseline	1	≤ 1	≤ 1
Day 7	7	2 – 10	
Day 14	14	11 – 17	
Day 21	21	18 – 24	
Day 28	28	25 – 35	2 – 42
Day 42	42	36 – 49	
Day 56	56	50 – 63	43 – 63

4 Sample Size

This trial is exploratory in nature, focusing on estimation of treatment effect and its variability as well as collecting data for future decision making and as a result, sample size was chosen from practical considerations. The trial will enroll approximately 201 subjects in expectation to have about 150 completers (50 per arm) at the end of the trial. It is evaluated via simulations that this sample size will be sufficient for making robust further development decision based on data from OPC-64005 and atomoxetine arms using concept of posterior probability.

5 Statistical Analysis Datasets

Five analysis sets are defined for the efficacy analysis and safety analysis in this trial.

5.1 Randomized Analysis Set (RAS)

The randomized analysis dataset includes all subjects that are randomized in the trial.

5.2 Safety Analysis Set (SAS)

The safety analysis dataset includes all subjects that are randomized and administered at least 1 dose of IMP during the trial. The safety analysis dataset will be used for safety analyses.

5.3 Full Analysis Set (FAS)

The full analysis set includes all randomized subjects who take at least one dose of IMP and have a baseline and at least one post randomization evaluation for the CAARS-O:SV ADHD Symptoms Total Score (18-items).

5.4 Completer Analysis Set (CAS)

The completer analysis set includes all randomized subjects who complete the trial and are also included in FAS.

5.5 Per-protocol Analysis Set (PAS)

The Per-protocol analysis set comprises those subjects in the FAS who complete at least first 2 weeks of double-blind medication and have at least 1 post baseline measurement after 2 weeks without major protocol violations deemed to compromise the assessment of efficacy. These major protocol violations will be any of the followings:

- Exclude subjects who have missed 5 consecutive days of dosing during the treatment before the final assessment or who were not at least 80% compliant with double-blind study medication, based on subject-reported (CRF) compliance or AiCure reported data
- Exclude subjects who reported prohibited concomitant antipsychotic use during the study
- Exclude patients who had a major protocol deviation as represented on the protocol deviation CRF page, which could affect the result of primary efficacy endpoint.

5.6 Pharmacokinetic Analysis Set (PKAS)

The Pharmacokinetic analysis set includes all subjects in the Safety Population who are in the OPC64005 arm and have post-dose drug concentration data available for analysis.

5.7 Primary Estimand

The primary estimand is defined as the following:

- Target population: Adult subjects with ADHD who have met the protocol inclusion/exclusion criteria
- Endpoint: Change from baseline to Week 8 in CAARS-O:SV 18-item ADHD symptoms total score
- Intercurrent events: premature treatment discontinuation
- Measure of intervention effect: difference in endpoint means between OPC64005 and atomoxetine had no subject discontinued.

5.8 Handling of Missing Data

The 18-item CAARS-O:SV is utilized as the primary efficacy assessment of a subject's level of ADHD. The 9-item Inattentive Symptoms Subscale is sum of items 1, 6, 7, 8, 11, 12, 15, 17, and 18) and the 9-item Hyperactive/Impulsive Symptoms Subscale is the sum of items 2, 3, 4, 5, 9, 10, 13, 14, and 16. The 18-item ADHD Symptoms Total Score (sum of the Inattentive Symptoms Subscale and the Hyperactive/Impulsive Symptoms Subscale) is the primary efficacy measure. Each item is rated on a 0 to 3 scale with 0 = Not at all, never; 1 = Just a little, once a while; 2 = Pretty much, often; and 3 = Very much, very frequently. Therefore, possible ADHD Symptoms Total Scores range from 0 to 54.

For Inattentive Symptoms Subscale and Hyperactive/Impulsive Symptoms Subscale, if more than 1 item is missing in either subscale, the subscale is considered as missing. For a single missing item, the mean score of the specific subscale will be used to impute the missing item and then to compute the subscale. The ADHD Symptoms Total Score will be missing if one of the subscales is missing.

Note the same rule for scoring will be used for the Conners' Adult ADHD Rating Scale-Self-Report: Screening Version (CAARS-S:SV).

To assess sensitivity of results due to missing data, the following analyses will be performed: mixed-model repeated measures (MMRM) on the FAS observed case (OC) data, ANCOVA based on the Last Observation Carried Forward (LOCF) data, analysis under the missing not at random assumption: Control-based imputation and Delta-adjusted imputation.

The primary efficacy analysis will be the MMRM analysis with an unstructured variance covariance structure. The OC data set will consist of the actual observations recorded at each visit. The LOCF data set will include data recorded at a scheduled visit or, if no observation is recorded at that visit, data carried forward from the previous scheduled visit. Baseline data will not be carried forward to impute missing values for the LOCF data set.

All safety data will be summarized for observed (non-missing) values only.

6 Primary and Other Outcome Variables

6.1 Primary Efficacy Variables

- Change from baseline to the Day 56 Visit on the investigator-administered Conners' Adult ADHD Rating Scales– Observer: Screening Version (CAARS-O:SV) 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group.

6.2 Other Efficacy Variables

Other efficacy endpoints are:

- Change from baseline to each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET) in the 18-item, investigator-administered CAARS-O:SV score in the OPC-64005 group relative to the atomoxetine and placebo groups
- Change from baseline to the Day 28 and Day 56 Visits for the AISRS with Adult Prompts score in the OPC-64005 group relative to the atomoxetine and placebo groups
- Change from baseline to each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET) in the CGI-S score in the OPC-64005 group relative to the atomoxetine and placebo groups
- CGI-I score at each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET) in the OPC-64005 group relative to the atomoxetine, and placebo groups
- Change from baseline to each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET) in the 18-item Conners' Adult ADHD Rating Scales– Self-Report: Screening Version (CAARS-S:SV) score in the OPC-64005 group relative to the atomoxetine and placebo groups
- Change from baseline to the Day 28 and Day 56 Visits in the Adult ADHD Quality of Life Scale (AAQoL) score in the OPC-64005 group relative to the atomoxetine and placebo groups
- OPC-64005 potential for abuse liability and dependence as assessed by the Drug Effects Questionnaire (DEQ) at baseline and each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET)

7 Summary of Trial Data

7.1 Subject Disposition

The number of subjects who have been randomized, the number of subjects who are treated, and the number of subjects who discontinue from Trial, together with reasons for discontinuation taken from the eCRF status page, will be tabulated by treatment group.

7.2 Demographic and Baseline Characteristics

Demographic characteristics include age, race, ethnicity, body weight, height, BMI and baseline disease characteristics include duration of disease (the time since the first diagnosis of ADHD in years), diagnosis confirmation and identification of comorbidities using the M.I.N.I., and Investigator assessment of previous and current ADHD treatment using the MGH-ATRQ-ADHD. Summary statistics will consist of mean, median, minimum, maximum, and standard deviation (SD) for continuous variables and tabulations of frequency distributions for categorical variables. Summary statistics for demographic and baseline disease characteristics will be provided for randomized sample, by treatment group.

Time since the first diagnosis of ADHD is calculated as (date of screening assessment - date of first diagnosis + 1)/365.25.

7.3 Treatment Compliance

For each subject, compliance of IMP will be derived from the total number of oral tablets/capsules taken by the subject during the trial divided by the expected total number of tablets/capsules taken during the trial.

Compliance of IMP will be summarized by the number (and proportion) of subjects with ≥ 50%, ≥60%, ≥70%, ≥80%, and ≥ 90% compliance, respectively for each treatment group.

Summary of Treatment compliance will be provided based on both CRF data and AiCure captured data, respectively.

7.4 Prior and Concomitant Medications

The proportion of subjects taking concomitant medications will be tabulated by drug classification using the B2 Enhanced version of WHO-DDE B2 (March 2017) for all randomized sample for 3 periods, i.e. prior to, during and after the trial medication.

In addition, listings of concomitant mediations will be provided.

7.5 Protocol Deviations

Protocol deviations data will be summarized by type of deviations (eg, deviations in entry criteria, dosing, randomization, concomitant medication, procedural, etc) by center and treatment group. In addition, a subject listing will be provided describing the deviations for each subject.

8 Efficacy Analyses

8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline to the Day 56 Visit in the CAARS-O:SV 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group.

8.1.1 Primary Efficacy Analysis

Analysis will be performed using FAS. Bayesian posterior probability of true baseline corrected difference at Week 8 between treatment arms (OPC-64005 and atomoxetine) being larger than 4 points on CAARS-O:SV given estimates of means and standard deviations (SD) in the treatment arms will be calculated. Estimates for means and SD will be derived from mixed-effect model as described below. Uninformative prior will be used in calculations.

The change from baseline in CAARS-O:SV will be analyzed using an MMRM methodology with the unstructured variance covariance matrix. The model will include fixed class-effect terms for treatment, trial site, visit week, an interaction term of treatment by visit week, and baseline CAARS-O:SV as a covariate. The need of additional fixed effects and its interactions in the model will be explored.

The SAS code for the Mixed procedure to carry out the above MMRM analysis is as following:

```
proc mixed;
  class treatment visit center subjid;
  model change=treatment center visit treatment*visit baseline / s
ddfm=kenwardroger;
  repeated visit /type=un subject=subjid r rcorr;
  lsmeans treament*visit / pdiff cl alpha=0.05 slice=visit;
run;
```

In case there is a convergence problem with MMRM model with the unstructured variance covariance matrix, the following structures other than unstructured will be used in order 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, and 3) heterogeneous compound symmetry and the first covariance structure converging to the best fit will be used for the primary analysis. If a structured covariance has to be used, the "sandwich" estimator of the standard error of the fixed effects parameters will be used in order to deal with possible model misspecification of the covariance matrix.

8.1.2 Sensitivity Analysis

As a sensitivity analysis, the 95% confidence interval of the difference between two treatment arms (OPC-64005 and atomoxetine) and p-value calculated from the mixed effect model above will be provided.

In addition, the analysis of covariance (ANCOVA) will be used to test the difference in change from baseline of the CAARS-O:SV ADHD Symptoms Total Score (18-items) between the two treatment arms at Week 8, based on the imputed data using Last-Observation-Carried-Forward (LOCF) method. The model will include baseline CAARS-O:SV ADHD Symptoms Total Score (18-items) as a covariate and treatment and study center as main effects.

In order to handle the missing data, the following analyses will be performed too.

8.1.2.1 Sensitivity Analyses for Primary Efficacy Endpoint to Handle Missing Data

Traditionally the dropout mechanisms are divided into three types (Little, 1995): (1) Missing Completely at Random (MCAR), in which the probability of dropout doesn't depend on the observed data and the missing data; (2) Missing at Random (MAR), in which the probability of dropout depends on the observed data, and (3) Missing Not at Random (MNAR), where the probability of dropout depends on the missing data and possibly the observed data.

Most of MNAR methods (Diggle 1994) have treated all observations with dropout as if they fall within the same dropout type. In practice, we would find that different dropout reasons may be related to the outcomes in different ways, for example, detailed dropout reasons for this study are: adverse events (AE), lost to follow-up, protocol deviation, sponsor discontinued study, subject met (protocol specified) withdrawal criteria, subject was withdrawn from participation by the investigator, and subject withdrew consent to participate. Dropout due to an AE may lead to MNAR dropout. Subject withdrew consent may also lead to MNAR dropout. However, it is debatable whether a dropout caused by subjects withdrew consent is MAR or MNAR. Except AE, and subject withdrew consent, all the other dropout reasons may be assumed as either MCAR or MAR dropout.

As sensitivity analyses for missing at random (MAR) assumption, analyses for missing not at random (MNAR) will be carried out. Pattern Mixture Models (PMM) based on Multiple Imputation (MI) with mixed missing data mechanisms will be used to investigate the response profile of dropout subjects by last dropout reason under MNAR mechanism for the following three scenarios:

1) Dropout reasons due to AE as MNAR
2) Dropout reasons due to either AE or subject withdrew consent as MNAR
3) All dropouts as MNAR

Delta Adjustment Imputation Methods

This MNAR sensitivity analysis is to departure from MAR assumption by progressively increasing the delta until conclusion from the primary analysis is overturned. The delta is 0%, 10%, 20%, 30%, ..., 100% of the expected treatment difference of 4 points and/or the observed treatment difference between OPC-64005 group relative to the atomoxetine group from the primary analysis of MMRM model until conclusion of the primary analysis is overturned. When delta=0 the missing data are assumed to be MAR. When delta > 0, the missing data are assumed to be MNAR.

1) Using Monte Carlo Markov Chain (MCMC) methodology from PROC MI to impute the intermittent missing data to a monotone missing pattern;
2) Using a standard MAR-based multiple imputation approach from PROC MI to impute the monotone missing data
3) For subjects in the treated group and with a dropout reason of AE or subject withdrew consent, a delta will be added for all the values after the dropout time.
4) Using MMRM model in the primary analysis to analyze the completed data using PROC MIXED on the multiple imputed data
5) Obtaining the overall results using PROC MIANALYZE.

Placebo Based Imputation Methods

Similar to “Standard” multiple imputations, except parameters for imputation model obtained from only the placebo (control) group. Missing data for both placebo and drug group are imputed based on the imputation model derived from placebo data. If drug improved outcomes prior to dropout, this benefit is carried into subsequent imputed values, but will diminish over time in accordance with the correlation structure.

8.1.3 Per-protocol Analysis

Bayesian analysis and MMRM analysis will be repeated on the Completer analysis dataset and Per-protocol analysis dataset as sensitivity analysis, reporting the posterior probability and p-value, respectively.

8.1.4 Checking of Model Assumptions

Statistical documentation will be provided on checks performed to investigate the underlying assumptions for the primary efficacy analysis. This will include SAS PROC MIXED output for the MMRM model with the unstructured variance covariance matrix. Other structured variance covariance matrix such as heterogeneous toeplitz, heterogeneous autoregressive of order 1, and heterogeneous compound symmetry and their goodness of fit will also be provided. Missing at random (MAR) is a reasonable assumption in ADHD trials based on low dropout rate due to lack of efficacy and adverse events and historical trials in adult ADHD.

For ANCOVA assumptions, it will include the distribution of residuals, assessment of homogeneity of variance, and a plot of residuals to predicted values. To test the model assumption of equality of the treatment regression slopes, a treatment-by-baseline interaction term will be added to the model.

8.1.5 Pooling of small centers

Primary efficacy analysis will be performed on FAS. Small centers will be defined as centers that do not have at least one evaluable subject (evaluable with regard to the primary efficacy variable) in each treatment arm. All small centers will be pooled to form “pseudo centers” for the purpose of analysis according to the following algorithm. Small centers will be ordered from the largest to the smallest based on the number of evaluable subjects (ie, subjects who have baseline and at least one post-baseline value for the primary endpoint). The process will start by pooling the largest of the small centers with the smallest of the small centers until a non-small center is formed. This process will be repeated using the centers left out of the previous pass. In case of ties in center size, the center with the smallest center code will be selected. If any centers are left out at the end of this process, they will be pooled with the smallest pseudo centers, or if no pseudo centers exist, they will be pooled with the smallest non-small center.

8.1.6 Subgroup Analysis

For the primary efficacy variable, subgroup analysis will be performed based on various subgroups as applicable:

(1) adult ADHD treatment history of one or two stimulants

(2) treatment-naive subjects

(3) investigational site

(4) gender

(5) age

(6) race

The change from baseline in CAARS-O:SV by subgroup will be analyzed using an MMRM methodology with the unstructured variance covariance matrix. The model will include fixed class-effect terms for treatment, trial site, visit week, an interaction term of treatment by visit week, and baseline CAARS-O:SV as a covariate if applicable.

8.2 Other Efficacy Endpoints

The other efficacy variables are listed as follows:

1) Change from baseline to each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET) in the 18-item, investigator-administered CAARS-O:SV score in the OPC-64005 group relative to the atomoxetine and placebo groups
2) Change from baseline to the Day 28 and Day 56 Visits for the Adult ADHD Investigator Symptom Rating Scale (AISRS) with Adult Prompts score in the OPC-64005 group relative to the atomoxetine and placebo groups
3) Change from baseline to each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET) in the CGI-S score in the OPC-64005 group relative to the atomoxetine and placebo groups
4) CGI-I score at each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET) in the OPC-64005 group relative to the atomoxetine, and placebo groups
5) Change from baseline to each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET) in the 18-item Conners' Adult ADHD Rating Scales - Self-Report: Screening Version (CAARS-S:SV) score in the OPC-64005 group relative to the atomoxetine and placebo groups
6) Change from baseline to the Day 28 and Day 56 Visits in the Adult ADHD Quality of Life Scale (AAQoL) score in the OPC-64005 group relative to the atomoxetine and placebo groups
7) Change from baseline to each scheduled visit in the Profile of Mood States-Brief Form (POMS) relative to the atomoxetine and placebo groups

For the exploratory efficacy endpoints, the difference in CGI-I between 3 arms will be evaluated by the Cochran–Mantel–Haenszel (CMH) method, stratified by study center, based on LOCF imputed data.

All other efficacy variables will be analyzed in the same way as the primary efficacy endpoint described in Section 8.1, using MMRM model in observed case (OC) data and ANCOVA based on LOCF imputed data.

8.2.1 Technical Computational Details

8.2.1.1 Conners' Adult ADHD Rating Scales-Observer: Screening Version (CAARS-O:SV)

The investigator-administered CAARS-O:SV is designed to measure a cross-section of ADHD-related symptoms and behaviors in adults using observer scales. The investigator-administered CAARS-O:SV consists of 30 items grouped into 3 subscales: Inattentive Symptoms (9 items), Hyperactive/Impulsive Symptoms (9 items), and ADHD Index (12 items). As is frequently done in adult ADHD trials, items will be modified using the Adler adult prompts and only the 18 DSM-5 criteria relevant items (9 Inattentive and 9 Hyperactive/Impulsive) will be administered.

The 9-item Inattentive Symptoms Subscale is sum of items 1, 6, 7, 8, 11, 12, 15, 17, and 18 and the 9-item Hyperactive/Impulsive Symptoms Subscale is the sum of items 2, 3, 4, 5, 9, 10, 13, 14, and 16. The 18-item ADHD Symptoms Total Score (sum of the Inattentive Symptoms Subscale and the Hyperactive/Impulsive Symptoms Subscale) is considered to be the primary efficacy measure. Each item is rated on a 0 to 3 scale with 0 = Not at all, never; 1 = Just a little, once a while; 2 = Pretty much, often; and 3 = Very much, very frequently. Therefore, possible ADHD Symptoms Total Scores CAARS-O:SV range from 0 to 54. The CAARS-O:SV is collected at screening, baseline and all post-baseline visits.

8.2.1.2 Conners' Adult ADHD Rating Scales-Self-Report: Screening Version (CAARS-S:SV)

The CAARS-S:SV includes the same 30 items as the investigator-administered CAARS-O:SV, worded in the first person for the subject’s impressions of their own ADHD behaviors (eg, “I talk too much,” “I am always on the go...”). Administration of the CAARS-S:SV in the current trial will be limited to the 18 DSM-5 criteria relevant items (9 Inattentive Symptoms and 9 Hyperactive/Impulsive Symptoms subscales).

The 9-item Inattentive Symptoms Subscale is sum of items 1, 6, 7, 8, 11, 12, 15, 17, and 18) and the 9-item Hyperactive/Impulsive Symptoms Subscale is the sum of items 2, 3, 4,

5, 9, 10, 13, 14, and 16. The 18-item ADHD Symptoms Total Score is the sum of the Inattentive Symptoms Subscale and the Hyperactive/Impulsive Symptoms Subscale. Each item is rated on a 0 to 3 scale with 0 = Not at all, never; 1 = Just a little, once a while; 2 = Pretty much, often; and 3 = Very much, very frequently. Therefore, possible ADHD Symptoms Total Scores CAARS-S:SV range from 0 to 54. The CAARS-S:SV is collected at baseline and all post-baseline visits.

Adult ADHD Investigator Symptom Rating Scale (AISRS with Adult Prompts)

The AISRS was published in 2010 by Drs. Lenard Adler, Thomas Spencer, and Joseph Biederman of New York University and Massachusetts General Hospital. The AISRS consists of the 18 DSM ADHD symptoms with adult-relevant wording. It has been validated for use as a primary efficacy scale in adult ADHD treatment trials. The 9-item Inattentive Symptoms Subscale is sum of items 1, 3, 5, 7, 9, 11, 13, 15, and 17 and the

9-item Hyperactive/Impulsive Symptoms Subscale is the sum of items 2, 4, 6, 8, 10, 12, 14, 16 and 18. Each item is scored as follows: 0 (none), 1 (mild), 2 (moderate), 3 (severe); the maximum total score for the scale is 54 points, with 27 points for each subscale. The AISRS total score is the sum of the inattentive and hyperactive-impulsive subscales. For Inattentive Subscale and Hyperactive/Impulsive Subscale, if more than 1 item is missing in either subscale, the subscale is considered as missing. For a single missing item, the mean score of the specific subscale will be used to impute the missing item and then to compute the subscale. The AISRS Total Score will be missing if one of the subscales is missing.

8.2.1.3 Clinical Global Impression (CGI)

CGI consists of two scales: CGI Severity (CGI-S), and CGI Improvement (CGI-I). CGI-S items are: 0 = not assessed, 1 = normal, not at all ill, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = among the most extremely ill subjects. The score 0 (= not assessed) will be set to missing. The CGI-S is therefore a 7-point scale from 1 through 7. CGI-S is assessed at screening, baseline and each subsequent visit from Day 7 through Day 56.

CGI-I items are: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse. The score of 0 (= not assessed) will be set to missing. The CGI-I is therefore a 7-point scale from 1 through 7. CGI-I is assessed at each postbaseline visit and improvement is judged with respect to the patient's condition at baseline.

8.2.1.4 Adult ADHD Quality of Life Scale (AAQoL)

The AAQoL is a validated, 29-item instrument for measuring the impact of ADHD symptoms on quality of life. The scale assesses 4 distinct functional domains: life productivity, psychological health, life outlook, and relationships. Scores for individual items range from 1 ("never/not at all") to 5 ("extremely/very often").

The AAQoL yields a total score (based on all 29 items) and four subscale scores:

- Life Productivity (11 items)
    1. Complete projects or tasks (either at work or at home)
    2. Get started with tasks you don't find interesting
    3. Balance multiple projects
    4. Get things done on time
    5. Keep track of important items (such as keys, wallet)
    6. Keep the house/apartment clean or uncluttered
    7. Manage your finances (such as cashing checks balancing your checkbook, paying bills on time)
    8. Remember important things
    9. Get your shopping done (such as for food, clothes or household items)
    10. Pay attention when interacting with others
    11. Getting things done requires too much effort
- Psychological Health (6 items)
    1. Anxious
    2. Depressed
    3. Feeling fatigued
    4. Fluctuations (ups and downs) in your emotions
    5. You have overreacted in difficult or stressful situations
    6. Overwhelmed
- Life Outlook (7 items)
    1. Your energy is well spent (has positive results)
    2. Able to enjoy time spent with others

3. You can successfully manage your life
4. As productive as you would like to be
5. Good about yourself
6. People enjoy spending time with you
7. Your intimate relationship is going well emotionally

- Relationships (five items)
  1. You annoyed people
  2. People are frustrated with you
  3. Tension in relationships
  4. Not having quality time to spend with others
  5. You have not been able to meet others' expectations of you (either at home or at work).

Total and subscale scores are computed by (1) reversing scores for all items except the seven items in the Life Outlook subscale; (2) transforming all item scores to a 0-100 point scale (1=0; 2=25; 3=50; 4=75; 5=100); and (3) summing item scores and dividing by the item count to generate subscale and total scores. The scoring algorithm indicates that the total score can be computed with up to three missing items, and each subscale score can be computed with up to one missing item.

8.2.1.5 POMS

The POMS is a 30-item self-report scale that generates the following subscales: Tension or Anxiety, Anger - Hostility, Vigor - Activity, Fatigue - Inertia, Depression - Dejection, and Confusion - Bewilderment. These subscales yield an overall total mood score. It will be used in the trial as an exploratory measure to assess potential changes in symptoms often associated with ADHD. The time period of interest for this trial is "during the past week". The subscale will be missing if response to any item contributed to subscale is missing. The total score will be missing if one of subscales is missing.

9 Safety Analyses

Safety analyses will be conducted based upon the safety dataset defined in Section 5.3. Safety variables to be analyzed include AEs, clinical laboratory tests, physical examinations, vital signs, ECGs, suicidality via the C-SSRS. For all safety variables,

baseline is defined as the last evaluable data prior to administration of the IMP on Day 1. Safety data will be summarized using descriptive statistics (where applicable) by treatment group.

9.1 Extent of Exposure

Extent of exposure to Trial medication will be summarized using descriptive statistics (n, percentage).

9.2 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities preferred term. The incidence of the following events will be summarized by treatment group:

- Treatment-emergent AEs (TEAEs) by severity
- Potentially drug-related TEAEs
- TEAEs with an outcome of death
- Serious TEAEs
- Discontinuations due to TEAEs

Adverse event data will also be presented in listings. In addition, the skin adverse event of special interest (AESI) will be summarized and listed too.

9.3 Clinical Laboratory Data

Clinical laboratory tests include serum chemistry, hematology and urinalyses tests. The potentially clinically significant laboratory test abnormalities will be listed by subject and by test. The incidences of potentially clinically significant laboratory tests abnormalities will be tabulated by treatment group. Summary statistics for changes from baseline in the clinical laboratory measurements will be provided. Shift tables will be produced assessing status (low-normal-high) changes from baseline using the laboratory reference range provided by the site lab. Criteria for Identifying Laboratory Values of Potential Clinical Relevance are provided in Appendix 1.

9.4 Vital Sign Data

The vital signs parameters include body temperature, heart rate, systolic and diastolic blood pressure. In addition, body weight will also be measured. The potentially clinically significant vital sign abnormalities will be listed by subject. Incidences of potentially clinical significant vital signs abnormalities will be tabulated by treatment group.

Incidences of weight gain or loss greater than 7% relative to baseline and incidences of Orthostatic Hypotension will also be provided. Changes from baseline of vital sign parameters as well as their original observations will be summarized using descriptive statistics (i.e., mean, standard deviation, minimum and maximum). Criteria for Identifying Vital Signs of Potential Clinical Relevance are provided in Appendix 2.

9.5 Physical Examination Data

Physical examination data will be presented in a listing.

9.6 Electrocardiogram Data

The potentially clinically significant ECG abnormalities will be listed by subject. The incidences of abnormal ECGs of potential clinical significance will be tabulated by treatment. Descriptive statistics of change from baseline in heart rate and ECG intervals of PR, QRS, QT, QTcB, QTcF, will be provided by visit.

The following QT corrections will be used:

1) QTcB is the corrected (for heart rate) QT interval by the Bazett formula: $QTcB=QT/(RR)^{0.5}$, and
2) QTcF is the corrected (for heart rate) QT interval by the Fridericia formula: $QTcB=QT/(RR)^{0.33}$

For ECG parameters, the diagnoses that involve quantitative measurements include tachycardia, bradycardia, sinus tachycardia, sinus bradycardia, first-degree atrioventricular block, and other intraventricular conductions block.

Criteria for Identifying ECG Measurements of Potential Clinical Relevance are provided in Appendix 3.

9.7 Other Safety Data

9.7.1 Columbia-Suicide Severity Rating Scale

Suicidality will be assessed based on C-SSRS data. Data for the Baseline Version of the C-SSRS and Since Last Visit Version of the C-SSRS data will be summarized descriptively and presented in a listing.

The Baseline/Screening version of C-SSRS is administered at screening and the Since Last Visit version is administered at Baseline before dosing and all post-baseline visits. Baseline and post-baseline C-SSRS data will be summarized to report the incidence of:

- Suicidality

- Suicidal behavior (and its 4 types)
- Suicidal ideation (and its 5 types)

Suicidality is defined as reporting at least one occurrence of any suicidal behavior or suicidal ideation. Suicidal behavior is defined as reporting any type of suicidal behaviors (actual attempt, interrupted attempt, aborted attempt and preparatory acts or behavior). Suicidal ideation is defined as reporting any type of suicidal ideation. In addition to these 3 incidences, C-SSRS data collected post-baseline will also be summarized to report the incidence of:

- Completed suicide
- Emergence of suicidal ideation
- Emergence of serious suicidal ideation
- Worsening of suicidal ideation
- Emergence of suicidal behavior

Any completed suicide is considered as complete suicidality. Emergence of suicidal ideation is defined as having no suicidal ideation at screening and baseline and reporting any type of ideation during treatment. Emergence of serious suicidal ideation is defined as having no suicidal ideation at screening and baseline and reporting any type of suicidal ideation with ideation severity rating of 4 or 5 during treatment. Worsening of suicidal ideation is defined as occurring when the most severe suicidal ideation rating during treatment is more severe than its worst rating at screening and baseline. Emergence of suicidal behavior is defined as having no suicidal behavior at screening and baseline and reporting any type of suicidal behavior during treatment.

Descriptive statistics for changes from baseline as well as their original observations in suicidal ideation intensity total score for the most severe ideation will be summarized at scheduled visits (including last visit). The suicidal ideation intensity total score is the sum of the intensity scores of 5 items (frequency, duration, controllability, deterrents and reasons for ideation). The intensity score of each item ranges from 1 (least severe) to 5 (most severe) which leads to the range of the total score from 0 to 25. A missing intensity score of any item will result in missing suicidal ideation intensity total score. If no suicidal ideation is reported, a score of 0 will be given to the intensity scale.

9.7.2 Drug Effects Questionnaire (DEQ)

The DEQ will be used to assess the potential for abuse of the IMP. The DEQ is a 5-item questionnaire completed by the subject that includes the following questions:

1. Do you FEEL a drug effect right now?
2. Are you HIGH right now?
3. Do you DISLIKE any of the effects you are feeling right now?
4. Do you LIKE any of the effects you are feeling right now?
5. Would you like MORE of the drug you took, right now?

The number (proportion) of subjects with positive response to the 5 questions will be provided by treatment group for all applicable visits.

9.7.3 Drug Induced Liver Injury (DILI)

Total bilirubin level should be checked for any subject with increased ALT or AST levels ≥ three times the upper normal limits (or baseline, if baseline > ULN).

- Reporting all DILI as SAE to the FDA based on Hy's Law:
    - AST or ALT $\geq$ 3 x normal and
    - T_Bili $\geq$ 2 x normal

A separate incidence table will be provided for DILI cases, and the corresponding listing will be provided.

10 Pharmacokinetics Analysis

Plasma concentrations of OPC-64005 will be summarized by time points using descriptive statistics. A separate population or pharmacokinetic/pharmacodynamic modeling may be performed using the data from this trial and other trials. In addition, the individual, mean and median plots of plasma concentrations will be provided too.

11 Interim Analysis

An interim analysis will be conducted after 90 subjects complete 8 weeks of treatment, around 30 completers in each arm. This analysis will be performed for purpose of planning future studies and will not change the study conduct (ie, regardless of the interim analysis outcome, this study will run to completion). Analysis methods will be the same as ones for the final analysis. Analysis will be performed by the Otsuka Pharmaceutical Development and Commercialization, Inc. (OPDC) Internal Independent Biostatistician who is not a member of the study team to minimize/avoid bias. Details of the interim analysis will be included in Interim Analysis Plan.

12 Changes in the Planned Analyses

None.

Appendix 1 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry[a]	
AST (SGOT)	≥ 3 x upper limit of normal (ULN)
ALT (SGPT)	≥ 3 x ULN
Alkaline phosphatase	≥ 3 x ULN
LDH	≥ 3 x ULN
BUN	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Uric Acid	
Men	≥ 10.5 mg/dL
Women	≥ 8.5 mg/dL
Bilirubin (total)	≥ 2.0 mg/dL
CPK	≥ 3 x ULN
Prolactin	> ULN
Hematology[a]	
Hematocrit	
Men	≤ 37 % and decrease of ≥ 3 percentage points from Baseline
Women	≤ 32 % and decrease of ≥ 3 percentage points from Baseline
Hemoglobin	
Men	≤ 11.5 g/dL
Women	≤ 9.5 g/dL
White blood count	≤ 2,800 mm3 or ≥ 16,000 mm3
Eosinophils	≥ 10%
Neutrophils	≤ 15%
Platelet count	≤ 75,000/ mm3 or ≥ 700,000/ mm3
Urinalysis[a]	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Casts	Increase of ≥ 2 units
Additional Criteria	
Chloride	≤ 90 mEq/L or ≥ 118 mEq/L
Potassium	≤ 2.5 mEq/L or ≥ 6.5 mEq/L
Sodium	≤ 126 mEq/L or ≥ 156 mEq/L
Calcium	≤ 8.2 mg/dL or ≥ 12 mg/dL
Glucose	
Fasting	≥ 115 mg/dL
Non-Fasting	≥ 200 mg/dL
Total Cholesterol, Fasting	≥ 240 mg/dL
LDL Cholesterol, Fasting	≥ 160 mg/dL
HDL Cholesterol, Fasting	≤ 30 mg/dL
Triglycerides, Fasting	
Men	≥ 160 mg/dL
Women	≥ 120 mg/dL

[a] As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

Appendix 2 Criteria for Identifying Vital Signs of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart Rate[b]	> 120 bpm < 50 bpm	≥ 15 bpm increase ≥ 15 bpm decrease
Systolic Blood Pressure[b]	> 180 mmHg < 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
Diastolic Blood Pressure[b]	> 105 mmHg < 50 mmHg	≥ 15 mmHg increase ≥ 15 mmHg decrease
Orthostatic Hypotension	≥ 20 mmHg decrease in systolic blood pressure and a ≥ 25 bpm increase in heart rate from supine to sitting/standing	Not Applicable (baseline status not considered)
Weight	-	≥ 7% increase ≥ 7% decrease
Temperature (°C)	>=37.8	Increase >= 1.1 °C

[a] In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

[b] As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

Appendix 3 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rate		
Tachycardia	≥ 120 bpm	increase of ≥ 15 bpm
Bradycardia	≤ 50 bpm	decrease of ≥ 15 bpm
Rhythm		
Sinus tachycardia[b]	≥ 120 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 50 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	all	not present → present
Ventricular premature beat	all	not present → present
Supraventricular tachycardia	all	not present → present
Ventricular tachycardia	all	not present → present
Atrial fibrillation	all	not present → present
Atrial flutter	all	not present → present
Conduction		
1° atrioventricular block	PR ≥ 0.20 second	increase of ≥ 0.05 second
2° atrioventricular block	all	not present → present
3° atrioventricular block	all	not present → present
Left bundle-branch block	all	not present → present
Right bundle-branch block	all	not present → present
Pre-excitation syndrome	all	not present → present
Other intraventricular conduction block[d]	QRS ≥ 0.12 second	increase of ≥ 0.02 second
Infarction		
Acute or subacute	all	not present → present
Old	all	not present → present ≥ 12 weeks post study entry
ST/TMorphological		
Myocardial Ischemia	all	not present → present
Symmetrical T-wave inversion	all	not present → present
Increase in QTc	QTc > 450 msec (males) or QTc > 470 msec (females) and increase from baseline >=30 msec	

[a] In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.
[b] No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.
[c] No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.
[d] No current diagnosis of left bundle branch block or right bundle branch block.

Appendix 4 Proposed Summary Tables and Data Listings (Final Analysis)

Summary Tables:

CT-1.1 Subject Disposition
CT-1.2 Enrollment by Country (Randomized Sample)
CT-1.3 Enrollment By Country By Age Group (Randomized Sample)
CT-2.1 Reasons for Discontinuation (Randomized Sample)
CT-3.1 Demographic Characteristics (Randomized Sample)
CT-3.2 Baseline Disease Characteristics (Randomized Sample)
CT-3.3 Psychiatric History Randomized Sample
CT-3.4.1 Mini International Neuropsychiatric Interview (M.I.N.I.) for Psychotic Disorders Primary Diagnosis (Randomized Sample)
CT-3.4.2 Mini International Neuropsychiatric Interview (M.I.N.I.) for Psychotic Disorders Meets Criteria (Randomized Sample)
CT-3.5.1 Summary of MGH Treatment Response Questionnaire (ATRQ) x ADHD For Stimulants (Randomized Sample)
CT-3.5.2 Summary of MGH Treatment Response Questionnaire (ATRQ) x ADHD For Non-Stimulants (Randomized Sample)
CT-4.1 Concomitant Medications: Medications Taken Prior to Start of Study Therapy (Safety Sample)
CT-4.2 Concomitant Medications: Medications Taken During Study Therapy Period (Safety Sample)
CT-4.3 Concomitant Medications: Medications Taken Post Study Therapy Period (Safety Sample)
CT-5.1.1 Summary of Efficacy Results at Week 8 (FAS Sample)
CT-5.1.2 Summary of Efficacy Results at Week 8 (Completer Sample)
CT-5.1.3 Summary of Efficacy Results at Week 8 on Subjects Having At Least 80% of Compliance (Completer Sample)
CT-5.1.4 Summary of Efficacy Results at Week 8 (Per-protocol Sample)
CT-5.2.1.1 Summary of Mean Change from Baseline to Week 8 by Study Week in CAARS-O:SV ADHD Symptoms Total Score - Bayesian Approach (Full Analysis Sample)
CT-5.2.1.2 Summary of Mean Change from Baseline to Week 8 by Study Week in CAARS-O:SV ADHD Symptoms Total Score - Bayesian Approach (Completer Sample)
CT-5.2.1.3 Summary of Mean Change from Baseline to Week 8 by Study Week in CAARS-O:SV ADHD Symptoms Total Score on Subjects Having At Least 80% of Compliance - Bayesian Approach (Completer Sample)
CT-5.2.1.4 Summary of Mean Change from Baseline to Week 8 by Study Week in CAARS-O:SV ADHD Symptoms Total Score - Bayesian Approach (Per-protocol Sample)
CT-5.2.2.1. Summary of Mean Change from Baseline to Week 8 by Study Week in CAARS-O:SV ADHD Symptoms Total Score - MMRM, UN (Full Analysis Sample)
CT-5.2.2.2. Summary of Mean Change from Baseline to Week 8 by Study Week in CAARS-O:SV ADHD Symptoms Total Score - MMRM, UN (Completer Sample)
CT-5.2.2.3. Summary of Mean Change from Baseline to Week 8 by Study Week in CAARS-O:SV ADHD Symptoms Total Score on Subjects Having At Least 80% of Compliance - MMRM, UN (Completer Sample)
CT-5.2.2.4. Summary of Mean Change from Baseline to Week 8 by Study Week in CAARS-O:SV ADHD Symptoms Total Score - MMRM, UN (Per-protocol Sample)
CT-5.2.3.1 Summary of Mean Change from Baseline to Week 8 by Study Week in CAARS-O:SV ADHD Symptoms Total Score - MMRM, TOEPH (Full Analysis Sample)
CT-5.2.3.2 Summary of Mean Change from Baseline to Week 8 by Study Week in CAARS-O:SV ADHD Symptoms Total Score - MMRM, TOEPH (Per-protocol Sample)
CT-5.2.4.1 Summary of Mean Change from Baseline to Week 8 by Study Week in CAARS-O:SV ADHD Symptoms Total Score - LOCF (Full Analysis Sample)

CT-10.5.2 Mean Change from Baseline in Clinical Laboratory Test Results - Hematology (Safety Sample)
CT-10.5.3 Mean Change from Baseline in Clinical Laboratory Test Results - Urinalysis (Safety Sample)
CT-10.5.4 Mean Change from Baseline in Clinical Laboratory Test Results - Other Laboratory Tests (Safety Sample)
CT-10.6.1 Shift Tables of Clinical Laboratory Test Results: Serum Chemistry (Safety Sample)
CT-10.6.2 Shift Tables of Clinical Laboratory Test Results: Hematology (Safety Sample)
CT-10.6.3 Shift Tables of Clinical Laboratory Test Results: Urinalysis (Safety Sample)
CT-10.7 Incidence of Laboratory Test Values with Potential Clinical Relevance (Safety Sample)
CT-11.1 Listing of Potentially Clinically Significant Abnormalities in Vital Signs (Safety Sample)
CT-11.2 Criteria for Potentially Clinically Relevant Abnormalities in Vital Signs
CT-11.3 Mean Change from Baseline in Vital Signs (Safety Sample)
CT-11.4 Incidence of Potentially Clinically Significant Abnormalities in Vital Signs (Safety Sample)
CT-12.1 Listing of Potentially Clinically Significant Abnormalities in ECG Evaluation (Safety Sample)
CT-12.2 Criteria for Potentially Clinically Significant Abnormalities in ECG Evaluations
CT-12.3 ECG Diagnosis Mapping for Potentially Clinically Significant Electrocardiogram Abnormalities
CT-12.4 Mean Change from Baseline in Electrocardiogram Results (Safety Sample)
CT-12.5 Incidence of Potentially Clinically Relevant Changes in ECG Evaluations (Safety Sample)
CT-13.1 Columbia-Suicide Severity Rating Scale (C-SSRS), Suicidality (Safety Sample)
CT-13.2 Columbia-Suicide Severity Rating Scale (C-SSRS), Suicidal Behavior by Type (Safety Sample)
CT-13.3 Columbia-Suicide Severity Rating Scale (C-SSRS), Suicidal Ideation by Type (Safety Sample)
CT-13.4 Columbia-Suicide Severity Rating Scale (C-SSRS), Treatment Emergent Suicidal Behavior and Ideation (Safety Sample)
CT-14.1 Summary of Drug Effects Questionnaire (DEQ) (Safety Sample)
CT-15.1 Incidence of Laboratory Test Values with Hy's Law (Safety Sample)

Data Listings:

DREAS-1 Discontinued Subjects and Reasons for Discontinuation
DREAS-2 Adverse Events for Subjects Who Discontinued from Trial due to Withdrew Consent
PDEV-1 Summary of Protocol Deviations by Center and Type of Deviation
PDEV-2 Protocol Deviations by Subject
PDEV-3 Protocol Deviation Criteria
DEMOG-1 Demographic Characteristics
SMED-1 Trial Medication Compliance for Randomized Subjects
EFF-1 Change from Baseline Over Time in Efficacy Endpoints
AE-1 Listing of Adverse Events
LAB-1 Laboratory Test Results: Serum Chemistry
LAB-2 Laboratory Test Results: Hematology
LAB-3 Laboratory Test Results: Urinalysis
LAB-4 Laboratory Test Results: Other Laboratory Tests
LAB-5 Laboratory Test Results: Urine Drug Screen
PDATA-1 Entrance Criteria
PDATA-2 Subject Randomization List
PDATA-3 Study Completion Status and Reasons for Discontinuation
PDATA-4 Demographic Characteristics
PDATA-5 Psychiatric History
PDATA-6.1 Concomitant Medications Taken Prior to Start of Study Therapy
PDATA-6.2 Concomitant Medications Taken During Study Therapy
PDATA-6.3 Concomitant Medications Taken Post Study Therapy
PDATA-7 Study Medication
PDATA-8 Medical History

PDATA-9 Physical Examination
PDATA-10 Adverse Events
PDATA-11 Vital Signs
PDATA-12 Electrocardiogram Results
PDATA-13 Drug Effects Questionnaire
PDATA-14.1 Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit Suicidal Ideation
PDATA-14.2 Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit Suicidal Behavior
PDATA-14.3 Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit Intensity of Ideation
PDATA-14.4 Columbia-Suicide Severity Rating Scale (C-SSRS) Screening/Baseline Suicidal Ideation
PDATA-14.5 Columbia-Suicide Severity Rating Scale (C-SSRS) Screening/Baseline Suicidal Behavior
PDATA-14.6 Columbia-Suicide Severity Rating Scale (C-SSRS) Screening/Baseline Intensity of Ideation
PDATA-15 PK Blood Draw Time
PDATA-16 Protocol Deviation
PDATA-17 Safety Follow-up Results
PDATA-18 Screening Failures
PDATA-19 Mini International Neuropsychiatric Interview (M.I.N.I.)
PDATA-20 MGH Treatment Response Questionnaire ATRQ