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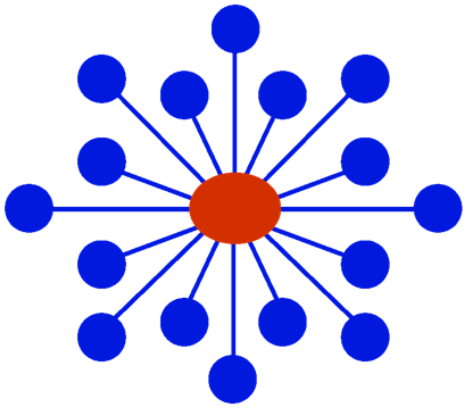
STATISTICAL ANALYSIS PLAN for

Title: NIDA CTN-0068 Accelerated Development of Additive Pharmacotherapy Treatment (ADAPT-2) for Methamphetamine Use Disorder

Version 3.0

Date: September 13, 2019



Statistical Analysis Plan
for
NIDA CTN-0068 Protocol

Accelerated Development of Additive Pharmacotherapy Treatment (ADAPT-2) for Methamphetamine Use Disorder

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Version 3.0

September 13, 2019

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NIDA CTN Data and Statistics Center

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AMC	Active Medication Combination
ATC	Anatomical Therapeutic Chemical
CCTN	Center for Clinical Trials Network
CHRT	Concise Health Risk Tracking
DSC	Data and Statistics Center
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EOM	End of Medication form
FSR	Final Study Report
IN2	Injection Administration 2 form
ITT	Intent-to-Treat
LFT	Liver Function Test
NIDA	National Institute on Drug Abuse
NNT	Number Needed to Treat
ODL	Oral Study Medication Dosing Log form
PHQ-9	Patient Health Questionnaire-9
PLB	Placebo
QOL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SPCD	Sequential Parallel Comparison Design
STC	Study Completion form
TEA	Treatment Effectiveness Assessment
TES	Treatment Effectiveness Score
TLFB	TimeLine Followback
UDS	Urine Drug Screen
VAS	Visual Analog Craving Scale
WHO	World Health Organization
XR-NTX	Extended-Release Naltrexone (as Vivitrol®)

1.0 SUMMARY OF STUDY DESIGN AND PROCESS

1.1 Study Objective

The primary objective of this study is to evaluate the efficacy of extended-release naltrexone plus bupropion as a combination pharmacotherapy for methamphetamine use disorder. Secondary objectives include assessing the safety of naltrexone plus bupropion and determining the efficacy of the combination pharmacotherapy on other substance use outcomes, on depression symptom scores, and on quality of life ratings.

1.2 Study Design and Procedures

1.2.1 Study Design

This is a double-blind, placebo-controlled, adaptive randomized clinical trial in which 400 individuals with moderate or severe methamphetamine use disorder will be randomly assigned to either 1) active medication combination (AMC) arm in which injections of extended-release naltrexone (XR-NTX; as Vivitrol®) plus once daily oral extended-release bupropion tablets or the 2) matching Placebo (PLB) arm in which injections of placebo and once daily oral placebo tablets will be provided during a 12 week medication phase.

This protocol will utilize a two-stage sequential parallel comparison design (SPCD), originally proposed by Fava et al. (2003), and later revised by Chen et al. (2011). Participants will be randomized to Placebo:AMC in the ratio of ***0.74:0.26*** in Stage 1 of the study and only Stage 1 placebo non-responders will be re-randomized at the beginning of Stage 2 in a 1:1 ratio. The 12-week medication phase is divided into two stages of approximately equal treatment duration.

The original designed sample size for this study was 370. After the pre-specified sample size re-estimation, the Center for Clinical Trials Network (CCTN) approved the increase of the sample size to 400 participants (See Section 8.4.1.1).

1.2.2 Study Procedures

Participants randomized to the AMC arm will receive injections of extended-release naltrexone (Vivitrol®) plus 450 mg of once-daily oral extended-release bupropion tablets while participants randomized to the Placebo arm will receive placebo injections plus once-daily oral placebo tablets. Injectable study medications will be administered every three weeks (Weeks 1, 4, 7, and 10). Take-home oral study medication will be dispensed once weekly for daily dosing. Once weekly medical management sessions with the study medical clinician will be provided. Medication adherence procedures will include smartphone app-confirmation of daily oral study medication dosing using AiCure. Participants will be asked to attend clinic twice weekly for observed oral study medication dosing, collection of urine drug screening samples, and self-report assessments. Compensation will be provided for visit attendance and dosing via AiCure.

Screening/baseline assessments include safety and medical measures including a medical and psychiatric history, a physical examination, clinical lab tests (blood chemistry, hematology, and urinalysis), 12-lead electrocardiogram, vital signs, and pregnancy tests (for females). Screening/baseline assessments also include psychological and drug use measures. Methamphetamine use outcome assessments include Urine Drug Screens (UDS), self-reported use via the Timeline Followback (TLFB), and Visual Analog Scale (VAS) craving scores. Other outcome assessments include UDS and TLFB (i.e., alcohol, tobacco, and/or illicit drugs), depression (Patient Health Questionnaire-9), quality of life (QOL), functioning (Treatment Effectiveness Assessment), and clinic attendance. Safety measures include monitoring vital signs, adverse events (AEs), concomitant medications, clinical lab results, and assessments of suicidality. Oral study medication adherence will be assessed by self-report, quantitative blood

levels of bupropion and its primary metabolite, and smartphone device-based dosing confirmation procedures. A blood sample for genetic analysis will be collected from participants who consent to this procedure and the deidentified sample will be sent to a cell and DNA repository.

At the end of the 12-week medication phase, participants will complete a follow-up phase, including an oral medication taper. Post-medication phase follow-up visits will occur during Weeks 13 and 16. Participants may be withdrawn from study medication for safety reasons due to the discretion of medical clinician. The participant will terminate study medication if there is an increase in liver function tests or a decrease in platelet test results. Refer to Protocol Section 7.2.5 for further information.

1.2.3 Randomization

Eligible participants will be randomized in Stage 1 of the medication phase in a ***0.74:0.26*** fashion following the SPCD, which is approximately 296:104 participants to the Placebo and AMC treatment arms, respectively (total target N = 400), stratifying by site. Participants who have not been withdrawn from study medication by medical staff will remain eligible to participate in Stage 2. Eligible Stage 1 participants assigned to Placebo and who did not meet the specified definition of responder (i.e., Placebo non-responders) and who attend a visit in the re-randomization window will be re-randomized in a 1:1 ratio to either the Placebo or AMC arm in Stage 2, stratifying by site. All other eligible Stage 1 participants, including participants who did not attend a visit during the re-randomization window, Placebo responders, and AMC participants, will remain in the same treatment arm during Stage 2 as was assigned in Stage 1.

The window for re-randomization opens on Week 7 Day 1 and closes on Week 8 Day 2. If a participant does not attend a visit on or between Week 7 Day 1 and Week 8 Day 2, the participant will not be re-randomized in Stage 2 and will continue receiving the treatment assigned in Stage 1. Re-randomization at Stage 2 helps ensure treatment balance in the two treatment groups within the Stage 2 population.

1.3 Inclusion and Exclusion Criteria

1.3.1 Inclusion Criteria

1. 18 to 65 years of age.
2. Interested in reducing or stopping methamphetamine use.
3. Able to speak English sufficiently to understand the study procedures and provide written informed consent to participate in the study.
4. Meet DSM-5 criteria for moderate or severe methamphetamine use disorder (4 or more criteria.)
5. Self-report methamphetamine use on 18 or more days in the 30-day period prior to consent on TLFB.
6. Provide at least 2 urine samples positive for methamphetamine out of a possible 3 tests to occur within a 10-day period during which clinic visits occur with at least 2 days between visits.
7. If female, agree to use acceptable birth control methods and have periodic urine pregnancy testing done during participation in the study unless documentation of hysterectomy provided.
8. Meet subjective and objective measures of being opioid-free prior to naltrexone induction per study medical clinician’s determination.
9. Willing to comply with all study procedures and medication instructions.

10. Agree to use a smartphone app (downloaded for free to own device or on a study provided smartphone device) to take daily videos of medication dosing.

1.3.2 Exclusion Criteria

1. Have an acute medical or psychiatric disorder that would, in the judgment of the study medical clinician, make participation difficult or unsafe.
2. Have suicidal or homicidal ideation that requires immediate attention.
3. Have a history of epilepsy, seizure disorder, or head trauma with neurological sequelae (e.g., loss of consciousness that required hospitalization); current anorexia nervosa or bulimia; or any other conditions that increase seizure risk in the opinion of the study medical clinician.
4. Have evidence of second- or third-degree heart block, atrial fibrillation, atrial flutter, prolongation of the QTc, or any other finding on the screening electrocardiogram (ECG) that, in the opinion of the study medical clinician, would preclude safe participation in the study.
5. Have Stage 2 hypertension as determined by the study medical clinician (e.g., greater than or equal to 160/100 in 2 out of 3 readings during screening.)
6. Have any elevated bilirubin test value per laboratory criteria OR any other liver function test (LFT) value > 5 times the upper limit of normal per laboratory criteria.
7. Have a platelet count < 100 x 10^3/μL.
8. Have a body habitus that precludes gluteal intramuscular injection of XR-NTX in accordance with the administration equipment (needle) and procedures.
9. Have a known allergy or sensitivity to bupropion, naloxone, naltrexone, PLG (polyactide-co-glycolide), carboxymethylcellulose or any other component of the XR-NTX diluents.
10. Have been in a prior study of pharmacological or behavioral treatment for methamphetamine use disorder within 6 months of study consent.
11. Have taken an investigational drug in another study within 30 days of study consent.
12. Have been prescribed and taken naltrexone or bupropion within 30 days of study consent.
13. Concurrently enrolled in formal behavioral or pharmacological addiction treatment services.
14. Receiving ongoing treatment with tricyclic antidepressants, xanthines (i.e., theophylline and aminophylline), systemic corticosteroids, nelfinavir, efavirenz, chlorpromazine, MAOIs, central nervous system stimulants (e.g., Adderall, Ritalin, etc.), or any medication that, in the judgment of the study medical clinician, could interact adversely with study medications.
15. Have a current pattern of alcohol, benzodiazepine, or other sedative hypnotic use which would preclude safe participation in the study as determined by the study medical clinician.
16. Require treatment with opioid-containing medications (e.g., opioid analgesics) during the study period.
17. Have a surgery planned or scheduled during the study period.

18. Are currently in jail, prison or any inpatient overnight facility as required by court of law or have pending legal action or other situation (e.g., unstable living arrangements) that could prevent participation in the study or in any study activities.
19. If female, be currently pregnant, breastfeeding, or planning on conception.

2.0 GENERAL DEFINITIONS AND PROCEDURES

2.1 Pre-screened Population

The pre-screened population consists of all participants who provided verbal consent for the pre-screen process.

2.2 Screened Population

The screened population consists of all participants who provided informed consent at the initiation of the screening process.

2.3 Randomized Population

The Randomized population consists of all participants randomized in Stage 1.

2.4 Intent-to-Treat Population

The Intent-to-Treat (ITT) population consists of all randomized participants in Stage 1. For Stage 2, the ITT population includes all participants who were re-randomized.

2.5 Per Protocol Population

The Per Protocol (PP) population is a subgroup of the ITT population. The PP population consists of participants who have not taken bupropion outside of the study medication, have not taken the incorrect treatment assignment, do not terminate study medication early, meet all entry criteria, complete the treatment period as defined in Section 2.10, and meet treatment exposure requirements. Four PP populations will be defined using the following treatment exposure criteria:

1. For each stage, participants who have greater than or equal to 75% treatment exposure for oral study medication and receive 2 injections. Each stage will have its own PP population.
2. For each stage, participants who have greater than or equal to 50% treatment exposure for oral study medication and receive at least one injection during the stage. Each stage will have its own PP population.
3. For each stage, participants who are greater than or equal to 50% compliant to oral study medication using AiCure confirmed dosing.
4. Participants randomized to AMC in Stage 1 who have 2 oral medication blood levels collected during Stage 1 which indicate bupropion dosing, as defined in Section 6.4, and participants re-randomized to AMC in Stage 2 who have 2 oral medication blood levels collected which indicate bupropion dosing. Each stage will have its own PP population.

2.6 Safety Population

The safety population includes all participants who completed informed consent during the screening visit.

2.7 Study Day Definition

Study Day 1 is defined as the day of randomization.

2.8 First Dose Date

The first dose date for oral study medication is the first date on the Oral Study Medication Dosing Log (ODL) on which it is indicated that tablets were taken. The first dose for injectable study medication is the first date an injection was administered on the Injection Administration 2 (IN2) form.

2.9 Last Dose Date

The last dose date for oral study medication is the last day on the ODL form on which it is indicated that tablets were taken. The last dose for injectable study medication is the last date an injection was administered on the IN2 form.

2.10 Treatment Period

The treatment period consists of Study Days 1-84, coinciding with the 12-week medication phase.

2.11 Follow-up Period

The follow-up period consists of two study visits during the post-medication phase occurring at Week 13 and Week 16.

2.12 Safety Window

The safety window begins at the first dose date of either oral or injectable study medication, whichever comes first, and ends either 7 days after the last oral medication dose or 28 days after the last injectable medication, whichever comes last.

2.13 Treatment Emergence

Treatment emergent AEs are defined as AEs with a start date during the safety window.

2.14 Summary Table Conventions

All analyses described in this document for the intent-to-treat population will be summarized over all randomized participants by stages (Stage 1 and 2) and treatment arm. Additionally, some analyses for the intent-to-treat population will also be summarized by site. For all summaries of ITT population, participants will be analyzed according to the treatment arm to which they were randomized regardless of the subsequent sequence of events regarding study drug exposure.

Descriptive summaries of the distribution of continuous variables will be presented with percentiles (median, 25^{th} and 75^{th} percentiles), and with mean, standard deviation, minimum and maximum. Categorical variables will be summarized in terms of frequencies and/or percentages.

Listings presented by treatment arm will include groups for non-re-randomized Placebo and AMC participants, and re-randomized Placebo and AMC participants (Placebo, Placebo/Placebo, Placebo/AMC, AMC).

2.15 Data and Statistics Center Responsibilities

The CTN's DSC will conduct analyses for the Final Study Report, including those related to the primary outcome measure and the supportive analyses listed in Section 7.3, and the analysis for the primary outcome paper, as discussed by and decided upon by the Lead Node, DSC, and Center for Clinical Trials Network (CCTN). The Lead Node will be responsible for the all secondary outcomes and analyses, the AiCure app-confirmed oral medication dosing described in Section 6.3, and the Per Protocol Population definition #3 detailed in Section 2.5 which uses AiCure treatment exposure information.

3.0 ENROLLMENT, PARTICIPANT DISPOSITION, AND FOLLOW-UP

The number of pre-screens and screens completed and the reasons for ineligibility on pre-screening and screening will be summarized by site. Note that participants might be screened twice. For participants who were screened twice, they will only be considered for the second screening.

The distribution of treatment assignments by site and stage will be presented. The trajectory of actual randomizations versus the expected number of randomizations according to the first date of randomization and under the assumption that three participants are expected to be randomized per month per site will be graphed by site and overall. Proposed versus actual randomizations will be summarized by site in a tabular fashion.

Participants are defined as study completers if the Week 16 Follow-up Visit is completed as indicated on the Study Completion (STC) form, and are considered as early study terminations if this visit is not completed. Participant disposition will be summarized by site, treatment arm, and stage for the number of participants completing the study, the number of participants early terminating from the study, and the reasons for early study termination. Early study terminations, using the date of last data collection or date of withdrawn consent on the STC form, will be attributed to Stage 1 if the termination occurred prior to the end of Week 6 (Day 42). Study terminations occurring from Day 43 to Day 84 will be considered to occur in Stage 2, and study terminations occurring after Day 84 will be considered to occur during follow-up.

The CONSORT flow diagram will be generated (Moher et al., 2010).

The number and percentage of participants who attend the bi-weekly treatment period study visits during Weeks 1-12 will be presented by treatment arm and stage, and the Week 13 and 16 follow-up visits will be presented by treatment arm. Information on missed visits during the treatment period and the follow-up period will be presented by treatment arm and stage, including the number of missed visits, the number of participants with at least one missed visit, and the reasons for the missed visits. The expected number of visits during the treatment period is calculated based on the general rule that two visits per week are expected per participant for a total of 12 expected visits per stage, and two visits are expected during the follow-up period. The average number of missed visits per participant will be calculated by dividing the number of missed visits by the number of participants. For early study terminations, visits are only considered missed during active study participation if they occur before the study termination date.

4.0 ANALYSIS OF PARTICIPANT CHARACTERISTICS

Baseline demographics and characteristics including sex, age, ethnicity, race, education level, marital status, employment status, and the number of methamphetamine use days in the 30 days prior to informed consent reported on TLFB will be summarized by site, treatment arm, and stage. Because randomization is expected to produce balance at baseline between the two arms of the trial, statistical comparisons of treatment groups with respect to baseline characteristics will be informal. If differences between treatments arms are suspected, statistical testing will be performed.

5.0 CONCOMITANT MEDICATIONS

Concomitant medications taken during the treatment period will be coded using the WHO Drug Dictionary. Summaries by treatment arm will be presented by Anatomical Therapeutic Chemical (ATC) Class level 1 and ATC Class level 2 and will include the number and percentage of participants receiving each drug class during the safety window defined in Section 2.12.

6.0 STUDY MEDICATION ADHERENCE

Exposure to study medication will be assessed by oral medication dosing, including self-report and AiCure app-confirmed dosing, injection administration, and medication blood levels.

6.1 Early Medication Terminations

Participants may terminate early from either oral study medication or injectable study medication, or from both study medications. Participants will be considered early oral medication terminations as of the date of last oral medication dose entered on the End of Medication (EOM) form. For injectable study medication the date of early medication termination is not collected, and participants will be considered to terminate from the medication for the injection number after the last injection administered on the IN2 form. Early injection termination participants receiving no injections or injection #1 only will be considered early injection terminations in Stage 1, and participants last receiving injection #2 or #3 will be considered early injection terminations in Stage 2. Note there is one exception that participants terminating the study or terminating both study medications on or before Day 42 (end of Week 6) who received both injection #1 and #2 will be considered as early injectable study medication terminations in Stage 1. Early oral study medication terminations occurring before the date of re-randomization or Day 43 for participants who are not re-randomized are considered to occur in Stage 1, and early oral study medications occurring on or after the date of re-randomization are assigned to Stage 2.

The number of participants terminating early from each study medications and the reasons for termination will be presented by site and by stage and treatment arm.

6.2 Treatment Exposure

During the treatment period (Days 1-84), 3 tablets per study day are expected and 4 injections should be administered. Oral study medication dosing is recorded on the ODL form and injection administration is recorded on the IN2 form. Treatment exposure is defined as the average of the percentage of expected oral study medication taken and the percentage of expected injections received. Oral medication taken after the end of the treatment period Day 84 will not be considered. Treatment exposure will be summarized by site, and by site, treatment arm and stage. Oral medication expected to be taken before the date of re-randomization or Study Day 43 for non-re-randomized participants is considered Stage 1, and oral medication expected to be taken on or after the date of re-randomization or Study Day 43 for non-re-randomized participants is considered Stage 2. Injections #1 and #2 are allocated to Stage 1 and injections #3 and #4 are in Stage 2.

A summary of the number of injections administered out of the 4 expected injections by site and by treatment arm and stage will be presented. Two injections are expected in each stage.

6.3 Video Confirmed Oral Medication Dosing

Exposure to oral medication will also be calculated using information from the smartphone app-based dosing confirmation procedures developed by AiCure. Video confirmed dosing adherence data is to be interpreted as an objective indicator of the lowest medication adherence rate participants achieve. Video confirmed adherence is defined as the percentage of expected oral study medication taken, with taken medication including dosing confirmed via video, confirmed by the site, and confirmed in the clinic. Oral medication taken after the end of the treatment period Day 84 will not be considered. Video confirmed adherence will be summarized by site and by treatment arm and stage.

6.4 Oral Medication Blood Levels

Exposure to bupropion will be assessed at Weeks 4, 7, 10, and 12 for participants randomized to AMC and Weeks 10 and 12 for participants re-randomized to AMC by examining quantitative blood levels of bupropion and its primary metabolite hydroxybupropion. Bupropion blood levels greater than 0.500 ng/mL (limit of detection) and hydroxybupropion blood levels greater than 1.00 ng/mL (limit of detection) will indicate adherence to oral bupropion dosing. A summary table of AMC participants adherent to bupropion dosing by stage will be provided.

7.0 ANALYSIS OF EFFICACY OUTCOME MEASURES

7.1 Definition of Primary Outcome Measure

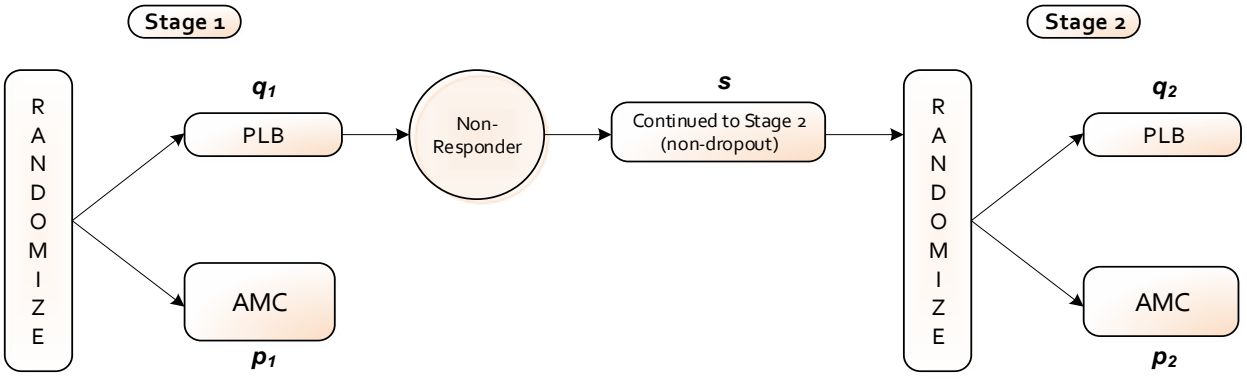
The evaluation period is the final two weeks of the medication phase in Stage 1 (Weeks 5-6) for all participants and Stage 2 (Weeks 11-12) for participants that have been re-randomized. The primary efficacy outcome is a measurement of treatment response at a specified threshold (3 of 4 UDS negative for methamphetamine during the two-week period). Thus, a participant will meet responder criterion by providing 3 or 4 methamphetamine-negative UDS tests during the final two weeks of each stage of the treatment period. All other participants without 3 or 4 methamphetamine-negative UDS will be considered non-responders.

It is hypothesized that the AMC arm will be associated with a greater number of responders, relative to the Placebo arm. The treatment groups will be compared as to the proportion of responders in Stage 1 and Stage 2. The treatment effect will be defined as a weighted combination of the response rates in the two stages. The weight was chosen to optimize the test under the alternative hypothesis as described below. In addition, clinically it is expected that a larger treatment effect will be observed in Stage 2 due to the exclusion of placebo responders from Stage 1. All treatment comparisons will be performed under the Intent-to-Treat (ITT) criteria.

7.2 Analysis of Primary Outcome Measure

Figure 1 shows the design parameters of the SPCD.

Figure 1: SPCD: Defining the Outcome



Let ***p1, q1*** be the response rates for AMC and Placebo in Stage 1; and ***p2, q2*** be the response rates of AMC and Placebo in Stage 2, that is, among Placebo non-responders. Assume that ***s*** is the rate of continuation into Stage 2 among Placebo non-responders, (i.e., *1-s* is the Stage 1 drop-out rate). The primary analysis alternative hypothesis is that the AMC group has higher

response rate than Placebo in the full population (Stage 1) OR in the sub-population of Placebo non-responders (Stage 2). The following null (H_0) vs alternate hypothesis (H_1) will be tested:

$$H_0: p_1 \leq q_1 \text{ AND } p_2 \leq q_2$$

$$H_1: p_1 > q_1 \text{ OR } p_2 > q_2$$

The randomization fraction, ***a*** and the weight, ***w*** are the parameters of the SPCD that are chosen to maximize the power of the test, based on the alternative hypothesis. Fava (2003) recommends that both ***a*** and ***w*** be chosen *a priori* based on the alternative hypothesis of interest. For the alternative hypothesis of this study, it is assumed ***p1=0.24, q1=0.15*** (response rates for AMC and Placebo, respectively, in Stage 1) and ***p2=0.24, q2=0.10*** (response rates for AMC and Placebo, respectively, in Stage 2), and ***s=0.85*** (rate of continuation into Stage 2 of the trial among Placebo non-responders). These assumptions lead to the conclusion that the randomization fraction, ***a=0.37*** and the weight, ***w=0.43*** will maximize the power of the test. The primary outcome analysis will be performed as described in Tamura and Huang (2007) using the Wald type test statistic Z = h/se(h), where

$$h = w(p_{1,obs} - q_{1,obs}) + (1-w)(p_{2,obs} - q_{2,obs})$$

$$var(h) = \frac{w^2 p_{1,obs}(1-p_{1,obs})}{n(1-2a)} + \frac{\left(\left(\frac{w^2}{4}\right) q_{1,obs}(1-q_{1,obs}) + \frac{(1-w)^2 q_{2,obs}(1-q_{2,obs})}{s_{obs}(1-q_{1,obs})}\right)}{na} + \frac{\left(\left(\frac{w^2}{4}\right) q_{1,obs}(1-q_{1,obs}) + \frac{(1-w)^2 p_{2,obs}(1-p_{2,obs})}{s_{obs}(1-q_{1,obs})}\right)}{na}$$

$$\text{and } se(h) = \sqrt{var(h)}$$

Note that Schoenfeld corrected the Tamura and Huang formula for the variance.

In the above test statistic both ***a*** and ***w*** are chosen *a priori* as 0.37 and 0.43; n is the sample size and the quantities $p_{1,obs}$, $q_{1,obs}$, s_{obs}, $p_{2,obs}$ and $q_{2,obs}$ will be estimated from the data. The null hypothesis will be rejected if Z > boundary (one-sided), where the boundary for interim and final analysis is defined as the O'Brien-Fleming boundary as described in Section 8.4.2. A one-sided p-value for the test of primary outcome will be presented. One-sided lower bound confidence limit for the responder rate will be calculated using h – boundary x se(h). See Section 8.2 for the boundary and cumulative alpha spent to be used at interim analysis and final analysis.

The Number Needed to Treat (NNT) will be calculated as 1/h. UDS availability and results in the evaluation periods will be summarized by treatment arm and stage. A graph of the percentage of negative methamphetamine UDS results during the treatment and follow-up periods will be presented.

7.3 Supportive Analyses of Primary Outcome Measure

The analysis will be repeated with the inclusion of selected covariates, for example, age of onset of methamphetamine use, baseline number of methamphetamine use days self-reported on Timeline Followback (TLFB) in the 30 days prior to informed consent, severity of methamphetamine use (presence or absence of using methamphetamine via injection route of administration on TLFB in the 30 days prior to informed consent; number of DSM-5 criteria met

during screening), tobacco use (number of days using cigarettes or e-cigarette on TLFB during 30 days prior to informed consent),Treatment Effectiveness Assessment score at screening, average of all Visual Analog Craving scale scores collected during screening, and site. A generalized linear mixed effect model will be used to assess the covariate adjusted treatment effects to use in the equation in Section 7.2 to compute h.

Subgroup analysis for sex, race, ethnicity and age will be performed as required by the NIH (NIH, 2016). A generalized linear mixed effect model will be used to assess the subgroup-by-stage-by-treatment interaction. A contrast will be written using the pre-specified weight (***w***=0.43) to test the difference in the primary hypothesis by subgroup.

The primary hypothesis is the difference in the weighted treatment effect in Stage 1 and 2. For example, the difference in the primary hypothesis by sex (Female = F, Male = M) is obtained by a contrast using the weighted treatment effects within males (h_M) and females (h_F) which are given by the following equations:

$$h_M = \{w(p_{1,M} - q_{1,M}) + (1-w)(p_{2,M} - q_{2,M})\}$$
$$h_F = \{w(p_{1,F} - q_{1,F}) + (1-w)(p_{2,F} - q_{2,F})\}$$

The estimates for the responder rate and standard error for males and females will be obtained using an LSMESTIMATE statement and the p-value for the comparison will be obtained using a CONTRAST statement in the SAS code below.

```
proc glimmix data=final method=quad;
  class sex stage trt patid;
  model responder = sex*stage*trt/noint solution;
  random intercept /subject=patid;
  contrast "MvsF" sex*stage*trt -.43 .43 -.57 .57 .43 -.43 .57 -.57;
  lsmestimate sex*stage*trt "Male" -.43 .43 -.57 .57;
  lsmestimate sex*stage*trt "Female" 0 0 0 0 -.43 .43 -.57 .57;
run;
```

Similarly, the subgroup analysis for site, race, ethnicity, and age will be conducted. If there are more than 2 levels of a subgroup e.g. race (black, white and other) an overall p-value will be reported and appropriate post-hoc testing will be conducted. Summary tables of primary outcome results by site and in the subgroups for sex, race, ethnicity, and age will be provided by treatment arm.

Responder rates in the Randomized Population and the Per Protocol Populations will be presented by treatment arm.

A sensitivity analysis using *w*=0.5 will be performed for the ITT Population.

7.4 Secondary Outcome Measures

Secondary outcome measures for the impact of the AMC, relative to the Placebo arm, on other substance use outcomes, depression scores, quality of life, overall functioning, clinic attendance, and medication adherence will be evaluated as follows.

1. Alternate measures and composites of methamphetamine use including:
    a) The Treatment Effectiveness Score (TES) (Ling et al., 1997), as measured by UDS results, during the treatment period. The TES is the percentage of the expected urine drug screens that were negative for each drug. Twelve urine drug screens are expected within each stage.

b) Methamphetamine use, as measured by UDS, during the treatment period. Outcomes include UDS results in the pre-evaluation period (Weeks 1-4 for Stage 1 and Weeks 7-10 in Stage 2), the maximum number of consecutive negative UDS (missing and positive UDS will reset the count to zero), and number of study weeks during the treatment period with two methamphetamine-negative UDS.

c) Frequency of methamphetamine use, as measured by self-report on TLFB, during the treatment period. The self-reported number of days abstinent from methamphetamine use will be assessed during the evaluation periods during Stage 1 and Stage 2 and over the entire treatment period.

d) Severity of methamphetamine craving, as measured by Visual Analog Craving Scales (VAS), during the treatment period. VAS scores range from 0 (no craving) to 100 (most intense craving possible). The VAS is completed at screening, once a week during the treatment period, and at the follow-up visits.

e) Methamphetamine use as measured by UDS and methamphetamine use self-reported on TLFB during the follow-up period. UDS results and the self-reported number of days abstinent from methamphetamine use during the follow-up will be assessed.

2. Other substance use, as measured by UDS, during the treatment period. Opioid use will also be assessed using the Opioid 2000 ng tests on the UDS.
3. Quantity and frequency of alcohol, quantity and frequency of cigarettes, frequency of e-cigarettes, and frequency of other drug use, as measured by self-report on TLFB during the treatment period.
4. Depressive symptoms, as measured by the PHQ-9, during the treatment period. The PHQ-9 is collected at screening, once a week during the treatment period, and at the follow-up visits.
5. Quality of life (QoL), as measured by the PhenX Core Tier 1 instrument and collected on the Quality of Life (QLP) form, during the treatment period. Ratings of general health, physical health, and mental health during the past 30 days at screening, mid-treatment (Week 6 Visit 2), and end-of-treatment (Week 12 Visit 2) are collected.
6. Overall functioning, as measured by the Treatment Effectiveness Assessment (TEA), during the treatment period. The Treatment Effectiveness Assessment (Ling, 2012) is a 4-item self-administered assessment that uses a Likert scale (1-10) to document changes in four life domains: substance use, health, lifestyle, and community and is collected at screening, mid-treatment (Week 6 Visit 2) and end-of-treatment (Week 12 Visit 2).
7. Percentage of participants who completed a visit in Week 12.
8. Ratings of participant and staff satisfaction with study procedures, including use of the medication adherence app, compensation, and medication.

The Lead Node will provide summary tables by treatment arm and stage for the above secondary outcomes.

7.5 Secondary Outcome Analyses

All secondary analyses described below will be conducted by the Lead Node. The secondary outcomes listed in Section 7.4 are classified in Table 1.

Table 1: Secondary Outcomes by Type of Outcome for SPCD Analysis		
Type of Outcome	**Frequency of Measurement**	**Outcomes**
Binary Cross-Sectional	one measurement per stage	Meth use from UDS (1.b, 1.e) Other substance use from UDS (2)
Ordinal	one measurement	Ratings of participant and staff satisfaction (8)
Ordinal Cross-Sectional	one measurement per stage	QOL (general health) (5)
Count	one measurement per stage	Number of weeks with meth-negative UDS (1.b) Number of consecutive meth-negative UDS (1.b) Number of meth-abstinent TLFB days (1.c, 1.e) Number of alcohol, cigarettes, e-cigarettes, and other substance use TLFB days (3)
Continuous	one measurement	Treatment completion (7)
Continuous Cross-Sectional	one measurement per stage	TES (1.a) Quantity of alcohol and cigarettes used from TLFB (3) QOL (physical health, mental health) (5) TEA (substance use, health, lifestyle, community) (6)
Continuous Repeated Measures	multiple measurements per stage	Severity of meth craving measured by VAS (1.d) PHQ-9 (4)

Binary cross-sectional outcomes will be analyzed using the same model as for the primary outcome. All repeated measures will be analyzed using the method of Doros et al, 2012. The mixed effects repeated measures models will control for baseline methamphetamine use days self-reported on TLFB and other key demographic and participant variables such as severity of methamphetamine use, tobacco use history, and visual analog craving scale. Nonparametric analyses will be used if the assumptions of the mixed effects analysis cannot be met. Participant and staff satisfaction ratings will be summarized. Analyses of secondary outcomes will be primarily performed on all individuals who are in the ITT population and inducted onto both study medications.

The analysis approach described in Doros et al, 2012 is preferred, however the approach defined in Chen (2011) may also be used, as appropriate (i.e., for continuous outcome ordinary least squares and mixed effects models for repeated measures (MMRM). Logistic regression may also be used for binary outcomes. The same weights as primary outcome will be used to calculate the weighted combination of the estimated treatment effects in the two stages for the secondary analyses.

Secondary analyses of outcomes not specified in Section 7.4 will also be performed. Adherence to oral study medication dosing will be measured by smartphone app-confirmation of daily oral study medication dosing and as recorded on the dosing log (ODL). In addition, per protocol analyses will be conducted using the Per Protocol population definitions in Section 2.5. Because

per protocol analyses may be biased (Sheiner and Rubin, 1995), an unbiased complier-adjusted causal effects analysis (Stuart and Jo, 2015) may also be used to adjust for adherence.

Additionally, methamphetamine and other substance use outcomes may be assessed for responders, non-responders, and other subgroups.

8.0 OTHER STATISTICAL CONSIDERATIONS

8.1 Handling Missing Data

Any participant who drops out before the last week in each evaluation period is, by definition, a non-responder. Therefore, any participant who drops out before Week 6 is a Stage 1 non-responder. In the SPCD design, Stage 1 Placebo non-responders are to be randomized again in Stage 2, but re-randomization is impossible if the participant has dropped out. Thus, Stage 1 dropouts will not contribute to the analysis in Stage 2. In Stage 2, dropouts (i.e., any participant who drops out before Week 12) are again considered to be non-responders by definition, and this causes no further complication in the SPCD computation.

It is unknown *a priori* how many participants will drop out in Stage 1 of the study, thus the 15% attrition rate (***s*=0.85**) was chosen as a conservative estimate. Also, as described above, an assumption was made that participants who dropped out early in a given stage will be considered as non-responders in that stage. Therefore, it is important to assess the impact of these missing data assumptions on the primary outcome analysis of the study. A series of sensitivity analyses will be performed to determine how the missing data affects the primary results. Analysis by imputing missing UDS as negative will be conducted, as well as a complete case analysis which includes all participants who have 4 UDS collected in the evaluation period for each stage. Based on the literature review on novel missing data methodology for SPCD, additional secondary analysis may be performed to support the primary outcome analysis.

8.2 Significance Testing

The primary outcome will be evaluated using a one-sided test with a type I error rate of α=0.025, adjusted based on O'Brien-Fleming boundaries for the interim analysis as described in Section 8.4.2. The boundary and the cumulative alpha spent used for interim and final analysis are noted below in Table 2.

Table 2: Primary Outcome Analysis Boundary and Cumulative Alpha Spent

Timepoint	Boundary for Declaring Statistical Significance	Alpha Level (Cumulative alpha spent)
Interim analysis	2.9626	0.00153
Final analysis	1.9686	0.025

The secondary outcomes will use a two-sided test with 5% error rate. There are several secondary outcomes; however, multiple testing will not be adjusted for in the secondary analyses, since these are not part of the study's primary objective. When multiple tests are conducted, the chance of finding a significant difference in one of the tests, when in fact no difference exists, is greater than the stated type I error rate. The investigators are aware of the issues associated with multiple testing and will interpret results with caution.

8.3 Sample Size and Power Calculations

The sample size calculation was conducted as described in Tamura and Huang (2007), with the randomization ratio for Placebo:AMC defined as ***2a:(1-2a)***, where ***a*** is defined as the

randomization fraction***.*** Table 2 shows the impact of various design assumptions on the parameters of the SPCD, the randomization fraction ***a***, and the weight ***w*** on the sample size. It is important to note that when the rate of discontinuation is 0% (***s***=1), the sample size calculation based on Tamura and Huang (2007) gives the same results as Fava et al. (2003) SPCD sample size calculations.

As described in Section 7.2 for the alternate hypothesis, it is assumed ***p1=0.24, q1=0.15*** (response rates for AMC and Placebo, respectively, in Stage 1) and ***p2=0.24, q2=0.10*** (response rates for AMC and Placebo, respectively, in Stage 2), and ***s=0.85*** (rate of continuation into Stage 2 of the trial among placebo non-responders). Corresponding to these, the randomization fraction ***a=0.37*** and the weight ***w=0.43*** would maximize the power of the test (Table 3). A sample size of 370 is chosen for this study and will provide 90% power to detect the weighted difference between the two treatment arms. In Stage 1, the random allocation to Placebo:AMC would be 274:96. Based on the above assumptions, it would be expected that:

- Of the 274 assigned to PLB, 15% (***q1=0.15)*** would be Placebo responders while 85% (or 233) would be Placebo non-responders.
- 198 (85% of 233, ***s=0.85***) participants would continue to Stage 2.
- In Stage 2, the random allocation to Placebo:AMC would be 99:99.
- During the course of the entire study 195 participants will receive the AMC, with 96 in Stage 1 and 99 in Stage 2.

See Section 8.4.1.1 for an update to the sample size after the sample size re-estimation was conducted.

Table 3: Sample Size Calculation								
SPCD Design Assumptions					Impact of Assumptions on			
Response Rates				Rate of Continuation in Stage 2				
AMC		PLB			Parameters		Sample Size for	
Stage 1 (p1)	Stage 2 (p2)	Stage 1 (q1)	Stage 2 (q2)	s	a	w	80% Power	90% Power
0.29	0.29	0.15	0.15	1	0.28	0.67	187	250
0.29	0.29	0.15	0.10	1	0.35	0.46	134	179
0.29	0.29	0.10	0.15	1	0.23	0.8	105	141
0.29	0.29	0.10	0.10	1	0.26	0.68	89	119
0.29	0.24	0.15	0.15	1	0.24	0.78	225	301
0.29	0.24	0.15	0.10	1	0.29	0.61	174	232
0.29	0.24	0.10	0.10	1	0.23	0.75	102	136
0.24	0.29	0.15	0.15	1	0.36	0.45	283	379
0.24	0.29	0.10	0.15	1	0.25	0.73	160	214
0.24	0.29	0.10	0.10	1	0.32	0.54	120	161
0.24	0.24	0.15	0.15	1	0.28	0.67	417	558
0.24	0.24	0.15	0.10	1	0.4	0.33	246	329
0.24	0.24	0.10	0.15	1	0.23	0.82	187	250
0.24	0.24	0.10	0.10	1	0.27	0.67	151	201
0.29	0.29	0.15	0.15	0.85	0.27	0.72	196	262
0.29	0.29	0.15	0.10	0.85	0.33	0.54	147	196
0.29	0.29	0.10	0.15	0.85	0.22	0.82	108	144
0.29	0.29	0.10	0.10	0.85	0.25	0.72	94	125
0.29	0.24	0.15	0.15	0.85	0.24	0.81	230	308
0.29	0.24	0.15	0.10	0.85	0.28	0.66	184	246
0.29	0.24	0.10	0.10	0.85	0.23	0.79	105	140
0.24	0.29	0.15	0.15	0.85	0.34	0.54	313	419
0.24	0.29	0.10	0.15	0.85	0.25	0.77	167	223
0.24	0.29	0.10	0.10	0.85	0.3	0.61	131	175
0.24	0.24	0.15	0.15	0.85	0.27	0.71	439	587
0.24	0.24	0.15	0.10	0.85	0.37	0.43	276	370
0.24	0.24	0.10	0.15	0.85	0.22	0.84	190	254
0.24	0.24	0.10	0.10	0.85	0.26	0.72	158	212

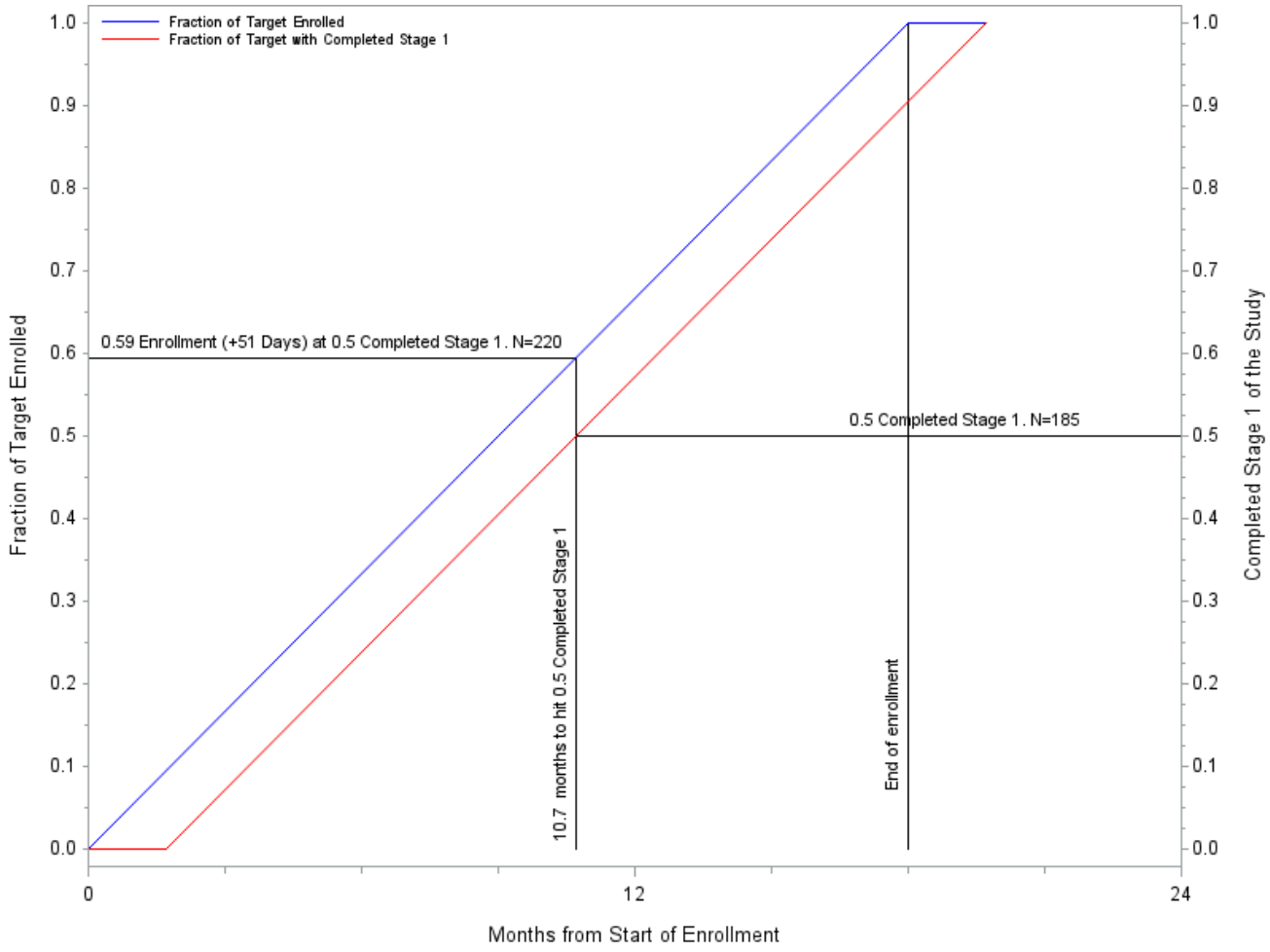
8.4 Interim Analyses

8.4.1 Sample Size Re-Estimation

Sample size re-estimation analysis will be conducted when approximately half of the participants have been enrolled and have passed the last day available for re-randomization, Week 8 Day 2, and will focus on the nuisance parameter ***s*** (rate of continuation into Stage 2 of the trial among Placebo non-responders). This analysis will not reveal the treatment effect observed in the trial at the time of this interim analysis. Fava (2003) suggested that both ***a*** and ***w*** be *a priori* chosen to maximize the power of the test based on the alternative hypothesis of interest, and therefore ***a*** and ***w*** will not be re-estimated. Under the design assumptions of ***p1=0.24, q1=0.15***, ***p2=0.24, q2=0.10,*** the randomization fraction ***a=0.37,*** and the weight ***w=0.43***, a sample size re-estimation will be performed using the estimated parameter ***s***, keeping the other parameters fixed***,*** to assess the adequacy of the projected study sample size and whether a sample size increase is warranted.

The timing of the sample size re-estimation is based on a number of factors: recruitment rate, timing of the primary outcome, amount of loss to follow-up, and time to perform the sample size re-estimation. ADAPT-2 will use the graphical tool presented in Figure 2 to assist in assessing the appropriate timing of sample size re-estimation. To illustrate, Figure 2 shows the timing of re-estimation when 50% of the participants have completed Stage 1 in the study (0.5 on the red line), assuming enrollment (blue line) in ADAPT-2 of 370 participants over an 18-month period. The time point to perform the sample size re-estimation corresponds to 10.7 months (9 months to enroll 50% participants plus completion of end of re-randomization window at Week 8 Day 2) after enrollment into ADAPT-2 has started, at which point, the study will have enrolled about 58% of the target sample size. If recruitment takes more or less time than expected, modifications can be made to the timing of the sample size re-estimation. The sample size re-estimation will be done only once and done before any interim analysis of the primary outcome is performed. The results of the sample size re-estimation analysis would be presented in a closed session of the DSMB, who will then provide a recommendation to the NIDA CCTN regarding whether the target sample size should be modified. A decision regarding any such modification would be made subsequently by the CCTN, taking into consideration the recommendation of the DSMB.

Figure 2: Completed Stage 1 and Fraction of Target Enrollment for Proposed Sample Size Re-Estimation Based on Months from Start of Enrollment



8.4.1.1 Sample Size Re-Estimation Results

The NIDA CTN DSMB reviewed the sample size re-estimation report dated July 23, 2018, prepared by the DSC. In this report, the sample size re-estimation was presented under the design assumptions of ***p1=0.24***, ***q1=0.15***, ***p2=0.24***, ***q2=0.10***, the randomization fraction ***a=0.37***, the weight ***w=0.43***, and using the estimated parameter ***s=0.75758***, keeping the other parameters fixed. The ***s*** parameter was estimated using the first 185 participants randomized. Table 4 shows the results of the sample size re-estimation.

Table 4: Sample Size Re-Estimation Results			
Sample Size Calculation	***s***	**N**	**Power**
Original design	0.85	276	80%
	0.85	370	90%
Power with current sample size and updated ***s*** parameter	0.75758	276	76.8%
	0.75758	370	87.7%
Maintaining original power with increased sample size using updated ***s*** parameter	0.75758	298	80%
	0.75758	399	90%

Based on the above results, the DSMB and NIDA CCTN concurred that although the loss of power compared to the original power calculations was negligible, the dropout rate that will occur in Stage 2 of the study is also unknown and recommended increasing the sample size by 30 additional participants (N = 400) to maintain the targeted 90% power. The CCTN approved the increase the sample size to 400 participants in a letter to the Lead Investigator dated August 13, 2018.

8.4.2 Interim Monitoring of Primary Efficacy Endpoint

Interim monitoring for efficacy will be performed of the primary alternative hypothesis that the AMC, relative to the Placebo, is associated with greater methamphetamine non-use. There will be no interim efficacy monitoring before a sample size re-estimation is performed (or a determination that re-estimation is not needed) because sample size re-estimation could change the target sample size, affecting the alpha spending function used in the interim efficacy monitoring. After sample size re-estimation, interim efficacy monitoring will be performed only once during the recruitment period. Because the Lan-DeMets approach (DeMets and Lan, 1994) requires an independent increments process, care must be taken in defining the population that will be used in the interim analysis. For example, including participants in an interim look who completed 6 weeks of Stage 1 and are Placebo non-responders, but have not yet had the opportunity to contribute Stage 2 responses, violates the independent-increments requirement. To avoid this, the following rule will be obeyed:

- For a look at study time *t* months, include only those participants who were randomized to Stage I no later than *t-3* months (i.e., have the opportunity to complete the 12 weeks (or 3 months) on study at the time of the analysis). The size of that sample, when divided by the target sample size, becomes the information fraction for the look at calendar time *t*.

Based on the above rule and using designed parameters, the Lan-DeMets alpha-spending approach to interim monitoring for SPCD trials was investigated by simulation. Enrollment was assumed to be constant over an 18–month period. Under the null hypothesis, (**p1, p2**) are set equal to (**q1, q2**) = (**0.15, 0.10**), while under the alternative, (**p1, p2**) = (**0.24, 0.24**) a 2-look scenario, in which information fraction = (0.5, 1.0), was simulated.

Table 5 gives the simulated probability of rejecting the null hypothesis at alpha = 0.025, 1-tailed, for each of these scenarios. More specifically, 10,000 time series of SPCD z-values were simulated, each with 2 values (when there are 2 looks) for each scenario. In each scenario, the proportion of time series that ever cross the relevant boundary is presented in Table 6. It shows that after using the O'Brien-Fleming-type boundaries the test size under the null and power under the alternative are as desired.

Table 5: Simulated Probability of Rejecting the Null Hypothesis at α = 0.025, 1-tailed		
	Null Hypothesis	**Alternative Hypothesis**
O'Brien-Fleming type	0.0237	0.90

All interim monitoring will use an O'Brien-Fleming-type boundary with information fraction equal to the proportion of the target sample size with primary outcome, and alpha = 0.025, one-tailed. This approach spends very little alpha at the interim look, therefore the impact of an interim monitoring on the sample size is negligible. Table 6 shows an example of boundary (Z-score) to stop early for efficacy and cumulative alpha spent at interim analysis with 0.5 information fraction.

Table 6: Boundary to Stop Early for Efficacy and Cumulative Alpha Spent at Interim Analysis			
Information Fraction	**Boundary**	**Alpha Spent**	**Cumulative Alpha Spent**
0.5 (Half-way)	2.9626	0.00153	0.00153
1 (End of study)	1.9686	0.02347	0.025

In addition, the observed parameters and number of participants assigned to each treatment arm in the two stages will be monitored against the designed parameters (***p1=0.24, q1=0.15, p2=0.24, q2=0.10, s=0.85)*** and expected assignment. The only criterion for early stopping for efficacy will be based on Z-scores and its relation to O'Brien-Fleming-type boundary.

Before recommending early termination, the DSMB should consider:

- Internal consistency of primary and secondary results.
- Internal consistency of primary and secondary results by subgroups defined by baseline characteristics (e.g., number of baseline MA use days on TLFB, severity of MA use, tobacco use history, treatment effectiveness assessment and visual analog craving scale).
- Distribution of baseline prognostic factors among the two groups.
- Consistency of primary and secondary results across clinical sites and among clinical sites enrolling larger numbers of participants.
- Possible impact of missing data from missed participant visits for assessment of the primary and secondary response variables.
- Possible differences in concomitant interventions or medications.

8.4.3 Safety Interim Analyses

Safety interim looks will be performed for the regular DSMB meetings or at unscheduled times per the DSMB's request. These will include analysis of adverse events and narrative report on serious adverse events.

Further, because the primary outcome analysis is a one-sided test to assess whether AMC is more efficacious than Placebo, simultaneous with primary interim efficacy monitoring analysis, a poor efficacy statistic will be calculated to assess whether the AMC, relative to the Placebo, is associated with greater methamphetamine use i.e., whether compared to AMC, the response rate

is greater in Placebo in both stages. This analysis will be conducted after the sample size re-estimation. If the poor efficacy of AMC statistic crosses its boundary, defined by the minimum of q1 – p1 and q2 – p2 being greater than 10%, the DSMB will consider whether to stop the trial early because of poor efficacy of AMC relative to Placebo. When reporting results of the trial, the one-sided superiority test will be considered the primary outcome, with the other tail considered as part of the poor efficacy analysis intended for the DSMB to monitor for safety. That is, as in a more usual trial design, the possibility of exit in the safety/poor efficacy tail will not be considered as possibly affecting the type I or type II error of the primary outcome statistical test.

8.4.4 Conditional Power and Futility

Unless otherwise requested, a futility/conditional power calculation will be performed when interim monitoring is performed. If at any DSMB meeting the conditional power falls below 0.3 (when hypothetical future observations are generated under the design alternative (***p1=0.24, q1=0.15***, ***p2=0.24, q2=0.10)*** but tested under the null), this will stimulate a discussion among the DSMB members about whether the trial should stop for futility.

8.4.5 Results of Interim Monitoring for Efficacy and Safety

The NIDA CTN DSMB met on October 24, 2018 to review the interim efficacy and safety analyses prepared by the DSC using the first 200 enrollment participants. The DSMB recommended the study should continue until 400 participants complete as determined by the sample size re-estimation.

8.5 Software to be Used for Analyses

The O'Brien-Fleming boundaries and the p-value for the primary outcome will be calculated in WinLD (Reboussin 2000). The interim analyses for sample size re-estimation and conditional power will be conducted in R Versions 3.4.2 and 3.5.1. All other analyses performed by the DSC and the Lead Node will use SAS® Version 9.4 software, including the calculation of the Wald type test statistic Z for the primary outcome. The Lead Node may also conduct analyses using R Versions 3.4.2 and 3.5.1.

9.0 ANALYSIS OF SAFETY OUTCOME MEASURES

9.1 Adverse Events

Treatment emergent adverse events (AEs) as defined in Section 2.13 will be summarized by presenting the number of events, number of participants experiencing AEs, and the severity and relatedness of adverse events by treatment arm and stage. Stage 1 events include AEs occurring before the date of re-randomization for re-randomized participants and in Weeks 1-6 for non-re-randomized participants, and Stage 2 AEs include events occurring on or after the date of re-randomization for re-randomized participants and in Weeks 7 or greater for non-re-randomized participants.

All adverse events will be coded using MedDRA® dictionary version 22.0 and higher and the number of participants experiencing each treatment emergent AE and the incidence rate will be provided by treatment arm and stage. Treatment emergent adverse event incidence rates will be summarized by System Organ Class (SOC) and Preferred Term (PT). The incidence rate of an AE is calculated as the number of participants who experience the event at least once during the safety window divided by the number of participants at risk times 100. Incidence rates will be calculated at the preferred term level, at the SOC level, and for participants with at least one treatment emergent adverse event. If a participant experiences multiple episodes of an event, then the event is only counted once. Detailed listings of treatment emergent adverse events and non-treatment emergent events in the safety population by treatment arm will be provided.

Treatment arm differences will be monitored by the DSMB.

9.2 Serious Adverse Events

Treatment emergent Serious Adverse Events (SAEs) will be summarized by presenting the number of events, number of participants experiencing SAEs, and the relatedness and type of SAEs by treatment arm and stage. SAEs will be presented by stage as described in Section 9.1. A summary of treatment emergent MedDRA® coded serious adverse events using incidence rates will be provided by treatment arm and stage. Incidence rates, as defined in Section 9.1, will be calculated at the preferred term level, at the SOC level, and for participants with at least one treatment emergent serious adverse event. A detailed listing of SAEs, including treatment emergent SAEs and non-treatment emergent SAEs, will be provided by treatment arm. Narratives for all serious adverse events will be included in the Final Study Report.

9.3 Injection Site Abnormalities

The injection site is examined by medical personnel at the next study visit following the injection administration. Injections #1 and #2 occur in Stage 1 and injections #3 and #4 occur in Stage 2. Injection site abnormalities will be summarized by presenting the number of abnormalities, number of participants experiencing abnormalities, type of abnormality, and the severity of the abnormality by treatment arm and stage. A detailed listing of injection site abnormalities for injections by treatment arm will be provided.

9.4 Laboratory Values

Laboratory values are collected at Screening, Week 6, and Week 12. Elevated liver function tests (LFTs) consisting of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin and decreased platelets are monitored by the safety and medical monitors at the CCC. There are multiple site- and sex-based normal ranges amongst the eight sites for the ALT, AST and total Bilirubin parameters. For practicality, the safety team reviewed these parameters and generated a global threshold for each: ALT and AST 250 IU/L, total bilirubin 2.2 mg/dL, and platelets below 75 x 10^3/μL. Table 7 provides the normal ranges for all study sites for LFTs and platelets.

Listings of elevated LFTs and decreased platelets will be presented by treatment arm.

Table 7: Normal Ranges by Site

Lab	SC BHS	WS CODA, Inc.	GNY SURC - Columbia	NS Hennepin County	WS SURU - SFDPH	TX UCLA CBAM	TX UT Health CNRA	TX UTSW
ALT	female 14-54 IU/L male 17-63 IU/L	Female 16-19 yrs 5-32 U/L Female 20+ yrs 6-29 U/L Male 16-19 yrs 8-46 U/L Male 20+ yrs 9-46 U/L	Female 1-31 IU/L Male 1-40 IU/L	Female up to 33 U/L Male up to 41 U/L	Female 7-35 U/L Male 10-40 U/L	8-64 units/L	Female 0-32 IU/L Male 0-44 IU/L	9-46 U/L
AST	15-41 IU/L	Female 7-19 yrs 12-32 U/L Female 20-49 yrs 10-30 U/L Female 50+ yrs 10-35 U/L Male 7-19 yrs 12-32 U/L Male 20-49 yrs 10-40 U/L Male 50+ yrs 10-35 U/L	Female 1-31 IU/L Male 1-37 IU/L	5-40 U/L	2-60 yrs 10-41 U/L 60-90 yrs 10-48 U/L	13-47 units/L	0-40 IU/L	10-40 U/L
Total Bilirubin	0.3-1.2 mg/dL	Female 10-19 yrs 0.2-1.1 mg/dL Female 20+ yrs 0.2-1.2 mg/dL Male 10-19 yrs 0.2-1.1 mg/dL Male 20+ yrs 0.2-1.2 mg/dL	0.1-1.1 mg/dL	0.0-1.2 mg/dL	0-60 years 0.1-1.2 mg/dL 60-90 yrs 0.1-1.1 mg/dL	0.1-1.2 mg/dL	0.0-1.2 mg/dL	0.2-1.2 mg/dL
Platelets	130-450 x thousand cells/µL	140-400 thousand/µL	130-400 K/mm^3	150-400 x 10^3 µL	150,000-400,000/mcL	143-398 x 10^3/µL	150-379 x 10^3/µL	140-400 x10^3 µL

9.5 Electrocardiogram

Electrocardiograms (ECG) are conducted at screening and at Week 12. A summary table displaying the count and frequency of participants with elevated QTc intervals greater than and equal to 500 milliseconds and changes from baseline will be presented by treatment arm. Participants experiencing second or third degree AV block at Week 12 will be listed by treatment arm.

9.6 Suicide Risk

The Concise Health Risk Tracking (CHRT) and Patient Health Questionnaire-9 (PHQ-9) surveys are conducted at screening, weekly during the treatment period, and at follow-up visits to assess suicide risk. A summary table of participants endorsing suicidality on either assessment during the treatment period will be presented by treatment arm and stage. A listing of visits where suicidality was endorsed by a participant will be generated.

Endorsement for the CHRT is defined as answering agree or strongly agree to any of the following: (1) I have been having thoughts of killing myself, (2) I have thoughts about how I might kill myself, or (3) I have a plan to kill myself. On the PHQ-9, a participant is considered to have endorsed suicidality if they indicate several days, more than half the days, and nearly every day having thoughts they are better off dead or of hurting themselves.

9.7 Pregnancy

A listing of pregnancies and pregnancy outcomes in randomized participants will be generated. Narratives will also be provided.

9.8 Deaths

A listing of deaths and narratives of deaths will be provided.

10.0 DATA QUALITY

10.1 Data Audits

A summary of data audit results from site interim monitoring visits conducted by CCC monitors will be presented by site.

10.2 Protocol Deviations

Protocol deviations will be summarized by site and will include the number of deviations reported, the number of participants each deviation affects, frequencies for the types of protocol deviations, and information on whether the protocol deviation was deemed minor or major. A detailed listing of protocol deviations by deviation category will be provided.

11.0 UPDATES TO THE STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) Version 0.1 was reviewed by the IRB and DSMB prior to the initiation of the study and contains unblinded information on the study design not included in the protocol. SAP Version 1.0 was updated to include all information necessary for interim analyses to be conducted and was finalized on July 5, 2018. SAP Version 2.0, which included a correction to the formula for standard error for the primary outcome analysis, was finalized on September 6, 2018 before interim analyses were conducted for the October 24, 2018 DSMB meeting. SAP Version 3.0 was finalized prior to data lock to include the remaining information necessary to analyze the study.

SAP Version 0.1 is included in Appendix 14.2 and a detailed Change Log from SAP Version 0.1 to SAP Version 2.0 is located in Appendix 14.3.

12.0 REFERENCES

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13.0 LIST OF PROPOSED TABLES, FIGURES, AND LISTINGS

The listing of tables below contains the tables, figures, and listings which will be provided by the DSC.

Section	Title	Population
Enrollment, Participant Disposition, and Follow-up	Summary of Pre-screens by Site	Pre-screened
	Summary of Screen Failures by Site	Screened
	Summary of Pre-screens, Screening, and Randomization by Site	Pre-screened
	Randomizations by Site, Stage and Treatment Arm	ITT
	Figure of Expected versus Actual Randomizations Overall	Randomized
	Figure of Expected versus Actual Randomizations by Site	Randomized
	Proposed and Actual Randomizations by Site	Randomized
	Summary of Disposition by Site	Randomized
	Summary of Disposition by Treatment Arm in Stage 1	Randomized
	Summary of Disposition by Treatment Arm in Stage 2	Randomized
	Summary of Disposition by Treatment Arm in Follow-up Period	Randomized
	CONSORT Flow Diagram	Pre-screened
	Summary of Attendance at Treatment Period Visits by Treatment Arm in Stage 1	Randomized
	Summary of Attendance at Treatment Period Visits by Treatment Arm in Stage 2	Randomized
	Summary of Attendance at Follow-up Visits by Treatment Arm	Randomized
	Summary of Missed Visits by Treatment Arm in Stage 1	Randomized
	Summary of Missed Visits by Treatment Arm in Stage 2	Randomized
	Summary of Missed Visits by Treatment Arm in Follow-up Period	Randomized
Participant Characteristics at Baseline	Summary of Baseline Characteristics by Site	Randomized
	Summary of Baseline Characteristics by Stage and Treatment Arm	Randomized
Concomitant Medications	Summary of Concomitant Medications by Treatment Arm	Randomized
Treatment Exposure	Summary of Early Medication Terminations by Site	Randomized
	Summary of Early Medication Terminations by Treatment Arm in Stage 1	Randomized
	Summary of Early Medication Terminations by Treatment Arm in Stage 2	Randomized
	Summary of Treatment Exposure by Site	Randomized

Section	Title	Population
	Summary of Treatment Exposure by Site, Stage and Treatment Arm	Randomized
	Summary of Injections by Site	Randomized
	Summary of Injections by Stage and Treatment Arm	Randomized
	Summary of Oral Medication Blood Levels in AMC Participants by Stage	Randomized
Primary Outcome	Summary of Primary Outcome Availability by Stage and Treatment Arm	ITT
	Summary of Primary Outcome Analysis by Stage and Treatment Arm	ITT
	Figure of UDS Results by Stage and Treatment Arm	ITT
	Summary of Primary Outcome Sensitivity Analyses by Stage and Treatment Arm	ITT
	Summary of Primary Outcome Availability by Stage and Site	ITT
	Summary of Primary Outcome by Site, Stage, and Treatment Arm	ITT
	Summary of Primary Outcome by Sex, Stage, and Treatment Arm	ITT
	Summary of Primary Outcome by Race, Stage, and Treatment Arm	ITT
	Summary of Primary Outcome by Ethnicity, Stage, and Treatment Arm	ITT
	Summary of Primary Outcome by Age, Stage, and Treatment Arm	ITT
	Primary Outcome Covariate Adjusted Analysis Results	ITT
	Summary of UDS Availability by Stage and Treatment Arm	Randomized
	Summary of Methamphetamine Negative UDS Results by Treatment Arm in Stage 1	Randomized
	Summary of Methamphetamine Negative UDS Results by Treatment Arm in Stage 2	Randomized
	Summary of Methamphetamine Negative UDS Results by Treatment Arm in Follow-up Period	Randomized
	Summary of Primary Outcome Sensitivity Analyses by Stage and Treatment Arm in the Randomized Population	Randomized
	Figure of UDS Results by Stage and Treatment Arm in Randomized Population	Randomized
	Summary of Primary Outcome by Stage and Treatment Arm in Per Protocol Populations	Per Protocol
Safety Outcomes	Summary of Treatment Emergent Adverse Events by Treatment Arm in Stage 1	Safety
	Summary of Treatment Emergent Adverse Events by Treatment Arm in Stage 2	Safety

Section	Title	Population
	Summary of Treatment Emergent MedDRA Coded Adverse Events by Treatment Arm in Stage 1	Safety
	Summary of Treatment Emergent MedDRA Coded Adverse Events by Treatment Arm in Stage 2	Safety
	Listing of Treatment Emergent Adverse Events by Treatment Arm	Safety
	Listing of Non-Treatment Emergent Adverse Events in Randomized Participants by Treatment Arm	Safety
	Listing of Non-Treatment Emergent Adverse Events in Screen Failure Participants	Safety
	Summary of Treatment Emergent Serious Adverse Events by Treatment Arm in Stage 1	Safety
	Summary of Treatment Emergent Serious Adverse Events by Treatment Arm in Stage 2	Safety
	Summary of Treatment Emergent MedDRA Coded Serious Adverse Events by Treatment Arm in Stage 1	Safety
	Summary of Treatment Emergent MedDRA Coded Serious Adverse Events by Treatment Arm in Stage 2	Safety
	Listing of Serious Adverse Events by Treatment Arm	Safety
	Summary of Injection Site Abnormalities by Treatment Arm in Stage 1	Safety
	Summary of Injection Site Abnormalities by Treatment Arm in Stage 2	Safety
	Listing of Injection Site Abnormalities by Treatment Arm	Safety
	Listing of Elevated LFTs by Treatment Arm	Safety
	Listing of Decreased Platelets by Treatment Arm	Safety
	Summary of Elevated QTc Intervals by Treatment Arm	Safety
	Listing of AV Block ECG Abnormalities by Treatment Arm	Safety
	Summary of Suicide Risk by Treatment Arm in Stage 1	Safety
	Summary of Suicide Risk by Treatment Arm in Stage 2	Safety
	Summary of Suicide Risk by Treatment Arm in Follow-up Period	Safety
	Listing of Suicide Risk by Treatment Arm	Safety
	Listing of Pregnancies by Treatment Arm	Safety
	Listing of Deaths by Treatment Arm	Safety
Data Quality	Summary of Data Audits	N/A
Protocol Deviations	Summary of Protocol Deviations	N/A
	Listing of Protocol Deviations	N/A

14.0 APPENDICES

14.1 Table Shells

Table 1: Summary of Pre-screens by Site									
	SC BHSPC	**WS CODA, Inc.**	**GNY SURC - Columbia**	**NS Hennepin Healthcare**	**WS SURU - SFDPH**	**TX UCLA CBAM**	**TX UT Health CNRA**	**TX UTSW**	**Total**
Number of pre-screens	N								
Number of ineligible pre-screens	N (%)								
Criteria resulting in ineligibility[1]:									
Have medical/mental health conditions require monitoring/care/medication	N (%)								
Taking meds for medical/mental health condition									
Cannot refrain from opioid use									
Currently enrolled in addiction treatment services									
Taken naltrexone/bupropion within the last 30 days									
Not used methamphetamine in the past 30 days									
Methamphetamine use days in the past 30 days (mean (SD))									
Not interested in study or willing to use study meds									
No current methamphetamine use									
Not willing to attend 2x week for 12 weeks									
Age < 18 or Age > 65									
No interest in reducing/stopping methamphetamine use									
Unwilling to use app									
Currently pregnant or breastfeeding									

[1] Percentages are calculated based on the denominator of the number of ineligibles and may exceed 100% if multiple ineligibility criteria are met for potential participants.

Table 2: Summary of Screen Failures by Site									
	SC BHSPC	**WS CODA, Inc.**	**GNY SURC - Columbia**	**NS Hennepin Healthcare**	**WS SURU - SFDPH**	**TX UCLA CBAM**	**TX UT Health CNRA**	**TX UTSW**	**Total**
Number consented	N								
Number of screen failures	N (%)								
Failed the following eligibility criteria[1]									
Meth use on 18+/30 day	N (%)								
Comply with study procedures									
2/3 positive meth urine in 10 days									
Conditions that increase seizure risk									
Medical/psychiatric disorder									
ECG finding									
Stage 2 hypertension									
Current alcohol/benzo use									
Opioid-free									
Elevated bilirubin/LFT 5x ULN									
Taking contraindicated meds									
Pregnant/breastfeeding									
Agrees to use birth control and do urine pregnancy testing									
DSM-5 meth use disorder									
Agrees to record videos									
Platelets< 100 x 10^3 µL									
Prescribed and taken study drugs									
Surgery planned/scheduled									
Jail									

[1] Percentages are calculated based on the denominator of the number of ineligibles and may exceed 100% if multiple ineligibility criteria are met for potential participants.

Table 3: Summary of Pre-screens, Screening, and Randomization by Site								
Site	**Number of Screens**	**Percent of Eligible Pre-Screens Screened**	**Average Number of Days Between Pre-Screen and Scheduled Screening Appointment**	**Number of Screen Fails**	**Percent of Screens Who Screen Fail**	**Number Randomized**	**Percent of Eligible Pre-Screens Randomized**	**Percent of Screens Randomized**
SC BHSPC	N	%	X.X	N	%	N	%	%
WS CODA, Inc.								
GNY SURC - Columbia								
NS Hennepin Healthcare								
WS SURU - SFDPH								
TX UCLA CBAM								
TX UT Health CNRA								
TX UTSW								
Total								

Table 4: Randomizations by Site, Stage and Treatment Arm				
	Stage 1		Stage 2 Re-randomized	
	Placebo	AMC	Placebo/ Placebo	Placebo/ AMC
SC BHSPC	N (%)			
WS CODA, Inc.				
GNY SURC - Columbia				
NS Hennepin Healthcare				
WS SURU - SFDPH				
TX UCLA CBAM				
TX UT Health CNRA				
TX UTSW				
Total				

Figure 3: Expected versus Actual Randomizations Overall

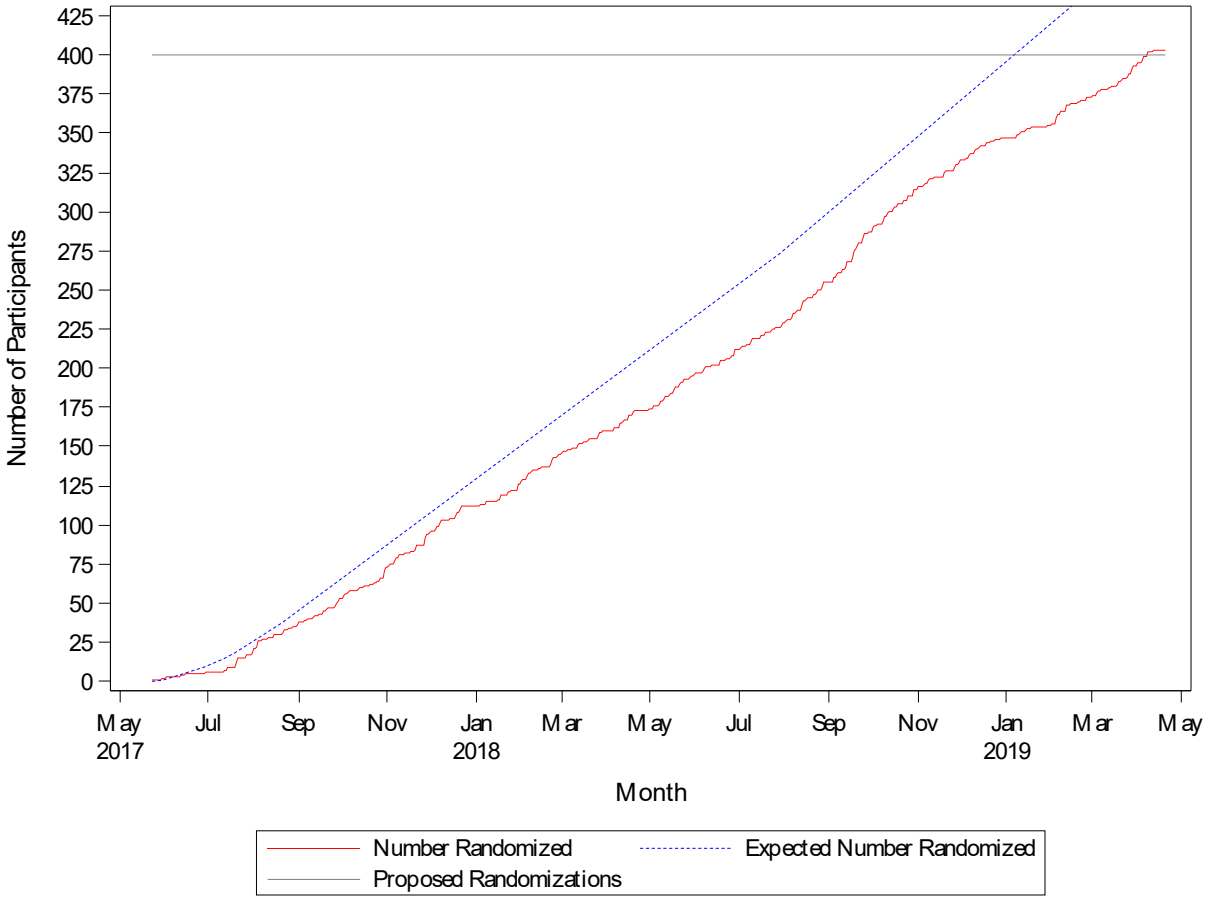


Figure 4: Expected versus Actual Randomizations by Site

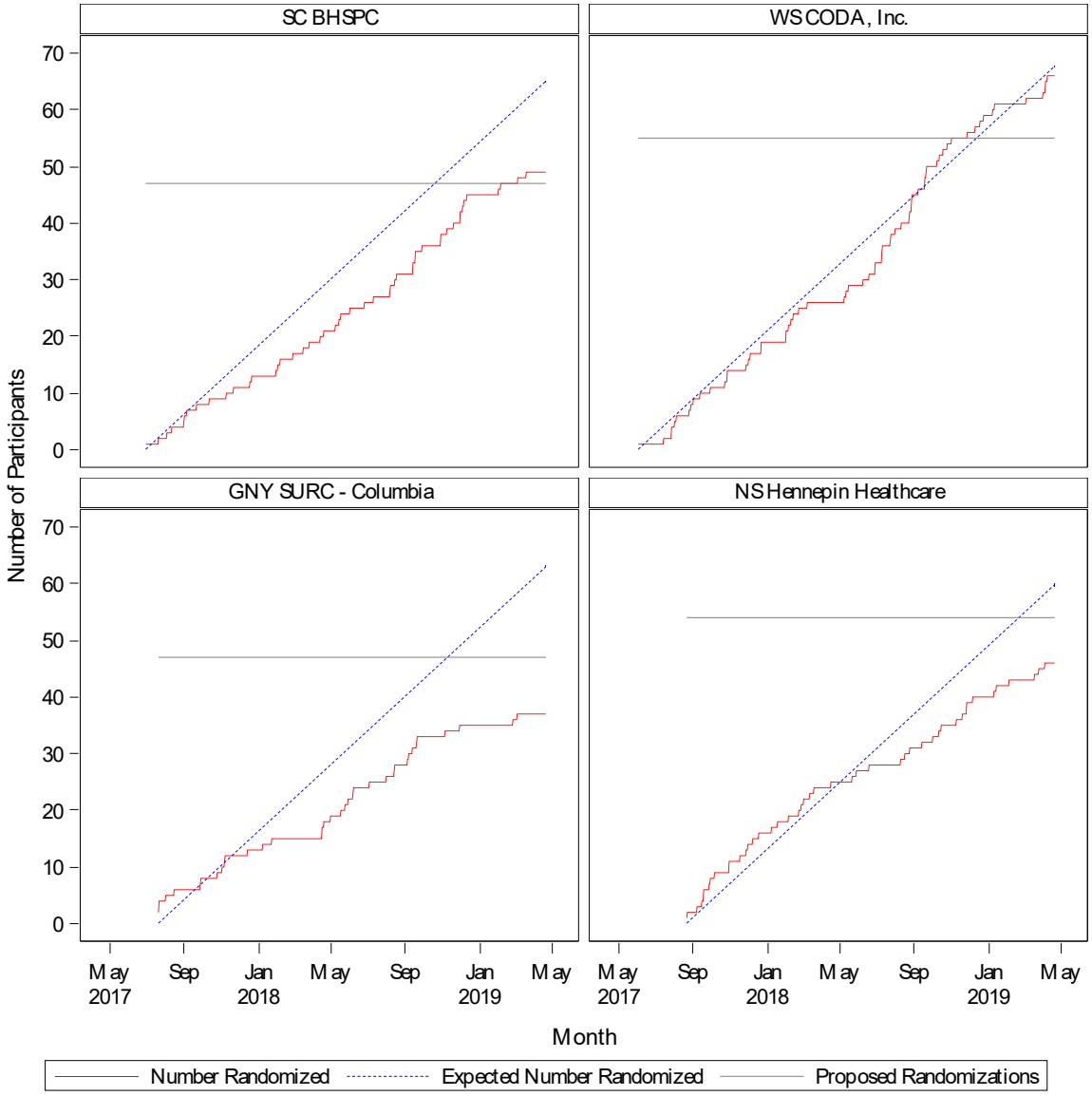


Figure 5: Expected versus Actual Randomizations by Site *(cont.)*

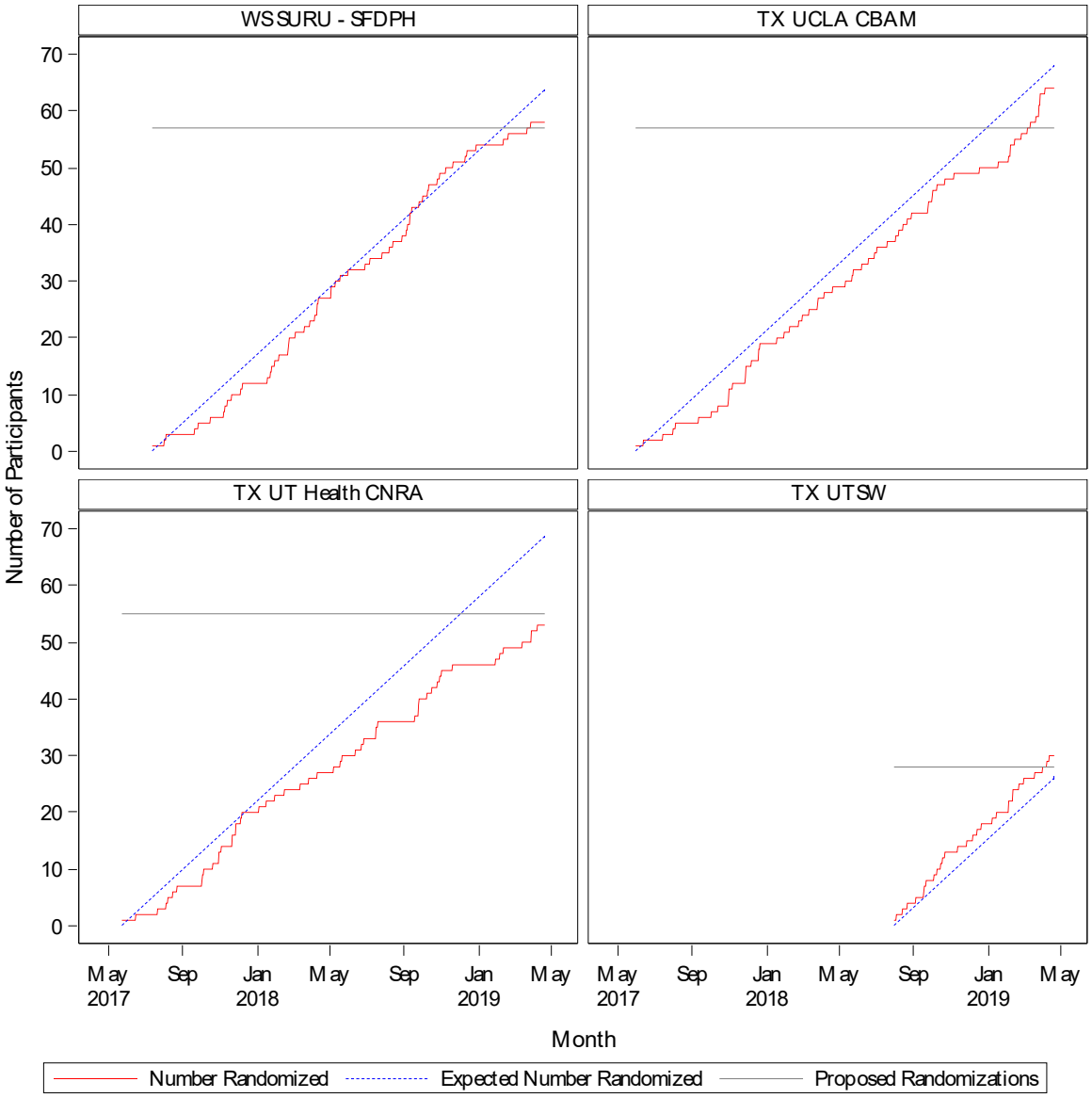


Table 5: Proposed and Actual Randomizations by Site						
Site	**Proposed Randomization**	**Date Site Opened for Enrollment**	**Date of First Randomization**	**Actual Randomizations**	**Actual/ Proposed (%)**	**Date of Last Randomization**
SC BHSPC	N			N	%	
WS CODA, Inc.						
GNY SURC - Columbia						
NS Hennepin Healthcare						
WS SURU - SFDPH						
TX UCLA CBAM						
TX UT Health CNRA						
TX UTSW						
Total						

Table 6: Summary of Disposition by Site									
	SC BHSPC	**WS CODA, Inc.**	**GNY SURC - Columbia**	**NS Hennepin Healthcare**	**WS SURU - SFDPH**	**TX UCLA CBAM**	**TX UT Health CNRA**	**TX UTSW**	**Total**
Number of participants randomized	N								
Number of study completers[1]	N (%)								
Number of early study terminations	N (%)								
Reasons for early study termination									
Participant failed to return to site and unable to contact	N (%)								
Participant withdrew consent/assent									
Participant stopped participation due to practical problems									
Participant moved from area									
Participant incarcerated									
Participant terminated due to AE/SAE									
Participant terminated for other clinical reasons									
Participant had a significant psychiatric risk									
Participant deceased									
Participant terminated due to protocol deviation									
Participant became pregnant									
Participant reports intolerable symptoms or side effects									
Participant reports use of medication that could adversely interact with study medication									
Clinical deterioration: New onset of psychiatric or medical condition									
Clinical deterioration: Worsening of pre-existing psychiatric or medical condition									
Clinical deterioration: Worsening of substance use disorder									
Clinical deterioration: Overdose									
Participant terminated for other reason									

[1] Participants who completed the study (Week 16) as reported on the Study Completion (STC) form.

Table 7: Summary of Disposition by Treatment Arm in Stage 1			
	Placebo	**AMC**	**Total**
Number of participants randomized	N		
Number of participants who completed Stage 1[1]	N (%)		
Number of participants re-randomized at the end of Stage 1	N (%)		
Number of early study terminations in Stage 1	N (%)		
Reasons for early study termination in Stage 1			
Participant failed to return to site and unable to contact	N (%)		
Participant withdrew consent/assent			
Participant stopped participation due to practical problems			
Participant moved from area			
Participant incarcerated			
Participant terminated due to AE/SAE			
Participant terminated for other clinical reasons			
Participant had a significant psychiatric risk			
Participant deceased			
Participant terminated due to protocol deviation			
Participant became pregnant			
Participant reports intolerable symptoms or side effects			
Participant reports use of medication that could adversely interact with study medication			
Clinical deterioration: New onset of psychiatric or medical condition			
Clinical deterioration: Worsening of pre-existing psychiatric or medical condition			
Clinical deterioration: Worsening of substance use disorder			
Clinical deterioration: Overdose			
Participant terminated for other reason			

[1] Participants who did not early terminate from the study in Weeks 1-6.

Table 8: Summary of Disposition by Treatment Arm in Stage 2					
	Re-randomized		**Not Re-randomized**		
	Placebo/ Placebo	**Placebo/ AMC**	**Placebo**	**AMC**	**Total**
Number of participants randomized	N				
Number of participants in Stage 2[1]	N				
Number of participants that completed Week 12[2]	N (%)				
Number of early study terminations in Weeks 7-12	N (%)				
Reasons for early study termination in Weeks 7-12					
Participant failed to return to site and unable to contact	N (%)				
Participant withdrew consent/assent					
Participant stopped participation due to practical problems					
Participant moved from area					
Participant incarcerated					
Participant terminated due to AE/SAE					
Participant terminated for other clinical reasons					
Participant had a significant psychiatric risk					
Participant deceased					
Participant terminated due to protocol deviation					
Participant became pregnant					
Participant reports intolerable symptoms or side effects					
Participant reports use of medication that could adversely interact with study medication					
Clinical deterioration: New onset of psychiatric or medical condition					
Clinical deterioration: Worsening of pre-existing psychiatric or medical condition					
Clinical deterioration: Worsening of substance use disorder					
Clinical deterioration: Overdose					

[1] Participants who completed Stage 1 (Weeks 1-6) and were re-randomized or were not re-randomized in Stage 2.

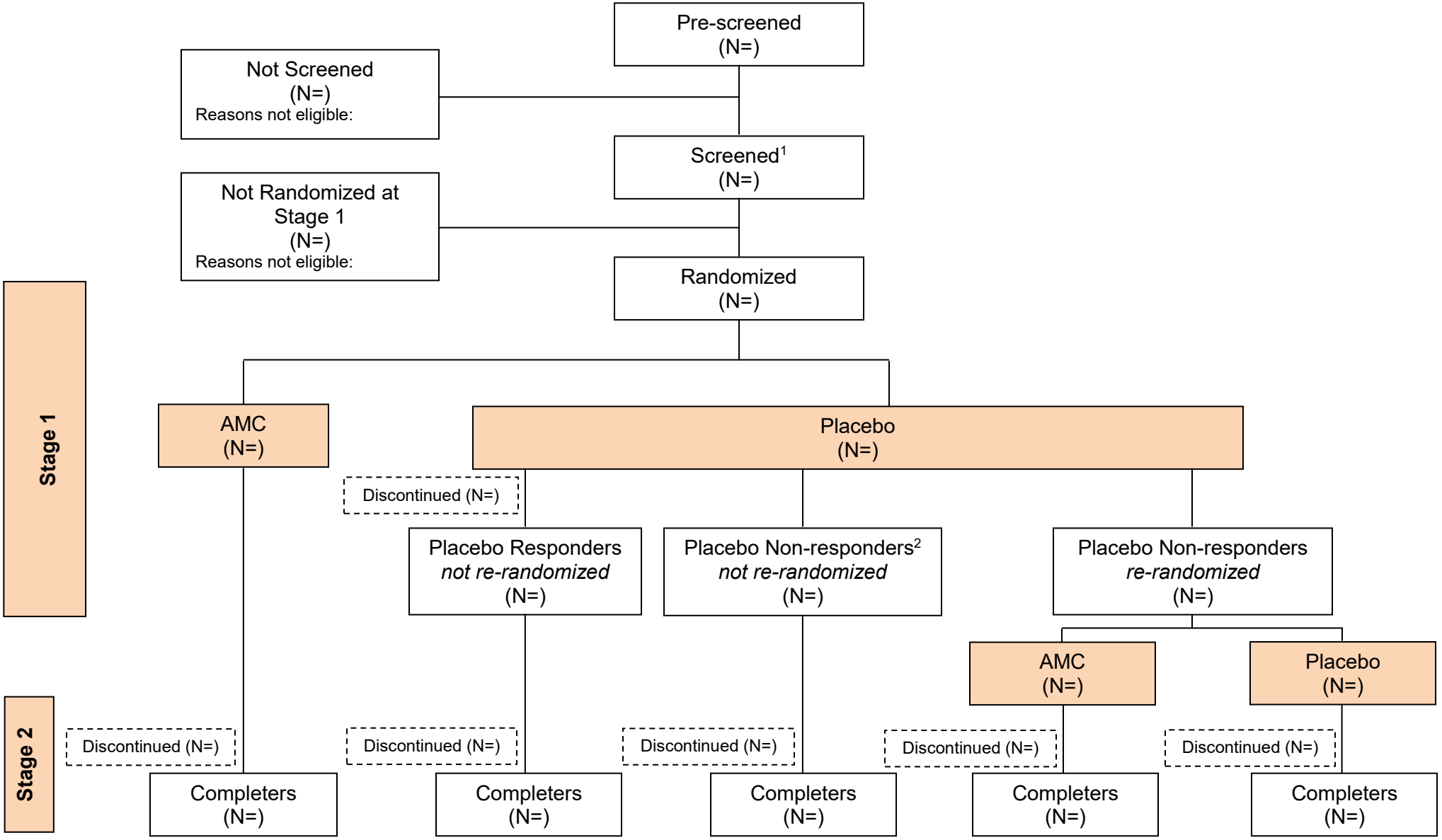
[2] Participants who did not early terminate from the study on the STC form in Weeks 7-12.

Table 9: Summary of Disposition by Treatment Arm in Follow-up Period					
	Re-randomized		**Not Re-randomized**		
	Placebo/ Placebo	**Placebo/ AMC**	**Placebo**	**AMC**	**Total**
Number of participants randomized	N				
Number of participants who entered the Follow-up Period[1]					
Number of participants who completed the study					
Number of early study terminations in Follow-up Period[2]	N (%)				
Reasons for early study termination in Follow-up Period					
Participant failed to return to site and unable to contact	N (%)				
Participant withdrew consent/assent					
Participant stopped participation due to practical problems					
Participant moved from area					
Participant incarcerated					
Participant terminated due to AE/SAE					
Participant terminated for other clinical reasons					
Participant had a significant psychiatric risk					
Participant deceased					
Participant terminated due to protocol deviation					
Participant became pregnant					
Participant reports intolerable symptoms or side effects					
Participant reports use of medication that could adversely interact with study medication					
Clinical deterioration: New onset of psychiatric or medical condition					
Clinical deterioration: Worsening of pre-existing psychiatric or medical condition					
Clinical deterioration: Worsening of substance use disorder					
Clinical deterioration: Overdose					
Participant terminated for other reason					

[1] Participants who completed the treatment period (Week 12).

[2] Participants who early terminated from the study in Weeks 13-16

Figure 6: CONSORT Flow Diagram



[1] X participants were re-screened.
[2] Placebo non-responders who did not attend a visit during the window for re-randomization were not re-randomized.

Table 10: Summary of Attendance at Treatment Period Visits by Treatment Arm in Stage 1			
Visit	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Visit 0101	N (%)		
Visit 0102			
Visit 0201			
Visit 0202			
Visit 0301			
Visit 0302			
Visit 0401			
Visit 0402			
Visit 0501			
Visit 0502			
Visit 0601			
Visit 0602			
Overall			

Table 11: Summary of Attendance at Treatment Period Visits by Treatment Arm in Stage 2					
	Re-randomized[1]		Not Re-randomized		
Visit	Placebo/ Placebo (N=)	Placebo/ AMC (N=)	Placebo (N=)	AMC (N=)	Total (N=)
Visit 0701	N (%)				
Visit 0702					
Visit 0801					
Visit 0802					
Visit 0901					
Visit 0902					
Visit 1001					
Visit 1002					
Visit 1101					
Visit 1102					
Visit 1201					
Visit 1202					
Overall					

[1] Participants may be re-randomized at Visit 0701, 0702, or 0801.

Table 12: Summary of Attendance at Follow-up Visits by Treatment Arm					
	Re-randomized		Not Re-randomized		
Visit	Placebo/ Placebo (N=)	Placebo/ AMC (N=)	Placebo (N=)	AMC (N=)	Total (N=)
Visit 1301	N (%)				
Visit 1601					
Overall					

Table 13: Summary of Missed Visits by Treatment Arm in Stage 1			
	Placebo (N=)	**AMC (N=)**	**Total (N=)**
Number of expected visits in Stage 1[1]	N		
Number of missed visits in Stage 1 due to early study termination	N (%)		
Number of missed visits during active Stage 1 participation	N (%)		
Number of participants with at least one missed visit during active Stage 1 participation	N (%)		
Average number of missed visits in Stage 1 per participant	X.X		
Reason for missed visit			
Participant failed to return to site and unable to contact	N (%)		
Participant unable to attend visit			
Participant withdrew consent			
Other			
Site closed			
Participant incarcerated			
Participant on vacation			
Participant in hospital, in-patient, or residential treatment			
Participant illness			
Participant moved from area			
Participant deceased			

[1] Two visits per week are expected per participant in Weeks 1-6.

Table 14: Summary of Missed Visits by Treatment Arm in Stage 2					
	Re-randomized		**Not Re-randomized**		
	Placebo/ Placebo (N=)	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Number of expected visits in Stage 2[1]	N				
Number of missed visits in Stage 2 due to early study termination	N (%)				
Number of missed visits during active Stage 2 participation	N (%)				
Number of participants with at least one missed visit during active Stage 2 participation	N (%)				
Average number of missed visits in Stage 2 per participant	X.X				
Reason for missed visit					
Participant failed to return to site and unable to contact	N (%)				
Participant unable to attend visit					
Participant withdrew consent					
Other					
Site closed					
Participant incarcerated					
Participant on vacation					
Participant in hospital, in-patient, or residential treatment					
Participant illness					
Participant moved from area					
Participant deceased					

[1] Two visits per week are expected per participant in Weeks 7-12.

Table 15: Summary of Missed Visits by Treatment Arm in Follow-up Period					
	Re-randomized		**Not Re-randomized**		
	Placebo/ Placebo (N=)	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Number of expected visits in follow-up period[1]	N				
Number of missed visits in follow-up period due to early study termination	N (%)				
Number of missed visits during active follow-up period participation	N (%)				
Number of participants with at least one missed visit during active follow-up period participation	N (%)				
Average number of missed visits in follow-up period per participant	X.X				
Reason for missed visit					
Participant failed to return to site and unable to contact	N (%)				
Participant unable to attend visit					
Participant withdrew consent					
Other					
Site closed					
Participant incarcerated					
Participant on vacation					
Participant in hospital, in-patient, or residential treatment					
Participant illness					
Participant moved from area					
Participant deceased					

[1] Two visits total are expected per participant in the follow-up period in Weeks 13-16.

Table 16: Summary of Baseline Characteristics by Site									
Characteristic	**SC BHSPC (N=)**	**WS CODA, Inc. (N=)**	**GNY SURC - Columbia (N=)**	**NS Hennepin Healthcare (N=)**	**WS SURU - SFDPH (N=)**	**TX UCLA CBAM (N=)**	**TX UT Health CNRA (N=)**	**TX UTSW (N=)**	**Total (N=)**
Sex									
Missing	N (%)								
Male									
Female									
Participant chose not to answer									
Age (Mean (SD))	XX (X.X)								
Age									
Missing	N (%)								
< 18									
18 - < 25									
25 - < 35									
35 - < 45									
45 - < 55									
55 - < 65									
65 - < 75									
75+									
Ethnicity									
Missing									
Not Hispanic or Latino	N (%)								
Hispanic or Latino									
Participant chose not to answer									

Table 16: Summary of Baseline Characteristics by Site									
Characteristic	**SC BHSPC (N=)**	**WS CODA, Inc. (N=)**	**GNY SURC - Columbia (N=)**	**NS Hennepin Healthcare (N=)**	**WS SURU - SFDPH (N=)**	**TX UCLA CBAM (N=)**	**TX UT Health CNRA (N=)**	**TX UTSW (N=)**	**Total (N=)**
Race									
Missing	N (%)								
American Indian or Alaska Native									
Asian									
Black or African American									
Native Hawaiian or Pacific Islander									
White									
Other									
Multiracial									
Unknown									
Participant chose not to answer									
Education completed									
Missing	N (%)								
Less than high school diploma									
High school graduate									
GED or equivalent									
Some college, no degree									
Associate's degree: occupational, technical, or vocational program									
Associate's degree: academic program									
Bachelor's degree									
Master's degree									

Table 16: Summary of Baseline Characteristics by Site									
Characteristic	**SC BHSPC (N=)**	**WS CODA, Inc. (N=)**	**GNY SURC - Columbia (N=)**	**NS Hennepin Healthcare (N=)**	**WS SURU - SFDPH (N=)**	**TX UCLA CBAM (N=)**	**TX UT Health CNRA (N=)**	**TX UTSW (N=)**	**Total (N=)**
Professional school degree									
Doctoral degree									
Don't know									
Refused									
Marital status									
Missing	N (%)								
Married									
Widowed									
Divorced									
Separated									
Never married									
Living with partner									
Refused									
Don't know									
Employment									
Missing	N (%)								
Working now									
Only temporarily laid off, sick leave, or maternity leave									
Looking for work, unemployed									
Retired									
Disabled permanently or temporarily									

Table 16: Summary of Baseline Characteristics by Site									
Characteristic	**SC BHSPC (N=)**	**WS CODA, Inc. (N=)**	**GNY SURC - Columbia (N=)**	**NS Hennepin Healthcare (N=)**	**WS SURU - SFDPH (N=)**	**TX UCLA CBAM (N=)**	**TX UT Health CNRA (N=)**	**TX UTSW (N=)**	**Total (N=)**
Keeping house									
Student									
Other									
Number of days of self-reported methamphetamine use in 30 days prior to informed consent									
N									
Mean									
SD									
Min									
25th Percentile									
Median									
75th Percentile									
Max									

Table 17: Summary of Baseline Characteristics by Stage and Treatment Arm						
	Stage 1		Stage 2			
			Re-randomized		Not Re-randomized	
Characteristic	**Placebo (N=)**	**AMC (N=)**	**Placebo/ Placebo (N=)**	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**
Sex						
Missing	N (%)					
Male						
Female						
Participant chose not to answer						
Age (Mean (SD))	XX (X.X)					
Age						
< 18	N (%)					
18 - < 25						
25 - < 35						
35 - < 45						
45 - < 55						
55 - < 65						
65 - < 75						
75+						
Ethnicity						
Missing	N (%)					
Not Hispanic or Latino						
Hispanic or Latino						

Table 17: Summary of Baseline Characteristics by Stage and Treatment Arm						
	Stage 1		Stage 2			
			Re-randomized		Not Re-randomized	
Characteristic	**Placebo (N=)**	**AMC (N=)**	**Placebo/ Placebo (N=)**	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**
Unknown						
Participant chose not to answer						
Race						
Missing	N (%)					
American Indian or Alaska Native						
Asian						
Black or African American						
Native Hawaiian or Pacific Islander						
White						
Other						
Multiracial						
Unknown						
Participant chose not to answer						
Education completed						
Missing	N (%)					
Less than high school diploma						
High school graduate						
GED or equivalent						
Some college, no degree						

Table 17: Summary of Baseline Characteristics by Stage and Treatment Arm						
	Stage 1		Stage 2			
			Re-randomized		Not Re-randomized	
Characteristic	**Placebo (N=)**	**AMC (N=)**	**Placebo/ Placebo (N=)**	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**
Associate's degree: occupational, technical, or vocational program						
Associate's degree: academic program						
Bachelor's degree						
Master's degree						
Professional school degree						
Doctoral degree						
Marital status						
Missing	N (%)					
Married						
Widowed						
Divorced						
Separated						
Never married						
Living with partner						
Refused						
Don’t know						
Employment						
Missing	N (%)					
Working now						

Table 17: Summary of Baseline Characteristics by Stage and Treatment Arm						
	Stage 1		Stage 2			
			Re-randomized		Not Re-randomized	
Characteristic	**Placebo (N=)**	**AMC (N=)**	**Placebo/ Placebo (N=)**	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**
Only temporarily laid off, sick leave, or maternity leave						
Looking for work, unemployed						
Retired						
Disabled permanently or temporarily						
Keeping house						
Student						
Other						
Number of days of self-reported methamphetamine use in 30 days prior to informed consent						
N						
Mean						
SD						
Min						
25th Percentile						
Median						
75th Percentile						
Max						

Table 18: Summary of Concomitant Medications by Treatment Arm[1]					
	Re-randomized		**Not Re-randomized**		
Anatomical Therapeutic Chemical Level 1/ Anatomical Therapeutic Chemical Level 2	**Placebo/ Placebo (N=)**	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Participants with at least one concomitant medication					
Gastrointestinal	**N (%)**				
Acid related	N (%)				
Antiemetics					
Constipation					
Antidiarrheal					
Diabetes					
Vitamins					
Mineral					
Other gastrointestinal					
Blood and Blood Forming Organs	**N (%)**				
Aspirin/coumadin/heparin	N (%)				
Anti-anemic					
Blood products/iv fluids					
Other blood and blood forming organs					
Cardiovascular System	**N (%)**				
Antihypertensives	N (%)				
Diuretics					
Beta blocking					
Calcium channel					
Lipid modifying agents					

Table 18: Summary of Concomitant Medications by Treatment Arm[1]					
	Re-randomized		Not Re-randomized		
Anatomical Therapeutic Chemical Level 1/ Anatomical Therapeutic Chemical Level 2	**Placebo/ Placebo (N=)**	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Other cardiovascular system					
All Skin Creams	**N (%)**				
All skin creams	N (%)				
Contraceptives/ED/Sex Hormones	**N (%)**				
Contraceptives/ED/sex hormones	N (%)				
Steroids/thyroid hormones	**N (%)**				
Steroids/thyroid hormones	N (%)				
Antibacterial/Antiviral/Antifungal/TB/Vaccines	**N (%)**				
Antibacterial/antiviral/antifungal/TB/vaccines	N (%)				
Musculoskeletal System	**N (%)**				
Anti-inflammatory and antirheumatic	N (%)				
Muscle relaxants					
Antigout					
Other musculoskeletal system					
Nervous System	**N (%)**				
Analgesics including antipyretics	N (%)				
Antiepileptics					
Anxiety/depression/sleep					
Other nervous system					
Respiratory System	**N (%)**				
Nasal	N (%)				

Table 18: Summary of Concomitant Medications by Treatment Arm[1]					
	Re-randomized		Not Re-randomized		
Anatomical Therapeutic Chemical Level 1/ Anatomical Therapeutic Chemical Level 2	**Placebo/ Placebo (N=)**	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Throat					
Obstructive airway					
Eye and Ear Drops	**N (%)**				
Eye and ear drops	N (%)				
Various	**N (%)**				
Allergens	N (%)				
All other therapeutic products					
Diagnostic agents					
General nutrients					
All other non-therapeutic products					
Contrast media					
Diagnostic radiopharmaceuticals					
Therapeutic radiopharmaceuticals					
Other	**N (%)**				

[1] Includes all medications taken during the safety window, which begins at the first dose date of either oral or injectable study medication, whichever comes first, and ends either 7 days after the last oral medication dose or 28 days after the last injectable medication, whichever comes last.

Table 19: Summary of Early Medication Terminations by Site									
	SC BHSPC (N=)	**WS CODA, Inc. (N=)**	**GNY SURC - Columbia (N=)**	**NS Hennepin Healthcare (N=)**	**WS SURU - SFDPH (N=)**	**TX UCLA CBAM (N=)**	**TX UT Health CNRA (N=)**	**TX UTSW (N=)**	**Total (N=)**
Number of early study medication terminations[1]	N (%)								
Number of participants who early terminated oral and injectable study medication	N (%)								
Number of early oral study medication terminations	N (%)								
Reason for early oral study medication termination									
Participant failed to return to site and unable to contact	N (%)								
Participant feels treatment no longer necessary, cured									
Participant feels treatment no longer necessary, not working									
Participant interested in seeking alternate treatment									
Contraindicated concomitant medication									
Clinical deterioration: New onset of psychiatric or medical condition									
Clinical deterioration: Worsening of pre-existing psychiatric or medical condition									
Clinical deterioration: Worsening of substance use disorder									
Clinical deterioration: Overdose									
Participant became pregnant									
Participant withdrew consent/assent									
Participant reports intolerable symptoms or side effects									
Other									
Number of early injectable study medication terminations	N (%)								

Table 19: Summary of Early Medication Terminations by Site									
	SC BHSPC (N=)	**WS CODA, Inc. (N=)**	**GNY SURC - Columbia (N=)**	**NS Hennepin Healthcare (N=)**	**WS SURU - SFDPH (N=)**	**TX UCLA CBAM (N=)**	**TX UT Health CNRA (N=)**	**TX UTSW (N=)**	**Total (N=)**
Reason for early injectable medication termination									
Participant failed to return to site and unable to contact	N (%)								
Participant feels treatment no longer necessary, cured									
Participant feels treatment no longer necessary, not working									
Participant interested in seeking alternate treatment									
Contraindicated concomitant medication									
Clinical deterioration: New onset of psychiatric or medical condition									
Clinical deterioration: Worsening of pre-existing psychiatric or medical condition									
Clinical deterioration: Worsening of substance use disorder									
Clinical deterioration: Overdose									
Participant became pregnant									
Participant withdrew consent/assent									
Participant reports intolerable symptoms or side effects									
Other									

[1] Participants who early terminated either oral or injectable study medication.

Table 20: Summary of Early Medication Terminations by Treatment Arm in Stage 1			
	Placebo (N=)	**AMC (N=)**	**Total (N=)**
Number of early study medication terminations in Stage 1[1]	N (%)		
Number of participants who early terminated oral and injectable study medication in Stage 1	N (%)		
Number of early oral study medication terminations in Stage 1	N (%)		
Reason for early oral study medication termination			
Participant failed to return to site and unable to contact	N (%)		
Participant feels treatment no longer necessary, cured			
Participant feels treatment no longer necessary, not working			
Participant interested in seeking alternate treatment			
Contraindicated concomitant medication			
Clinical deterioration: New onset of psychiatric or medical condition			
Clinical deterioration: Worsening of pre-existing psychiatric or medical condition			
Clinical deterioration: Worsening of substance use disorder			
Clinical deterioration: Overdose			
Participant became pregnant			
Participant withdrew consent/assent			
Participant reports intolerable symptoms or side effects			
Other			
Number of early injectable study medication terminations	N (%)		
Reason for early injectable study medication termination			
Participant failed to return to site and unable to contact	N (%)		
Participant feels treatment no longer necessary, cured			
Participant feels treatment no longer necessary, not working			
Participant interested in seeking alternate treatment			
Contraindicated concomitant medication			
Clinical deterioration: New onset of psychiatric or medical condition			
Clinical deterioration: Worsening of pre-existing psychiatric or medical condition			
Clinical deterioration: Worsening of substance use disorder			
Clinical deterioration: Overdose			
Participant became pregnant			
Participant withdrew consent/assent			
Participant reports intolerable symptoms or side effects			
Other			

[1] Participants who early terminated either oral study medication before the date of re-randomization or Day 43 for non-re-randomized participants, or early terminated injectable study medication and received no injections or only injection #1.

Table 21: Summary of Early Medication Terminations by Treatment Arm in Stage 2					
	Re-randomized		Not Re-randomized		
	Placebo/ Placebo (N=)	Placebo/ AMC (N=)	Placebo (N=)	AMC (N=)	Total (N=)
Number of early study medication terminations in Stage 2[1]	N (%)				
Number of participants who early terminated oral and injectable study medication in Stage 2	N (%)				
Number of early oral study medication terminations in Stage 2	N (%)				
Reason for early oral study medication termination					
Participant failed to return to site and unable to contact	N (%)				
Participant feels treatment no longer necessary, cured					
Participant feels treatment no longer necessary, not working					
Participant interested in seeking alternate treatment					
Contraindicated concomitant medication					
Clinical deterioration: New onset of psychiatric or medical condition					
Clinical deterioration: Worsening of pre-existing psychiatric or medical condition					
Clinical deterioration: Worsening of substance use disorder					
Clinical deterioration: Overdose					
Participant became pregnant					
Participant withdrew consent/assent					
Participant reports intolerable symptoms or side effects					
Other					
Number of early injectable study medication terminations	N (%)				
Reason for early injectable study medication termination					
Participant failed to return to site and unable to contact	N (%)				
Participant feels treatment no longer necessary, cured					
Participant feels treatment no longer necessary, not working					
Participant interested in seeking alternate treatment					
Contraindicated concomitant medication					
Clinical deterioration: New onset of psychiatric or medical condition					
Clinical deterioration: Worsening of pre-existing psychiatric or medical condition					
Clinical deterioration: Worsening of substance use disorder					
Clinical deterioration: Overdose					
Participant became pregnant					
Participant withdrew consent/assent					
Participant reports intolerable symptoms or side effects					
Other					

[1] Participants who early terminated either oral study medication on or after the date of re-randomization or Day 43 for non-re-randomized participants, or early terminated injectable study medication after last receiving injection #2 or #3.

Table 22: Summary of Treatment Exposure by Site								
		Tablets[1]			Injections[2]			Overall Treatment Exposure[2]
Site	**Participants Randomized**	**Taken**	**Expected**	**%**	**Administered**	**Expected**	**%**	**%**
SC BHSPC	N	N	N	%	N	N	%	%
WS CODA, Inc.								
GNY SURC - Columbia								
NS Hennepin Healthcare								
WS SURU - SFDPH								
TX UCLA CBAM								
TX UT Health CNRA								
TX UTSW								
Total								

[1] Three tablets per day are expected during the 12-week treatment period.

[2] Four injections are expected during the 12-week treatment period.

[3] Overall treatment exposure percentage is an average of the percentage for tablets and percentage for injections. This percentage represents medication adherence across all treatment groups (i.e., Placebo, AMC, Placebo/Placebo, placebo/AMC).

Table 23: Summary of Treatment Exposure by Site, Stage and Treatment Arm								
					Stage 2			
			Stage 1		Re-randomized		Not Re-randomized	
Site	**Treatment Exposure**		**Placebo (N=)**	**AMC (N=)**	**Placebo/ Placebo (N=)**	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**
SC BHSPC	Tablets[1]	Number Taken	N					
		Number Expected	N					
		Percent Taken	%					
	Injections[2]	Number Administered	N					
		Number Expected	N					
		Percent Administered	%					
	Overall[3]	Treatment Exposure	%					
WS CODA, Inc.	Tablets[1]	Number Taken						
		Number Expected						
		Percent Taken						
	Injections[2]	Number Administered						
		Number Expected						
		Percent Administered						
	Overall[3]	Treatment Exposure						
GNY SURC - Columbia	Tablets[1]	Number Taken						
		Number Expected						
		Percent Taken						
	Injections[2]	Number Administered						
		Number Expected						
		Percent Administered						
	Overall[3]	Treatment Exposure						
NS Hennepin Healthcare	Tablets[1]	Number Taken						
		Number Expected						
		Percent Taken						
	Injections[2]	Number Administered						
		Number Expected						
		Percent Administered						
	Overall[3]	Treatment Exposure						

Table 23: Summary of Treatment Exposure by Site, Stage and Treatment Arm								
					Stage 2			
			Stage 1		Re-randomized		Not Re-randomized	
Site	Treatment Exposure		Placebo (N=)	AMC (N=)	Placebo/ Placebo (N=)	Placebo/ AMC (N=)	Placebo (N=)	AMC (N=)
WS SURU - SFDPH	Tablets[1]	Number Taken						
		Number Expected						
		Percent Taken						
	Injections[2]	Number Administered						
		Number Expected						
		Percent Administered						
	Overall[3]	Treatment Exposure						
TX UCLA CBAM	Tablets[1]	Number Taken						
		Number Expected						
		Percent Taken						
	Injections[2]	Number Administered						
		Number Expected						
		Percent Administered						
	Overall[3]	Treatment Exposure						
TX UT Health CNRA	Tablets[1]	Number Taken						
		Number Expected						
		Percent Taken						
	Injections[2]	Number Administered						
		Number Expected						
		Percent Administered						
	Overall[3]	Treatment Exposure						
Total	Tablets[1]	Number Taken						
		Number Expected						
		Percent Taken						
	Injections[2]	Number Administered						
		Number Expected						
		Percent Administered						
	Overall[3]	Treatment Exposure						

[1] Three tablets per day are expected during Stage 1 (Weeks 1-6) and Stage 2 (Weeks 7-12).

[2] Two injections are expected in each stage.

[3] Overall treatment exposure percentage is an average of the percentage for tablets and percentage for injections.

Table 24: Summary of Injections by Site					
Site	**Participants Randomized**	**Participants Who Received Injection #1**	**Participants Who Received Injection #2**	**Participants Who Received Injection #3**	**Participants Who Received Injection #4**
SC BHSPC	N	N (%)	N (%)	N (%)	N (%)
WS CODA, Inc.					
GNY SURC - Columbia					
NS Hennepin Healthcare					
WS SURU - SFDPH					
TX UCLA CBAM					
TX UT Health CNRA					
TX UTSW					
Total					

Table 25: Summary of Injections by Stage and Treatment Arm						
			Stage 2			
	Stage 1		**Re-randomized**		**Not Re-randomized**	
	Placebo (N=)	**AMC (N=)**	**Placebo/ Placebo (N=)**	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**
Participants who received injection #1	N (%)					
Participants who received injection #2	N (%)					
Participants who received injection #3			N (%)			
Participants who received injection #4			N (%)			

Table 26: Summary of Oral Medication Blood Levels by Stage AMC Participants				
	Stage 1	**Stage 2**		
		Re-randomized	**Not Re-randomized**	
	AMC (N=)	**Placebo/ AMC (N=)**	**AMC (N=)**	**Total (N=)**
Bupropion adherence[1]				
Visit 0401	n/N (%)			
Visit 0701				
Visit 1001				
Visit 1201				
Hydroxybupropion adherence[2]				
Visit 0401	n/N (%)			
Visit 0701				
Visit 1001				
Visit 1201				

[1] A participant is considered adherent if bupropion blood level is greater than 0.500 ng/mL.

[2] A participant is considered adherent if hydroxybupropion blood level is greater than 1.00 ng/mL.

Table 27: Summary of Primary Outcome Availability by Stage and Treatment Arm ITT Population					
			Re-randomized		
	Stage 1 (Weeks 5-6)		**Stage 2 (Weeks 11-12)**		
	Placebo (N=)	**AMC (N=)**	**Placebo/ Placebo (N=)**	**Placebo/ AMC (N=)**	**Total (N=)**
Number of UDS methamphetamine results collected[1]	N				
Number of UDS expected[2]	N				
Percentage of expected UDS methamphetamine results collected	%				

[1] Number of UDS with methamphetamine results collected in Weeks 5 and 6 in Stage 1 and Weeks 11 and 12 in Stage 2.

[2] Two UDS are expected per participant each week.

**Table 28: Summary of Primary Outcome Analysis by Stage and Treatment Arm
ITT Population**

Design Parameters		Stage 1				Stage 2			Results					
Random-ization fraction *a*	Weight *w*	N	Placebo Responder Rate *q1*	AMC Responder Rate *p1*	Rate of Continuation into Stage 2 among Placebo Non-responders *s*	N	Placebo Responder Rate *q2*	AMC Responder Rate *p2*	Treatment Effect *h*	Standard Error of *h*	Wald Type Test Statistic Z	p-value[1]	95% Lower Confidence Limit	Number Needed to Treat (1/*h*)
0.37	0.43	N	X/X (X.X%)	X/X (X.X%)	X.XXXX	N	X/X (X.X%)	X/X (X.X%)	X.XXXX	X.XXXX	X.XXXX	X.XXXX	X.XXXX	XX

[1] The p-value was calculated adjusting for interim efficacy analysis.

**Figure 7: Methamphetamine Negative UDS Results by Stage and Treatment Arm
ITT Population**

**Table 29: Summary of Primary Outcome Sensitivity Analyses by Stage and Treatment Arm
ITT Population**

		Stage 1			Stage 2			Results	
Method	**Results**	**Number Randomized**	**Placebo Responder Rate *q1***	**AMC Responder Rate *p1***	**Number Re-randomized**	**Placebo Responder Rate *q2***	**AMC Responder Rate *p2***	**Treatment Effect *h***	**Standard Error of *h***
Protocol defined primary outcome	Primary outcome	N	X/X (X.X%)	X/X (X.X%)	N	X/X (X.X%)	X/X (X.X%)	X.XXXX	X.XXXX
Imputation of missing UDS	Missing UDS imputed as negative								
	Missing UDS imputed as positive								
	Complete cases[1]								
Using weight *w*=0.5	Adjusted primary outcome								

[1] Includes participants with all four UDS collected in the stage.

**Table 30: Summary of Primary Outcome Availability by Stage and Site
ITT Population**

	Stage 1 (Weeks 5-6)				Re-randomized Stage 2 (Weeks 11-12)				
Site	**N**	**Number of UDS methamphetamine results collected**	**Number of UDS expected[1]**	**Percentage of expected UDS methamphetamine results collected**	**N**	**Number of UDS methamphetamine results collected**	**Number of UDS expected[1]**	**Percentage of expected UDS methamphetamine results collected**	**Total**
SC BHSPC	XX	XXX	XXX	XX.X%	XX	XXX	XXX	XX.X%	XX.X%
WS CODA, Inc.									
GNY SURC - Columbia									
NS Hennepin Healthcare									
WS SURU - SFDPH									
TX UCLA CBAM									
TX UT Health CNRA									
TX UTSW									

[1] Two UDS are expected per participant in Weeks 5, 6, 11, and 12.

Table 31: Summary of Primary Outcome by Site, Stage, and Treatment Arm
ITT Population

	Stage 1			Stage 2			Results[1]		
Site	**Number Randomized**	**Placebo Responder Rate *q1***	**AMC Responder Rate *p1***	**Number Re-randomized**	**Placebo Responder Rate *q2***	**AMC Responder Rate *p2***	**Treatment Effect *h***	**Standard Error of *h***	**p-value**
SC BHSPC	N	X/X (X.X%)	X/X (X.X%)	N	X/X (X.X%)	X/X (X.X%)	X.XXXX	X.XXXX	X.XXXX
WS CODA, Inc.									
GNY SURC - Columbia									
NS Hennepin Healthcare									
WS SURU - SFDPH									
TX UCLA CBAM									
TX UT Health CNRA									
TX UTSW									

[1] Results are obtained from the generalized linear mixed effects model.

Table 32: Summary of Primary Outcome by Sex, Stage, and Treatment Arm
ITT Population

	Stage 1			Stage 2			Results[1]		
Subgroup	**Number Randomized**	**Placebo Responder Rate *q1***	**AMC Responder Rate *p1***	**Number Re-randomized**	**Placebo Responder Rate *q2***	**AMC Responder Rate *p2***	**Treatment Effect *h***	**Standard Error of *h***	**p-value**
Male	N	X/X (X.X%)	X/X (X.X%)	N	X/X (X.X%)	X/X (X.X%)	X.XXXX	X.XXXX	X.XXXX
Female	N	X/X (X.X%)	X/X (X.X%)	N	X/X (X.X%)	X/X (X.X%)	X.XXXX	X.XXXX	

[1] Results are obtained from a generalized linear mixed effects model.

Table 33: Summary of Primary Outcome by Race, Stage, and Treatment Arm
ITT Population

	Stage 1			Stage 2			Results[1]		
Subgroup	**Number Randomized**	**Placebo Responder Rate *q1***	**AMC Responder Rate *p1***	**Number Re-randomized**	**Placebo Responder Rate *q2***	**AMC Responder Rate *p2***	**Treatment Effect *h***	**Standard Error of *h***	**p-value**
Black or African American	N	X/X (X.X%)	X/X (X.X%)	N	X/X (X.X%)	X/X (X.X%)	X.XXXX	X.XXXX	X.XXXX
White	N	X/X (X.X%)	X/X (X.X%)	N	X/X (X.X%)	X/X (X.X%)	X.XXXX	X.XXXX	
Other[2]	N	X/X (X.X%)	X/X (X.X%)	N	X/X (X.X%)	X/X (X.X%)	X.XXXX	X.XXXX	

[1] Results are obtained from a generalized linear mixed effects model.

[2] Includes American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, Multiracial, Other, Don't Know, and Refused to Answer.

Table 34: Summary of Primary Outcome by Ethnicity, Stage, and Treatment Arm
ITT Population

	Stage 1			Stage 2			Results[1]		
Subgroup	**Number Randomized**	**Placebo Responder Rate *q1***	**AMC Responder Rate *p1***	**Number Re-randomized**	**Placebo Responder Rate *q2***	**AMC Responder Rate *p2***	**Treatment Effect *h***	**Standard Error of *h***	**p-value**
Hispanic or Latino	N	X/X (X.X%)	X/X (X.X%)	N	X/X (X.X%)	X/X (X.X%)	X.XXXX	X.XXXX	X.XXXX
Not Hispanic or Latino/Other[2]	N	X/X (X.X%)	X/X (X.X%)	N	X/X (X.X%)	X/X (X.X%)	X.XXXX	X.XXXX	

[1] Results are obtained from a generalized linear mixed effects model.

[2] Includes Not Hispanic or Latino, Don't Know, and Refused to Answer.

Table 35: Summary of Primary Outcome by Age, Stage, and Treatment Arm
ITT Population

	Stage 1			Stage 2			Results[1]		
Subgroup	**Number Randomized**	**Placebo Responder Rate *q1***	**AMC Responder Rate *p1***	**Number Re-randomized**	**Placebo Responder Rate *q2***	**AMC Responder Rate *p2***	**Treatment Effect *h***	**Standard Error of *h***	**p-value**
≤ 40 years	N	X/X (X.X%)	X/X (X.X%)	N	X/X (X.X%)	X/X (X.X%)	X.XXXX	X.XXXX	X.XXXX
> 40 years	N	X/X (X.X%)	X/X (X.X%)	N	X/X (X.X%)	X/X (X.X%)	X.XXXX	X.XXXX	

[1] Results are obtained from a generalized linear mixed effects model.

Table 36: Primary Outcome Covariate Adjusted Analysis Results[1]
ITT Population

Model Results	**Treatment Effect *h***	**Standard Error of *h***	**p-value**
Treatment Effect	X.XXXX	X.XXXX	**X.XXXX**
Other Covariates in the Model			
Site			X.XXXX
Age at onset of methamphetamine use			X.XXXX
Baseline number of methamphetamine use days self-reported			X.XXXX
Baseline IV methamphetamine use self-reported			X.XXXX
Number of DSM-5 criteria met during screening			X.XXXX
Baseline number of days of cigarette or e-cigarette use self-reported			X.XXXX
Baseline Treatment Effectiveness Assessment Score			X.XXXX
Baseline average Visual Analog Craving Scale Score			X.XXXX

[1] Results are obtained from a generalized linear mixed effects model.

Table 37: Summary of UDS Availability[1] by Stage and Treatment Arm Randomized Population

			Stage 2			
	Stage 1		Re-randomized		Not Re-randomized	
Weeks	Placebo (N=)	AMC (N=)	Placebo/ Placebo (N=)	Placebo/ AMC (N=)	Placebo (N=)	AMC (N=)
1-2	n/N (%)					
3-4						
5-6[2]						
7-8						
9-10						
11-12[2]						
13[3]						
16[3]						

[1] UDS Availability is presented as number of collected UDS over number of expected UDS. Two UDS per participant are expected each week, with the exception of one UDS expected during Week 1. A UDS is considered collected if the UDS has a methamphetamine result.

[2] Weeks 5-6 and 11-12 are the primary outcome evaluation period.

[3] Week 13 and Week 16 occur during the Follow-up Period. One UDS per participant per visit is expected at Week 13 and at Week 16.

Table 38: Summary of Methamphetamine Negative UDS Results by Treatment Arm in Stage 1 Randomized Population			
Visit	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
0101	n/N (%)		
0102			
0201			
0202			
0301			
0302			
0401			
0402			
0501			
0502			
0601			
0602			

Table 39: Summary of Methamphetamine Negative UDS Results by Treatment Arm in Stage 2 Randomized Population

	Re-randomized		Not Re-randomized		
Visit	**Placebo/ Placebo (N=)**	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
0701	n/N (%)				
0702					
0801					
0802					
0901					
0902					
1001					
1002					
1101					
1102					
1201					
1202					

Table 40: Summary of Methamphetamine Negative UDS Results by Treatment Arm in Follow-up Period Randomized Population					
	Re-randomized		Not Re-randomized		
Visit	Placebo/ Placebo (N=)	Placebo/ AMC (N=)	Placebo (N=)	AMC (N=)	Total (N=)
1301	n/N (%)				
1601					

**Table 41: Summary of Primary Outcome Sensitivity Analyses by Stage and Treatment Arm
Randomized Population**

		Stage 1			Stage 2					
					Re-randomized			Not Re-randomized		
Method	**Results**	**N**	**Placebo Responder Rate *q1***	**AMC Responder Rate *p1***	**N**	**Placebo/ Placebo Responder Rate *q2***	**Placebo/ AMC Responder Rate *p2***	**N**	**Placebo Responder Rate**	**AMC Responder Rate**
Protocol defined primary outcome	Primary outcome	N	X/X (X.X%)	X/X (X.X%)	N	X/X (X.X%)	X/X (X.X%)	N	X/X (X.X%)	X/X (X.X%)
Imputation of missing UDS	Missing UDS imputed as negative									
	Missing UDS imputed as positive									
	Complete cases[1]									

[1] Includes participants with all four UDS collected in the stage.

Figure 8: Methamphetamine Negative UDS Results by Stage and Treatment Arm Randomized Population

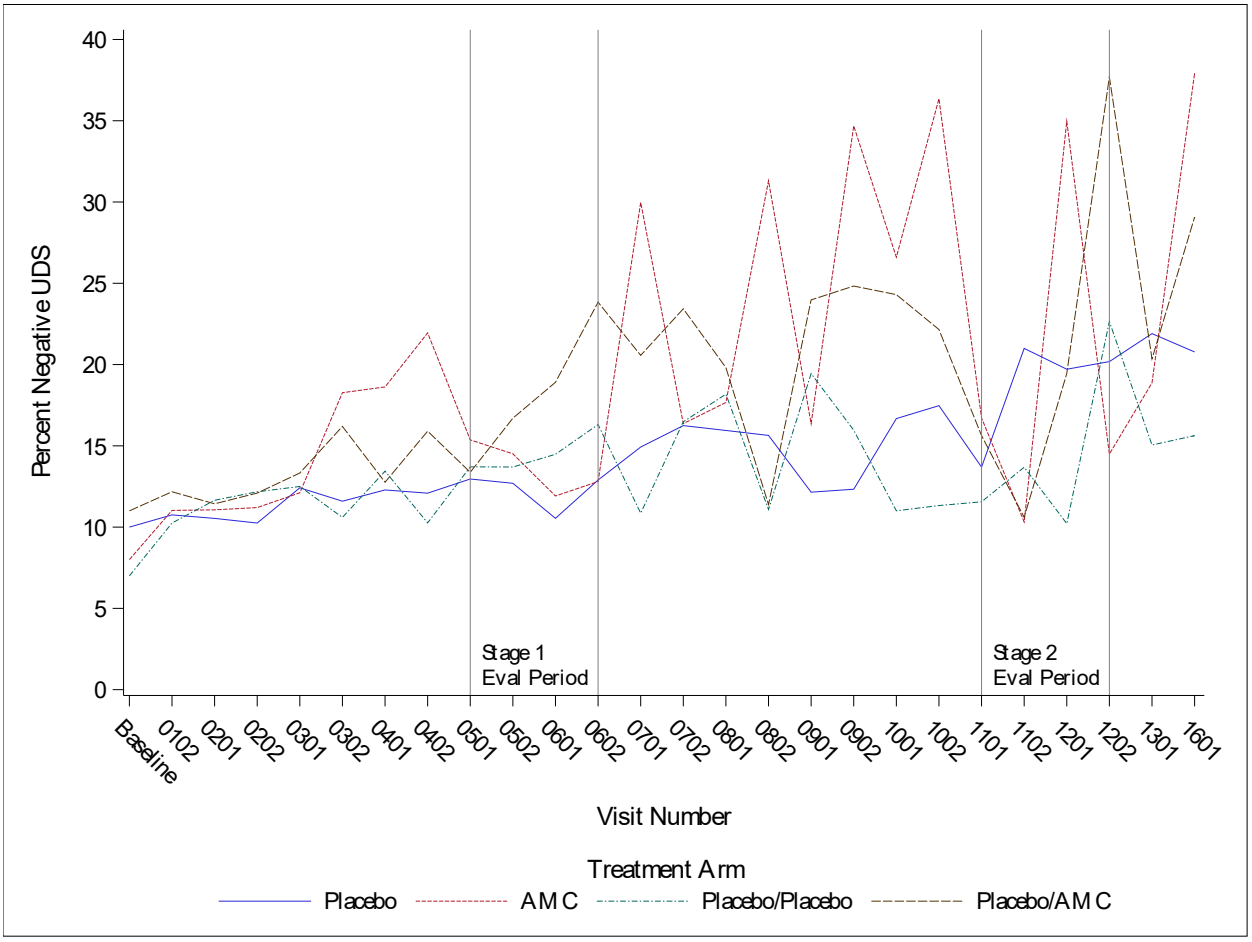


Table 42: Summary of Primary Outcome by Stage and Treatment Arm Per Protocol Populations

	Stage 1			Stage 2			Results	
Per Protocol Population	**Number Randomized**	**Placebo Responder Rate *q1***	**AMC Responder Rate *p1***	**Number Re-randomized**	**Placebo Responder Rate *q2***	**AMC Responder Rate *p2***	**Treatment Effect *h***	**Standard Error of *h***
Definition 1	N	X.X (X.X%)	X.X (X.X%)	N	X.X (X.X%)	X.X (X.X%)	X.XXXX	X.XXXX
Definition 2	N	X.X (X.X%)	X.X (X.X%)	N	X.X (X.X%)	X.X (X.X%)	X.XXXX	X.XXXX
Definition 4	N		X.X (X.X%)	N		X.X (X.X%)		

Table 43: Summary of Treatment Emergent Adverse Events by Treatment Arm in Stage 1

	Placebo (N=)	AMC (N=)	Total (N=)
Number of participants with treatment emergent adverse events in Stage 1[1]	N (%)		
Number of treatment emergent adverse events	N		
Severity of adverse event			
Missing	N (%)		
Grade 1 - Mild			
Grade 2 - Moderate			
Grade 3 - Severe			
Relationship of treatment emergent adverse event to oral study medication			
Missing	N (%)		
No			
Yes			
Relationship of treatment emergent adverse event to injectable study medication			
Missing	N (%)		
No			
Yes			

[1] Stage 1 AEs include adverse events occurring before the date of re-randomization for re-randomized participants and in Weeks 1-6 for non-re-randomized participants.

Table 44: Summary of Treatment Emergent Adverse Events by Treatment Arm in Stage 2

	Re-randomized		Not Re-randomized		
	Placebo/ Placebo (N=)	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Number of participants with treatment emergent adverse events in Stage 2[1]	N (%)				
Number of treatment emergent adverse events	N				
Severity of adverse event					
Missing	N (%)				
Grade 1 - Mild					
Grade 2 - Moderate					
Grade 3 - Severe					
Relationship of treatment emergent adverse event to oral study medication					
No	N (%)				
Yes					
Relationship of treatment emergent adverse event to injectable study medication					
No	N (%)				
Yes					

[1] Stage 2 AEs include adverse events occurring on or after the date of re-randomization for re-randomized participants and in Weeks 7 or greater for non-re-randomized participants.

Table 45: Summary of Treatment Emergent MedDRA Coded Adverse Events by Treatment Arm in Stage 1			
System Organ Class/ Preferred Term (MedDRA v22.0)	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Participants with at least one adverse event in Stage 1[1]	**N (%)**		
Gastrointestinal disorders	**N (%)**		
Nausea	N (%)		
Diarrhoea			
Constipation			
Vomiting			
Dry mouth			
Toothache			
Abdominal discomfort			
Abdominal pain upper			
Abdominal pain			
Dyspepsia			
Chapped lips			
Breath odour			
Abdominal pain lower			
Vomiting projectile			
Stomatitis			
Rectal haemorrhage			
Abdominal distension			
Pancreatitis			
Oral disorder			
Melaena			
Loose tooth			
Gastrooesophageal reflux disease			
Gastrointestinal pain			
Gastritis			
Food poisoning			
Psychiatric disorders	**N (%)**		
Anxiety	N (%)		
Insomnia			
Irritability			
Affect lability			
Abnormal dreams			
Depression			

Table 45: Summary of Treatment Emergent MedDRA Coded Adverse Events by Treatment Arm in Stage 1			
System Organ Class/ Preferred Term (MedDRA v22.0)	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Depressed mood			
Libido decreased			
Nervous system disorders	**N (%)**		
Headache	N (%)		
Dizziness			
Somnolence			
Lethargy			
Tremor			
Dysgeusia			
Cognitive disorder			
Hypersomnia			
Head discomfort			
Loss of consciousness			
Hypoaesthesia			
Disturbance in attention			
Depressed level of consciousness			
Syncope			
Restless legs syndrome			
Parosmia			
Nerve compression			
Migraine			
Infections and infestations	**N (%)**		
Upper respiratory tract infection	N (%)		
Nasopharyngitis			
Cellulitis			
Gonorrhoea			
Gastroenteritis			
Urinary tract infection			
Syphilis			
Abscess			
Viral infection			
Abscess limb			
Pharyngitis			
Influenza			

Table 45: Summary of Treatment Emergent MedDRA Coded Adverse Events by Treatment Arm in Stage 1			
System Organ Class/ Preferred Term (MedDRA v22.0)	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Gastroenteritis viral			
Furuncle			
Ear infection			
Cystitis			
General disorders and administration site conditions	**N (%)**		
Fatigue	N (%)		
Pain			
Feeling jittery			
Injury, poisoning and procedural complications	**N (%)**		
Laceration	N (%)		
Contusion			
Skin abrasion			
Thermal burn			
Road traffic accident			
Ligament sprain			
Injection site pain			
Skin and subcutaneous tissue disorders	**N (%)**		
Hyperhidrosis	N (%)		
Rash			
Acne			
Ecchymosis			
Eczema			
Blister			
Laceration			
Erythema			
Musculoskeletal and connective tissue disorders	**N (%)**		
Myalgia	N (%)		
Arthralgia			
Back pain			

[1] Stage 1 AEs include adverse events occurring before the date of re-randomization for re-randomized participants and in Weeks 1-6 for non-re-randomized participants.

Table 46: Summary of Treatment Emergent MedDRA Coded Adverse Events by Treatment Arm in Stage 2

	Re-randomized		Not Re-randomized		
System Organ Class/ Preferred Term (MedDRA v22.0)	**Placebo/ Placebo (N=)**	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Participants with at least one adverse event in Stage 2[1]	**N (%)**				
Infections and infestations	**N (%)**				
Nasopharyngitis	N (%)				
Upper respiratory tract infection					
Cellulitis					
Paronychia					
Oral herpes					
Abscess					
Viral infection					
Pneumonia					
Influenza					
Herpes virus infection					
Gastroenteritis viral					
Epididymitis					
Chlamydial infection					
Breast abscess					
Body tinea					
Urosepsis					
Urinary tract infection					
Appendicitis					
Tooth abscess					
Tinea infection					
Syphilis					
Pharyngitis					
Infectious mononucleosis					
Gastrointestinal disorders	**N (%)**				
Nausea	N (%)				
Vomiting					
Abdominal pain upper					
Diarrhoea					
Constipation					
Dyspepsia					
Abdominal discomfort					

Table 46: Summary of Treatment Emergent MedDRA Coded Adverse Events by Treatment Arm in Stage 2

	Re-randomized		Not Re-randomized		
System Organ Class/ Preferred Term (MedDRA v22.0)	**Placebo/ Placebo (N=)**	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Toothache					
Gastritis					
Flatulence					
Dry mouth					
Abdominal pain					
Glossodynia					
General disorders and administration site conditions	**N (%)**				
Fatigue	N (%)				
Pain					
Influenza like illness					
Chest pain					
Pyrexia					
Asthenia					
Injection site swelling					
Injection site haematoma					
Injection site discomfort					
Drug withdrawal syndrome					
Vessel puncture site bruise					
Peripheral swelling					
Injury, poisoning and procedural complications	**N (%)**				
Laceration	N (%)				
Joint injury					
Arthropod bite					
Muscle strain					
Eye injury					
Contusion					
Thermal burn					
Road traffic accident					
Procedural nausea					
Limb injury					
Ligament sprain					
Skin abrasion					
Nervous system disorders	**N (%)**				

Table 46: Summary of Treatment Emergent MedDRA Coded Adverse Events by Treatment Arm in Stage 2

	Re-randomized		Not Re-randomized		
System Organ Class/ Preferred Term (MedDRA v22.0)	**Placebo/ Placebo (N=)**	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Headache	N (%)				
Dizziness					
Dysgeusia					
Tremor					
Nerve compression					
Migraine					
Psychiatric disorders	**N (%)**				
Depression	N (%)				
Anxiety					
Paranoia					
Insomnia					
Homicidal ideation					
Hallucination					
Feeling guilty					
Disorientation					
Anhedonia					
Musculoskeletal and connective tissue disorders	**N (%)**				
Myalgia	N (%)				
Pain in extremity					
Back pain					
Musculoskeletal pain					
Neck pain					
Musculoskeletal chest pain					
Muscular weakness					
Joint stiffness					
Arthralgia					
Pain in jaw					

[1] Stage 2 AEs include adverse events occurring on or after the date of re-randomization for re-randomized participants and in Weeks 7 or greater for non-re-randomized participants.

Listing 1: Treatment Emergent Adverse Events by Treatment Arm
Treatment Arm = Placebo

											MedDRA v22.0	
Site	**Participant ID**	**Random-ization Date**	**Onset Date**	**AE Description**	**Severity of AE**	**Related-ness to Oral Study Drug**	**Related-ness to Injectable Study Drug**	**Outcome**	**Resolu-tion Date**	**AE Associated With**	**Preferred Term**	**System Organ Class**
SC BHSPC												
WS CODA, Inc.												
GNY SURC - Columbia												
NS Hennepin Healthcare												
WS SURU - SFDPH												
TX UCLA CBAM												
TX UT Health CNRA												
TX UTSW												

SAEs are highlighted in gray.

Listing 1: Treatment Emergent Adverse Events by Treatment Arm
Treatment Arm = Placebo/Placebo

												MedDRA v22.0	
Site	**Participant ID**	**Random-ization Date**	**Re-ran-domi--zation Date**	**Onset Date**	**AE Description**	**Severity of AE**	**Related-ness to Oral Study Drug**	**Related-ness to Injectable Study Drug**	**Outcome**	**Resolu-tion Date**	**AE Associ-ated With**	**Preferred Term**	**System Organ Class**
SC BHSPC													
WS CODA, Inc.													
GNY SURC - Columbia													
NS Hennepin Healthcare													
WS SURU - SFDPH													
TX UCLA CBAM													
TX UT Health CNRA													
TX UTSW													

SAEs are highlighted in gray.

Listing 1: Treatment Emergent Adverse Events by Treatment Arm
Treatment Arm = Placebo/AMC

												MedDRA v22.0 and higher	
Site	**Participant ID**	**Random-ization Date**	**Re-ran-domi-zation Date**	**Onset Date**	**AE Description**	**Severity of AE**	**Related-ness to Oral Study Drug**	**Related-ness to Injectable Study Drug**	**Outcome**	**Resolu-tion Date**	**AE Associ-ated With**	**Preferred Term**	**System Organ Class**
SC BHSPC													
WS CODA, Inc.													
GNY SURC - Columbia													
NS Hennepin Healthcare													
WS SURU - SFDPH													
TX UCLA CBAM													
TX UT Health CNRA													
TX UTSW													

SAEs are highlighted in gray.

Listing 1: Treatment Emergent Adverse Events by Treatment Arm
Treatment Arm = AMC

											MedDRA v22.0 and higher	
Site	**Participant ID**	**Random-ization Date**	**Onset Date**	**AE Description**	**Severity of AE**	**Related-ness to Oral Study Drug**	**Related-ness to Injectable Study Drug**	**Outcome**	**Resolu-tion Date**	**AE Associated With**	**Preferred Term**	**System Organ Class**
SC BHSPC												
WS CODA, Inc.												
GNY SURC - Columbia												
NS Hennepin Healthcare												
WS SURU - SFDPH												
TX UCLA CBAM												
TX UT Health CNRA												
TX UTSW												

SAEs are highlighted in gray.

Listing 2: Non-Treatment Emergent Adverse Events in Randomized Participants by Treatment Arm
Treatment Arm = Placebo

											MedDRA v22.0	
Site	**Participant ID**	**Random-ization Date**	**Onset Date**	**AE Description**	**Severity of AE**	**Related-ness to Oral Study Drug**	**Related-ness to Injectable Study Drug**	**Outcome**	**Resolu-tion Date**	**AE Associated With**	**Preferred Term**	**System Organ Class**
SC BHSPC												
WS CODA, Inc.												
GNY SURC - Columbia												
NS Hennepin Healthcare												
WS SURU - SFDPH												
TX UCLA CBAM												
TX UT Health CNRA												
TX UTSW												

SAEs are highlighted in gray.

Listing 2: Non-Treatment Emergent Adverse Events in Randomized Participants by Treatment Arm
Treatment Arm = Placebo/Placebo

												MedDRA v22.0	
Site	**Participant ID**	**Random-ization Date**	**Re-ran-domi-zation Date**	**Onset Date**	**AE Description**	**Severity of AE**	**Related-ness to Oral Study Drug**	**Related-ness to Injectable Study Drug**	**Outcome**	**Resolu-tion Date**	**AE Associ-ated With**	**Preferred Term**	**System Organ Class**
SC BHSPC													
WS CODA, Inc.													
GNY SURC - Columbia													
NS Hennepin Healthcare													
WS SURU - SFDPH													
TX UCLA CBAM													
TX UT Health CNRA													
TX UTSW													

SAEs are highlighted in gray.

Listing 2: Non-Treatment Emergent Adverse Events in Randomized Participants by Treatment Arm
Treatment Arm = Placebo/AMC

												MedDRA v22.0	
Site	**Participant ID**	**Random-ization Date**	**Re-ran-domi-zation-Date**	**Onset Date**	**AE Description**	**Severity of AE**	**Related-ness to Oral Study Drug**	**Related-ness to Injectable Study Drug**	**Outcome**	**Resolu-tion Date**	**AE Associ-ated With**	**Preferred Term**	**System Organ Class**
SC BHSPC													
WS CODA, Inc.													
GNY SURC - Columbia													
NS Hennepin Healthcare													
WS SURU - SFDPH													
TX UCLA CBAM													
TX UT Health CNRA													
TX UTSW													

SAEs are highlighted in gray.

Listing 2: Non-Treatment Emergent Adverse Events in Randomized Participants by Treatment Arm
Treatment Arm = AMC

											MedDRA v22.0	
Site	**Participant ID**	**Random-ization Date**	**Onset Date**	**AE Description**	**Severity of AE**	**Related-ness to Oral Study Drug**	**Related-ness to Injectable Study Drug**	**Outcome**	**Resolu-tion Date**	**AE Associated With**	**Preferred Term**	**System Organ Class**
SC BHSPC												
WS CODA, Inc.												
GNY SURC - Columbia												
NS Hennepin Healthcare												
WS SURU - SFDPH												
TX UCLA CBAM												
TX UT Health CNRA												
TX UTSW												

SAEs are highlighted in gray.

Listing 3: Non-Treatment Emergent Adverse Events in Screen Failure Participants											
										MedDRA v22.0	
Site	**Participant ID**	**Onset Date**	**AE Description**	**Severity of AE**	**Related-ness to Oral Study Drug**	**Related-ness to Injectable Study Drug**	**Outcome**	**Resolu-tion Date**	**AE Associated With**	**Preferred Term**	**System Organ Class**
SC BHSPC											
WS CODA, Inc.											
GNY SURC - Columbia											
NS Hennepin Healthcare											
WS SURU - SFDPH											
TX UCLA CBAM											
TX UT Health CNRA											
TX UTSW											

SAEs are highlighted in gray.

Table 47: Summary of Treatment Emergent Serious Adverse Events by Treatment Arm in Stage 1

	Placebo (N=)	AMC (N=)	Total (N=)
Number of participants with treatment emergent serious adverse events in Stage 1[1]	N (%)		
Number of treatment emergent serious adverse events	N		
Type of treatment emergent serious adverse event			
Death	N (%)		
Life-threatening event			
Inpatient admission to hospital or prolongation of existing hospitalization			
Persistent or significant incapacity			
Congenital anomaly or birth defect			
Important medical event that required intervention to prevent any of the above			
Seizure			
Relationship of treatment emergent serious adverse event to oral study medication			
No	N (%)		
Yes			
Relationship of treatment emergent serious adverse event to injectable study medication			
No	N (%)		
Yes			

[1] Stage 1 SAEs include serious adverse events occurring before the date of re-randomization for re-randomized participants and in Weeks 1-6 for non-re-randomized participants.

Table 48: Summary of Treatment Emergent Serious Adverse Events by Treatment Arm in Stage 2

	Re-randomized		Not Re-randomized		
	Placebo/ Placebo (N=)	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Number of participants with treatment emergent serious adverse events in Stage 2[1]	N (%)				
Number of treatment emergent serious adverse events	N				
Type of treatment emergent serious adverse event					
Death	N (%)				
Life-threatening event					
Inpatient admission to hospital or prolongation of existing hospitalization					
Persistent or significant incapacity					
Congenital anomaly or birth defect					
Important medical event that required intervention to prevent any of the above					
Seizure					
Relationship of treatment emergent serious adverse event to oral study medication					
No	N (%)				
Yes					
Relationship of treatment emergent serious adverse event to injectable study medication					
No	N (%)				
Yes					

[1] Stage 2 SAEs include serious adverse events occurring on or after the date of re-randomization for re-randomized participants and in Weeks 7 or greater for non-re-randomized participants.

Table 49: Summary of Treatment Emergent MedDRA Coded Serious Adverse Events by Treatment Arm in Stage 1			
System Organ Class/ Preferred Term (MedDRA v22.0)	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Psychiatric disorders	**N (%)**		
Suicidal ideation	N (%)		
Suicide attempt			
Self-injurious behavior			
Psychotic disorder			
Depression suicidal			
Depression			
Delirium			
Anxiety			
Affective disorder			
Injury, poisoning and procedural complications	**N (%)**		
Overdose	N (%)		
Multiple fractures			
Burns third degree			
Infections and infestations	**N (%)**		
Cellulitis	N (%)		
Abscess limb			
Pneumonia			
Influenza			
Groin abscess			
Gastroenteritis			
Bronchitis			
Nervous system disorders	**N (%)**		
Syncope	N (%)		
Seizure			
Facial paresis			
Respiratory, thoracic and mediastinal disorders	**N (%)**		
Respiratory depression	N (%)		
Asthma			
Musculoskeletal and connective tissue disorders	**N (%)**		
Back pain	N (%)		
Metabolism and nutrition disorders	**N (%)**		
Dehydration	N (%)		

[1] Stage 1 SAEs include serious adverse events occurring before the date of re-randomization for re-randomized participants and in Weeks 1-6 for non-re-randomized participants.

Table 50: Summary of Treatment Emergent MedDRA Coded Serious Adverse Events by Treatment Arm in Stage 2

	Re-randomized		Not Re-randomized		
System Organ Class/ Preferred Term (MedDRA v22.0)	**Placebo/ Placebo (N=)**	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Participants with at least one serious adverse event in Stage 2[1]	**N (%)**				
Psychiatric disorders	**N (%)**				
Suicidal ideation	N (%)				
Suicide attempt					
Self-injurious behavior					
Psychotic disorder					
Depression suicidal					
Depression					
Delirium					
Anxiety					
Affective disorder					
Injury, poisoning and procedural complications	**N (%)**				
Overdose	N (%)				
Multiple fractures					
Burns third degree					
Infections and infestations	**N (%)**				
Cellulitis	N (%)				
Abscess limb					
Pneumonia					
Influenza					
Groin abscess					
Gastroenteritis					
Bronchitis					
Nervous system disorders	**N (%)**				
Syncope	N (%)				
Seizure					
Facial paresis					
Respiratory, thoracic and mediastinal disorders	**N (%)**				
Respiratory depression	N (%)				
Asthma					
Musculoskeletal and connective tissue disorders	**N (%)**				
Back pain	N (%)				

[1] Stage 2 AEs include adverse events occurring on or after the date of re-randomization for re-randomized participants and in Weeks 7 or greater for non-re-randomized participants.

Listing 4: Serious Adverse Events by Treatment Arm Treatment Arm = Not Randomized											
										MedDRA v22.0	
Treatment Emergent	Participant ID	Onset Date	AE Description	Severity of AE	Related-ness to Oral Study Drug	Related-ness to Injectable Study Drug	Outcome	Resolu-tion Date	AE Associated With	Preferred Term	System Organ Class
No											

Listing 4: Serious Adverse Events by Treatment Arm Treatment Arm = Placebo												
											MedDRA v22.0	
Treatment Emergent	Participant ID	Random-ization Date	Onset Date	AE Description	Severity of AE	Related-ness to Oral Study Drug	Related-ness to Injectable Study Drug	Outcome	Resolu-tion Date	AE Associated With	Preferred Term	System Organ Class
No												
Yes												

Listing 4: Serious Adverse Events by Treatment Arm
Treatment Arm = Placebo/Placebo

												MedDRA v22.0	
Treatment Emergent	Participant ID	Random-ization Date	Re-random-ization Date	Onset Date	AE Description	Severity of AE	Related-ness to Oral Study Drug	Related-ness to Injectable Study Drug	Outcome	Resolu-tion Date	AE Associated With	Preferred Term	System Organ Class
No													
Yes													

Listing 4: Serious Adverse Events by Treatment Arm
Treatment Arm = Placebo/AMC

												MedDRA v22.0	
Treatment Emergent	Participant ID	Random-ization Date	Re-random-ization Date	Onset Date	AE Description	Severity of AE	Related-ness to Oral Study Drug	Related-ness to Injectable Study Drug	Outcome	Resolu-tion Date	AE Associated With	Preferred Term	System Organ Class
No													
Yes													

Listing 4: Serious Adverse Events by Treatment Arm
Treatment Arm = AMC

												MedDRA v22.0	
Treatment Emergent	**Participant ID**	**Random-ization Date**	**Re-random-ization Date**	**Onset date**	**AE Description**	**Severity of AE**	**Related-ness to Oral Study Drug**	**Related-ness to Injectable Study Drug**	**Outcome**	**Resolu-tion Date**	**AE Associated With**	**Preferred Term**	**System Organ Class**
No													
Yes													

Table 51: Summary of Injection Site Abnormalities by Treatment Arm in Stage 1			
	Placebo (N=)	**AMC (N=)**	**Total (N=)**
Number of participants with an injection site abnormality in Stage 1[1]			
Number of injection site abnormalities reported			
Type of injection site abnormality			
Pain			
Tenderness			
Bruising			
Induration			
Erythema (redness)			
Hematoma			
Swelling			
Pruritus			
Other			
Cellulitis			
Warmth			
Nodule			
Abscess			
Sterile abscess			
Necrosis			
Severity of injection site abnormality			
Mild			
Moderate			
Severe			

[1] Abnormalities occurring after injection #1 and injection #2 are reported in Stage 1.

Table 52: Summary of Injection Site Abnormalities by Treatment Arm in Stage 2					
	Re-randomized		Not Re-randomized		
	Placebo/ Placebo (N=)	Placebo/ AMC (N=)	Placebo (N=)	AMC (N=)	Total (N=)
Number of participants with an injection site abnormality in Stage 2[1]	N (%)				
Number of injection site abnormalities reported	N				
Type of injection site abnormality					
Pain	N (%)				
Tenderness					
Bruising					
Induration					
Erythema (redness)					
Hematoma					
Swelling					
Pruritus					
Other					
Cellulitis					
Warmth					
Nodule					
Abscess					
Sterile abscess					
Necrosis					
Severity of injection site abnormality					
Mild	N (%)				
Moderate					
Severe					

[1] Abnormalities occurring after injection #3 and injection #4 are reported in Stage 2.

Listing 5: Injection Site Abnormalities by Treatment Arm Treatment Arm = Placebo									
Site	**Participant ID**	**Randomization Date**	**Date of Injection**	**Injection Number**	**Event Start Date**	**Event Resolution Date**	**Abnormal Event**	**Severity**	**Treatment**
SC BHSPC									
WS CODA, Inc.									
GNY SURC – Columbia									
NS Hennepin Healthcare									
WS SURU – SFDPH									
TX UCLA CBAM									
TX UT Health CNRA									
TX UTSW									

Listing 5: Injection Site Abnormalities by Treatment Arm
Treatment Arm = Placebo/Placebo

Site	Participant ID	Randomization Date	Re-randomization Date	Date of Injection	Injection Number	Event Start Date	Event Resolution Date	Abnormal Event	Severity	Treatment
SC BHSPC										
WS CODA, Inc.										
GNY SURC – Columbia										
NS Hennepin Healthcare										
WS SURU – SFDPH										
TX UCLA CBAM										
TX UT Health CNRA										
TX UTSW										

Listing 5: Injection Site Abnormalities by Treatment Arm
Treatment Arm = Placebo/AMC

Site	Participant ID	Randomization Date	Re-randomization Date	Date of Injection	Injection Number	Event Start Date	Event Resolution Date	Abnormal Event	Severity	Treatment
SC BHSPC										
WS CODA, Inc.										
GNY SURC – Columbia										
NS Hennepin Healthcare										
WS SURU – SFDPH										
TX UCLA CBAM										
TX UT Health CNRA										
TX UTSW										

Listing 5: Injection Site Abnormalities by Treatment Arm
Treatment Arm = AMC

Site	Participant ID	Randomization Date	Date of Injection	Injection Number	Event Start Date	Event Resolution Date	Abnormal Event	Severity	Treatment
SC BHSPC									
WS CODA, Inc.									
GNY SURC – Columbia									
NS Hennepin Healthcare									
WS SURU – SFDPH									
TX UCLA CBAM									
TX UT Health CNRA									
TX UTSW									

Listing 6: Elevated LFTs by Treatment Arm
Treatment Arm = Placebo

Site	Participant ID	Randomization Date	Date of Lab Collection	Visit	Aspartate Aminotransferase (IU/L)	Alanine Aminotransferase (IU/L)	Total Bilirubin (mg/dL)
SC BHSPC							
WS CODA, Inc.							
GNY SURC - Columbia							
NS Hennepin Healthcare							
WS SURU - SFDPH							
TX UCLA CBAM							
TX UT Health CNRA							
TX UTSW							

Lab values above thresholds are highlighted in yellow. This includes ALT values higher than 250 IU/L based on 5x ULN, AST values higher than 250 IU/L based on 5x ULN, and total bilirubin values higher than 2.2 mg/dL based on 2x ULN.

All visits are included for participants who experienced elevated LFTs at any visit.

Listing 6: Elevated LFTs by Treatment Arm
Treatment Arm = Placebo/Placebo

Site	Participant ID	Randomization Date	Re-randomization Date	Date of Lab Collection	Visit	Aspartate Aminotransferase (IU/L)	Alanine Aminotransferase (IU/L)	Total Bilirubin (mg/dL)
SC BHSPC								
WS CODA, Inc.								
GNY SURC - Columbia								
NS Hennepin Healthcare								
WS SURU - SFDPH								
TX UCLA CBAM								
TX UT Health CNRA								
TX UTSW								

Lab values above thresholds are highlighted in yellow. This includes ALT values higher than 250 IU/L based on 5x ULN, AST values higher than 250 IU/L based on 5x ULN, and total bilirubin values higher than 2.2 mg/dL based on 2x ULN.

All visits are included for participants who experienced elevated LFTs at any visit.

Listing 6: Elevated LFTs by Treatment Arm
Treatment Arm = Placebo/AMC

Site	Participant ID	Randomization Date	Re-randomization Date	Date of Lab Collection	Visit	Aspartate Aminotransferase (IU/L)	Alanine Aminotransferase (IU/L)	Total Bilirubin (mg/dL)
SC BHSPC								
WS CODA, Inc.								
GNY SURC - Columbia								
NS Hennepin Healthcare								
WS SURU - SFDPH								
TX UCLA CBAM								
TX UT Health CNRA								
TX UTSW								

Lab values above thresholds are highlighted in yellow. This includes ALT values higher than 250 IU/L based on 5x ULN, AST values higher than 250 IU/L based on 5x ULN, and total bilirubin values higher than 2.2 mg/dL based on 2x ULN.

All visits are included for participants who experienced elevated LFTs at any visit.

Listing 6: Elevated LFTs by Treatment Arm
Treatment Arm = AMC

Site	Participant ID	Randomization Date	Date of Lab Collection	Visit	Aspartate Aminotransferase (IU/L)	Alanine Aminotransferase (IU/L)	Total Bilirubin (mg/dL)
SC BHSPC							
WS CODA, Inc.							
GNY SURC - Columbia							
NS Hennepin Healthcare							
WS SURU - SFDPH							
TX UCLA CBAM							
TX UT Health CNRA							
TX UTSW							

Lab values above thresholds are highlighted in yellow. This includes ALT values higher than 250 IU/L based on 5x ULN, AST values higher than 250 IU/L based on 5x ULN, and total bilirubin values higher than 2.2 mg/dL based on 2x ULN.

All visits are included for participants who experienced elevated LFTs at any visit.

Listing 7: Decreased Platelets by Treatment Arm Treatment Arm = Placebo					
Site	**Participant ID**	**Randomization Date**	**Date of Lab Collection**	**Visit**	**Platelets (µL)**
SC BHSPC					
WS CODA, Inc.					
GNY SURC - Columbia					
NS Hennepin Healthcare					
WS SURU - SFDPH					
TX UCLA CBAM					
TX UT Health CNRA					
TX UTSW					

Platelet values under the threshold of $75x10^3$/µL are highlighted in yellow.
All visits are included for participants who experienced decreased platelets at any visit.

Listing 7: Decreased Platelets by Treatment Arm Treatment Arm = Placebo/Placebo						
Site	**Participant ID**	**Randomization Date**	**Re-randomization Date**	**Date of Lab Collection**	**Visit**	**Platelets (µL)**
SC BHSPC						
WS CODA, Inc.						
GNY SURC - Columbia						
NS Hennepin Healthcare						
WS SURU - SFDPH						
TX UCLA CBAM						
TX UT Health CNRA						
TX UTSW						

Platelet values under the threshold of $75x10^3$/µL are highlighted in yellow.
All visits are included for participants who experienced decreased platelets at any visit.

Listing 7: Decreased Platelets by Treatment Arm Treatment Arm = Placebo/AMC						
Site	**Participant ID**	**Randomization Date**	**Re-randomization Date**	**Date of Lab Collection**	**Visit**	**Platelets (µL)**
SC BHSPC						
WS CODA, Inc.						
GNY SURC - Columbia						
NS Hennepin Healthcare						
WS SURU - SFDPH						
TX UCLA CBAM						
TX UT Health CNRA						
TX UTSW						

Platelet values under the threshold of $75x10^3$/µL are highlighted in yellow.
All visits are included for participants who experienced decreased platelets at any visit.

Listing 7: Decreased Platelets by Treatment Arm Treatment Arm = AMC					
Site	**Participant ID**	**Randomization Date**	**Date of Lab Collection**	**Visit**	**Platelets (µL)**
SC BHSPC					
WS CODA, Inc.					
GNY SURC - Columbia					
NS Hennepin Healthcare					
WS SURU - SFDPH					
TX UCLA CBAM					
TX UT Health CNRA					
TX UTSW					

Platelet values under the threshold of $75x10^3$/µL are highlighted in yellow.
All visits are included for participants who experienced decreased platelets at any visit.

Table 53: Summary of Elevated QTc Intervals by Treatment Arm					
	Re-randomized		Not Re-randomized		
	Placebo/ Placebo (N=)	Placebo/ AMC (N=)	Placebo (N=)	AMC (N=)	Total (N=)
Participants with elevated QTc intervals ≥ 500 ms at Week 12	n/N (%)				
Baseline QTc interval (ms)					
N					
Mean					
SD					
Min					
25th percentile					
Median					
75th percentile					
Max					
Week 12 QTc interval (ms)					
N					
Mean					
SD					
Min					
25th percentile					
Median					
75th percentile					
Max					

Table 53: Summary of Elevated QTc Intervals by Treatment Arm					
	Re-randomized		**Not Re-randomized**		
	Placebo/ Placebo (N=)	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**	**Total (N=)**
Change from baseline QTc interval (ms) at Week 12					
N					
Mean					
SD					
Min					
25th percentile					
Median					
75th percentile					
Max					

Listing 8: AV Block ECG Abnormalities by Treatment Arm Treatment Arm = Placebo					
Site	**Participant ID**	**Randomization Date**	**Date of ECG**	**Week 12 Second Degree AV Block Present**	**Week 12 Third Degree AV Block Present**
SC BHSPC					
WS CODA, Inc.					
GNY SURC - Columbia					
NS Hennepin Healthcare					
WS SURU - SFDPH					
TX UCLA CBAM					
TX UT Health CNRA					
TX UTSW					

Listing 8: AV Block ECG Abnormalities by Treatment Arm Treatment Arm = Placebo/Placebo						
Site	**Participant ID**	**Randomization Date**	**Re-randomi-zation Date**	**Date of ECG**	**Week 12 Second Degree AV Block Present**	**Week 12 Third Degree AV Block Present**
SC BHSPC						
WS CODA, Inc.						
GNY SURC - Columbia						
NS Hennepin Healthcare						
WS SURU - SFDPH						
TX UCLA CBAM						
TX UT Health CNRA						
TX UTSW						

Listing 8: AV Block ECG Abnormalities by Treatment Arm Treatment Arm = Placebo/AMC						
Site	**Participant ID**	**Randomization Date**	**Re-randomi-zation Date**	**Date of ECG**	**Week 12 Second Degree AV Block Present**	**Week 12 Third Degree AV Block Present**
SC BHSPC						
WS CODA, Inc.						
GNY SURC - Columbia						
NS Hennepin Healthcare						
WS SURU - SFDPH						
TX UCLA CBAM						
TX UT Health CNRA						
TX UTSW						

Listing 8: AV Block ECG Abnormalities by Treatment Arm Treatment Arm = AMC					
Site	**Participant ID**	**Randomization Date**	**Date of ECG**	**Week 12 Second Degree AV Block Present**	**Week 12 Third Degree AV Block Present**
SC BHSPC					
WS CODA, Inc.					
GNY SURC - Columbia					
NS Hennepin Healthcare					
WS SURU - SFDPH					
TX UCLA CBAM					
TX UT Health CNRA					
TX UTSW					

Table 54: Summary of Suicide Risk by Treatment Arm in Stage 1			
	Placebo (N=)	**AMC (N=)**	**Total (N=)**
Number endorsing on CHRT or PHQ-9	N (%)		
Number endorsing on CHRT only	N (%)		
Number endorsing on PHQ-9 only	N (%)		
Number endorsing on CHRT and PHQ-9	N (%)		

Endorsing suicide risk on CHRT is defined as responses of Agree or Strongly Agree on any of CHRT questions 13, 14, or 15. Endorsing suicide risk on PHQ-9 is defined as responses of Several Days or More than Half the Days or Nearly Every Day to PHQ-9 question 9.

Table 55: Summary of Suicide Risk by Treatment Arm in Stage 2				
	Re-randomized		**Not Re-randomized**	
	Placebo/ Placebo (N=)	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**
Number endorsing on CHRT or PHQ-9	N (%)			
Number endorsing on CHRT only	N (%)			
Number endorsing on PHQ-9 only	N (%)			
Number endorsing on CHRT and PHQ-9	N (%)			

Endorsing suicide risk on CHRT is defined as responses of Agree or Strongly Agree on any of CHRT questions 13, 14, or 15. Endorsing suicide risk on PHQ-9 is defined as responses of Several Days or More than Half the Days or Nearly Every Day to PHQ-9 question 9.

Table 56: Summary of Suicide Risk by Treatment Arm in Follow-up Period				
	Re-randomized		**Not Re-randomized**	
	Placebo/ Placebo (N=)	**Placebo/ AMC (N=)**	**Placebo (N=)**	**AMC (N=)**
Number endorsing on CHRT or PHQ-9	N (%)			
Number endorsing on CHRT only	N (%)			
Number endorsing on PHQ-9 only	N (%)			
Number endorsing on CHRT and PHQ-9	N (%)			

Endorsing suicide risk on CHRT is defined as responses of Agree or Strongly Agree on any of CHRT questions 13, 14, or 15. Endorsing suicide risk on PHQ-9 is defined as responses of Several Days or More than Half the Days or Nearly Every Day to PHQ-9 question 9.

Listing 9: Suicide Risk by Treatment Arm
Treatment Arm = Placebo

			CHRT			PHQ-9
Site	**Participant ID**	**Visit**	**I Have Been Having Thoughts of Killing Myself**	**I Have Thoughts about How I Might Kill Myself**	**I Have a Plan to Kill Myself**	**Thoughts You are Better Off Dead or of Hurting Yourself**
SC BHSPC						
WS CODA, Inc.						
GNY SURC - Columbia						
NS Hennepin Healthcare						
WS SURU - SFDPH						
TX UCLA CBAM						
TX UT Health CNRA						
TX UTSW						

All visits are included for participants who endorsed suicide risk at any visit on either CHRT or PHQ-9.

CHRT responses of Agree are highlighted in orange and Strongly Agree are highlighted in red. PHQ-9 responses of Several Days are highlighted in yellow, More than Half the Days are highlighted in orange, and Nearly Every Day are highlighted in red.

Listing 9: Suicide Risk by Treatment Arm
Treatment Arm = Placebo/Placebo

			CHRT			PHQ-9
Site	**Participant ID**	**Visit**	**I Have Been Having Thoughts of Killing Myself**	**I Have Thoughts about How I Might Kill Myself**	**I Have a Plan to Kill Myself**	**Thoughts You are Better Off Dead or of Hurting Yourself**
SC BHSPC						
WS CODA, Inc.						
GNY SURC - Columbia						
NS Hennepin Healthcare						
WS SURU - SFDPH						
TX UCLA CBAM						
TX UT Health CNRA						
TX UTSW						

All visits are included for participants who were endorse suicide risk at any visit on either CHRT or PHQ-9.

CHRT responses of Agree are highlighted in orange and Strongly Agree are highlighted in red. PHQ-9 responses of Several Days are highlighted in yellow, More than Half the Days are highlighted in orange, and Nearly Every Day are highlighted in red.

Listing 9: Suicide Risk by Treatment Arm
Treatment Arm = Placebo/AMC

			CHRT			PHQ-9
Site	**Participant ID**	**Visit**	**I Have Been Having Thoughts of Killing Myself**	**I Have Thoughts about How I Might Kill Myself**	**I Have a Plan to Kill Myself**	**Thoughts You are Better Off Dead or of Hurting Yourself**
SC BHSPC						
WS CODA, Inc.						
GNY SURC - Columbia						
NS Hennepin Healthcare						
WS SURU - SFDPH						
TX UCLA CBAM						
TX UT Health CNRA						
TX UTSW						

All visits are included for participants who were endorse suicide risk at any visit on either CHRT or PHQ-9.

CHRT responses of Agree are highlighted in orange and Strongly Agree are highlighted in red. PHQ-9 responses of Several Days are highlighted in yellow, More than Half the Days are highlighted in orange, and Nearly Every Day are highlighted in red.

Listing 9: Suicide Risk by Treatment Arm
Treatment Arm = AMC

			CHRT			PHQ-9
Site	**Participant ID**	**Visit**	**I Have Been Having Thoughts of Killing Myself**	**I Have Thoughts about How I Might Kill Myself**	**I Have a Plan to Kill Myself**	**Thoughts You are Better Off Dead or of Hurting Yourself**
SC BHSPC						
WS CODA, Inc.						
GNY SURC - Columbia						
NS Hennepin Healthcare						
WS SURU - SFDPH						
TX UCLA CBAM						
TX UT Health CNRA						
TX UTSW						

All visits are included for participants who were endorse suicide risk at any visit on either CHRT or PHQ-9.

CHRT responses of Agree are highlighted in orange and Strongly Agree are highlighted in red. PHQ-9 responses of Several Days are highlighted in yellow, More than Half the Days are highlighted in orange, and Nearly Every Day are highlighted in red.

Listing 10: Pregnancies by Treatment Arm
Treatment Arm = Placebo

Site	Participant ID	Date of Randomization	Date Staff Aware of Pregnancy	Date Pregnancy Confirmed	Date of Last Dose of Oral Study Medication	Date of Last Injectable Study Medication	Pregnancy Outcome	Date of Pregnancy Outcome	Normal Infant?
SC BHSPC									
WS CODA, Inc.									
GNY SURC - Columbia									
NS Hennepin Healthcare									
WS SURU - SFDPH									
TX UCLA CBAM									
TX UT Health CNRA									
TX UTSW									

Listing 10: Pregnancies by Treatment Arm
Treatment Arm = Placebo/Placebo

Site	Participant ID	Date of Randomization	Date of Re-randomization	Date Staff Aware of Pregnancy	Date Pregnancy Confirmed	Date of Last Dose of Oral Study Medication	Date of Last Injectable Study Medication	Pregnancy Outcome	Date of Pregnancy Outcome	Normal Infant?
SC BHSPC										
WS CODA, Inc.										
GNY SURC - Columbia										
NS Hennepin Healthcare										
WS SURU - SFDPH										
TX UCLA CBAM										
TX UT Health CNRA										
TX UTSW										

Listing 10: Pregnancies by Treatment Arm
Treatment Arm = Placebo/AMC

Site	Participant ID	Date of Randomization	Date of Re-randomization	Date Staff Aware of Pregnancy	Date Pregnancy Confirmed	Date of Last Dose of Oral Study Medication	Date of Last Injectable Study Medication	Pregnancy Outcome	Date of Pregnancy Outcome	Normal Infant?
SC BHSPC										
WS CODA, Inc.										
GNY SURC - Columbia										
NS Hennepin Healthcare										
WS SURU - SFDPH										
TX UCLA CBAM										
TX UT Health CNRA										
TX UTSW										

Listing 10: Pregnancies by Treatment Arm
Treatment Arm = AMC

Site	Participant ID	Date of Randomization	Date Staff Aware of Pregnancy	Date Pregnancy Confirmed	Date of Last Dose of Oral Study Medication	Date of Last Injectable Study Medication	Pregnancy Outcome	Date of Pregnancy Outcome	Normal Infant?
SC BHSPC									
WS CODA, Inc.									
GNY SURC - Columbia									
NS Hennepin Healthcare									
WS SURU - SFDPH									
TX UCLA CBAM									
TX UT Health CNRA									
TX UTSW									

Listing 11: Deaths by Treatment Arm
Treatment Arm = Placebo

Site	Participant ID	Randomization Date	Date of Death	Description	MedDRA v22.0	
					Preferred Term	System Organ Class
SC BHSPC						
WS CODA, Inc.						
GNY SURC - Columbia						
NS Hennepin Healthcare						
WS SURU - SFDPH						
TX UCLA CBAM						
TX UT Health CNRA						
TX UTSW						

Listing 11: Deaths by Treatment Arm Treatment Arm = Placebo/Placebo							
						MedDRA v22.0	
Site	Participant ID	Randomization Date	Re-randomization Date	Date of Death	Description	Preferred Term	System Organ Class
SC BHSPC							
WS CODA, Inc.							
GNY SURC - Columbia							
NS Hennepin Healthcare							
WS SURU - SFDPH							
TX UCLA CBAM							
TX UT Health CNRA							
TX UTSW							

Listing 11: Deaths by Treatment Arm Treatment Arm = Placebo/AMC							
						MedDRA v22.0	
Site	Participant ID	Randomization Date	Re-randomization Date	Date of Death	Description	Preferred Term	System Organ Class
SC BHSPC							
WS CODA, Inc.							
GNY SURC - Columbia							
NS Hennepin Healthcare							
WS SURU - SFDPH							
TX UCLA CBAM							
TX UT Health CNRA							
TX UTSW							

Listing 11: Deaths by Treatment Arm Treatment Arm = AMC						
					MedDRA v22.0	
Site	Participant ID	Randomization Date	Date of Death	Description	Preferred Term	System Organ Class
SC BHSPC						
WS CODA, Inc.						
GNY SURC - Columbia						
NS Hennepin Healthcare						
WS SURU - SFDPH						
TX UCLA CBAM						
TX UT Health CNRA						
TX UTSW						

Table 57: Summary of Data Audits				
Site	**Date of Audit**	**Total Fields Audited[1]**	**Total Data Discrepancies[2]**	**Error Rate (%)**
SC BHSPC				
	Subtotal			
WS CODA, Inc.				
	Subtotal			
GNY SURC - Columbia				
	Subtotal			
NS Hennepin Healthcare				
	Subtotal			
WS SURU - SFDPH				
	Subtotal			
TX UCLA CBAM				
	Subtotal			
TX UT Health CNRA				
	Subtotal			
TX UTSW				
	Subtotal			
Total				

[1] Fields reviewed at monitoring visit comparing the database to source documentation.
[2] Fields discrepant between database and source documentation.

Table 58: Summary of Protocol Deviations									
	SC BHSPC	**WS CODA, Inc.**	**GNY SURC - Columbia**	**NS Hennepin Healthcare**	**WS SURU - SFDPH**	**TX UCLA CBAM**	**TX UT Health CNRA**	**TX UTSW**	**Total**
Total number of protocol deviations	N								
Number of participants impacted per protocol deviation									
None	N (%)								
One									
More than one									
Total number of major protocol deviations	N								
Type of major protocol deviation									
Safety assessment (e.g. labs, ECG, clinical referral to care) not conducted per protocol	N (%)								
Medication dosing errors (protocol specified dose not dispensed)									
Total number of minor protocol deviations	N								
Type of minor protocol deviation									
AE/SAE reported out of protocol specified reporting timeframe	N (%)								
Biologic specimen not collected/processed as per protocol									
Study assessments not completed/followed as per protocol									
Study medication management - Other									
Other study procedures/assessments issues									
Informed consent/assent process not properly conducted and/or documented									
Other significant deviations issues									
Protocol required visit/assessment not scheduled or conducted									
Other informed consent/assent procedures issues									
AE not reported									
Other inclusion/exclusion criteria issues									
Other study devices issues									
Non IRB approved/outdated/obsolete informed consent/assent documents used									
AE/SAE not elicited, observed and/or documented as per protocol									

Listing 12: Listing of Protocol Deviations
Deviation Category = Informed consent procedures

Site	Related Participant IDs	Date of Protocol Deviation	Date Protocol Deviation Entered in eClinical	Deviation Type	Deviation Type (other)	Deviation Description	Resolution Corrective Action	IRB Reporting Required?	IRB Notified at Continuing Review?	Expected/ Actual IRB Report date
SC BHSPC										
WS CODA, Inc.										
GNY SURC – Columbia										
NS Hennepin Healthcare										
WS SURU – SFDPH										
TX UCLA CBAM										
TX UT Health CNRA										
TX UTSW										

Major PDs are highlighted in gray.

Listing 12: Listing of Protocol Deviations
Deviation Category = Inclusion/exclusion criteria

Site	Related Participant IDs	Date of Protocol Deviation	Date Protocol Deviation Entered in eClinical	Deviation Type	Deviation Type (other)	Deviation Description	Resolution Corrective Action	IRB Reporting Required?	IRB Notified at Continuing Review?	Expected/ Actual IRB Report date
SC BHSPC										
WS CODA, Inc.										
GNY SURC – Columbia										
NS Hennepin Healthcare										
WS SURU – SFDPH										
TX UCLA CBAM										
TX UT Health CNRA										
TX UTSW										

Major PDs are highlighted in gray.

Listing 12: Listing of Protocol Deviations
Deviation Category = Laboratory Assessments

Site	Related Participant IDs	Date of Protocol Deviation	Date Protocol Deviation Entered in eClinical	Deviation Type	Deviation Type (other)	Deviation Description	Resolution Corrective Action	IRB Reporting Required?	IRB Notified at Continuing Review?	Expected/ Actual IRB Report date
SC BHSPC										
WS CODA, Inc.										
GNY SURC – Columbia										
NS Hennepin Healthcare										
WS SURU – SFDPH										
TX UCLA CBAM										
TX UT Health CNRA										
TX UTSW										

Major PDs are highlighted in gray.

Listing 12: Listing of Protocol Deviations
Deviation Category = Study Procedures/Assessments

Site	Related Participant IDs	Date of Protocol Deviation	Date Protocol Deviation Entered in eClinical	Deviation Type	Deviation Type (other)	Deviation Description	Resolution Corrective Action	IRB Reporting Required?	IRB Notified at Continuing Review?	Expected/ Actual IRB Report date
SC BHSPC										
WS CODA, Inc.										
GNY SURC – Columbia										
NS Hennepin Healthcare										
WS SURU – SFDPH										
TX UCLA CBAM										
TX UT Health CNRA										
TX UTSW										

Major PDs are highlighted in gray.

Listing 12: Listing of Protocol Deviations
Deviation Category = Adverse Event

Site	Related Participant IDs	Date of Protocol Deviation	Date Protocol Deviation Entered in eClinical	Deviation Type	Deviation Type (other)	Deviation Description	Resolution Corrective Action	IRB Reporting Required?	IRB Notified at Continuing Review?	Expected/ Actual IRB Report date
SC BHSPC										
WS CODA, Inc.										
GNY SURC – Columbia										
NS Hennepin Healthcare										
WS SURU – SFDPH										
TX UCLA CBAM										
TX UT Health CNRA										
TX UTSW										

Major PDs are highlighted in gray.

Listing 12: Listing of Protocol Deviations
Deviation Category = Study Medication Management

Site	Related Participant IDs	Date of Protocol Deviation	Date Protocol Deviation Entered in eClinical	Deviation Type	Deviation Type (other)	Deviation Description	Resolution Corrective Action	IRB Reporting Required?	IRB Notified at Continuing Review?	Expected/ Actual IRB Report date
SC BHSPC										
WS CODA, Inc.										
GNY SURC – Columbia										
NS Hennepin Healthcare										
WS SURU – SFDPH										
TX UCLA CBAM										
TX UT Health CNRA										
TX UTSW										

Major PDs are highlighted in gray.

Listing 12: Listing of Protocol Deviations
Deviation Category = Study Devices

Site	Related Participant IDs	Date of Protocol Deviation	Date Protocol Deviation Entered in eClinical	Deviation Type	Deviation Type (other)	Deviation Description	Resolution Corrective Action	IRB Reporting Required?	IRB Notified at Continuing Review?	Expected/ Actual IRB Report date
SC BHSPC										
WS CODA, Inc.										
GNY SURC – Columbia										
NS Hennepin Healthcare										
WS SURU – SFDPH										
TX UCLA CBAM										
TX UT Health CNRA										
TX UTSW										

Major PDs are highlighted in gray.

Listing 12: Listing of Protocol Deviations
Deviation Category = Other Significant Deviations

Site	Related Participant IDs	Date of Protocol Deviation	Date Protocol Deviation Entered in eClinical	Deviation Type	Deviation Type (other)	Deviation Description	Resolution Corrective Action	IRB Reporting Required?	IRB Notified at Continuing Review?	Expected/ Actual IRB Report date
SC BHSPC										
WS CODA, Inc.										
GNY SURC – Columbia										
NS Hennepin Healthcare										
WS SURU – SFDPH										
TX UCLA CBAM										
TX UT Health CNRA										
TX UTSW										

Major PDs are highlighted in gray.