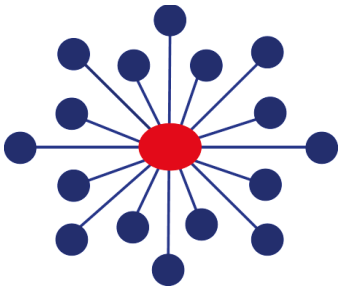

CTN-0051

Extended-Release Naltrexone vs. Buprenorphine for Opioid Treatment (X:BOT)

Statistical Analysis Plan (SAP)

Version 3.0

April 27, 2017

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Listing of Appendix A Tables and Figures

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
ASI-Lite	Addiction Severity-Index-Lite
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
BUP	Buprenorphine
BUP-NX	Buprenorphine+Naloxone (Suboxone®)
CAP	College of American Pathologists
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulations
CHRT	Concise Health Risk Tracking
CLIA	Clinical Laboratory Improvement Amendment of 1988
CNS	Central Nervous System
CoC	Certificate of Confidentiality
CRF	Case Report Form
CTN	Clinical Trials Network
CTP	Community Treatment Program
DEA	Drug Enforcement Agency
DHHS	Department of Health and Human Services
DSC	Data and Statistics Center
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ERC	Ethics Review Committee
FDA	Food and Drug Administration
FTND	Fagerström Test for Nicotine Dependence
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HAM-D	Hamilton Depression Scale
HBsAB	Hepatitis B surface antibody
HBsAG	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IND	Investigational New Drug
IRB	Institutional Review Board
IM	Intramuscular
IV	Intravenous
LFTs	Liver Function Tests (AST, ALT, albumin and bilirubin)
LI	Lead Investigator
MD	Medical Doctor
MDMA	Methylenedioxymethamphetamine (Ecstasy)
MedDRA	The Medical Dictionary for Regulatory Activities
Mg	Milligrams

LIST OF ABBREVIATIONS (cont.)

Abbreviation	Definition
MM	Medical Management
MOP	Manual of Operations
NDA	New Drug Application
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NMS	Non-Study Medical and Other Services
NP	Nurse Practitioner
NTX	Naltrexone
NX	Naloxone
OHRP	Office for Human Research Protections
PA	Physician Assistant
PI	Principal Investigator
PLG	Polylactide-co-glycolide
QA	Quality Assurance
RAB	Risk Assessment Battery
RAP-C	Research Advisory Panel of California
RRTC	Regional Research and Training Center
SAE	Serious Adverse Event
SC	Subcutaneous
SOWS	Subjective Opiate Withdrawal Scale
TAU	Treatment as Usual
TLFB	Timeline Follow-Back
UDS	Urine Drug Screen
VA	Veterans Administration
VAS	Visual Analog Scale
XR-NTX	Extended-Release Naltrexone (Vivitrol®)

1.0 INTRODUCTION

1.1 Study Objective

The primary goal of the study is to estimate the difference, if one exists, between XR-NTX and BUP-NX in the distribution of the time to relapse (i.e., loss of persistent abstinence) during the 6-month trial. Secondary objectives are to: (1) compare outcome on XR-NTX versus BUP-NX across a range of clinical safety and secondary efficacy domains, (2) explore demographic, clinical, and genetic predictors of successful treatment and moderators of differential effectiveness (i.e., what variables may help clinicians choose which of these treatments is best for a given patient), and (3) collect a limited dataset to permit analyses of economic costs and benefits of the two treatments.

1.2 Study Design

This is a multi-center, two-arm, 6-month (24-week), parallel-group, open-label, randomized controlled trial to examine the comparative effectiveness and safety of XR-NTX versus BUP-NX. Candidates will be individuals seeking treatment for opioid dependence (heroin or prescription opioids) who are admitted to an inpatient (detoxification and/or short term residential treatment) program for treatment of substance dependence. The study will be conducted in approximately 8 CTPs that: (a) provide opioid detoxification services (inpatient/residential), (b) have the capacity to maintain participants opioid-free, (c) have the capacity to initiate patients onto XR-NTX or BUP-NX, (d) have the capacity to maintain participants on XR-NTX or BUP-NX for the duration of the 24-week trial, (e) have a sufficient flow of patients completing detoxification and who do not routinely receive long-term medication-assisted therapy as to provide a sufficient population of potential participants to achieve study enrollment goals, and (f) can provide a minimum level of outpatient care (at least one group and/or individual counseling session per week) for 24 weeks. Candidates will be consented, screened, and randomized at the time of admission, during detoxification or during early abstinence. Participants meeting all eligibility criteria will be randomized to one of two treatment conditions, XR-NTX or BUP-NX. Treatment will be for 24 weeks in the context of a protocol-directed medical management treatment program and individual or group psychosocial counseling. Research visits will occur weekly for collection of urine samples and safety and other assessments. XR-NTX will be administered by injection on an approximately every-four-week basis; BUP-NX will be provided for take-home, initially on a weekly basis, transitioning to an every-two-week and then to an every-four-week schedule. Medical management for both conditions will be on a similar (weekly, transitioning to every-two-weeks, to every-four-weeks) schedule. The primary outcome measure will be the time to the event of relapse. XR-NTX will be provided as Vivitrol®. BUP-NX will be provided as Suboxone® film.

The Protocol will proceed in four phases.

Phase 1: Informed Consent, Screening, and Randomization (Days -15 through Day 0): This phase begins with informed consent during the index admission, and initiates enrollment, the conduct of all study-specific procedures and the collection of study data. During the first several days of an index admission, clinical and/or research staff will provide information about the study to potential participants (for scheduled admissions this information may be provided in advance of the admission). Guidelines for opioid detoxification are provided in the study MOP; data on detoxification utilization will be collected. This phase may take place from 1 day to 15 days. Following final review and confirmation of all eligibility criteria, randomization may proceed. Randomization may take place on the same day as informed consent and screening if recent liver function results are available, but in most cases will likely take place 2 or 3 days

later. Regardless of when randomization takes place, the date of randomization will be defined as “Day 0”.

Phase 2: Induction (Day 0 through Day 156): Following randomization, participants will be inducted onto their assigned active medication condition and treated as outpatients for 24 weeks per protocol. Guidelines for induction onto XR-NTX and onto BUP-NX are provided in the study MOP. Following induction, XR-NTX will be administered by injection approximately every 4 weeks; and BUP-NX will be quickly titrated upwards to maintenance doses. Induction should occur as soon as practicable following randomization, but may occur as late as week 22. Participants will continue into Phases 3 and 4 for research visits, even if not yet inducted onto their assigned medication.

Phase 3: Active Treatment (Week 1 through Week 24): Following randomization, participants will be inducted as soon as practicable and treated per their assigned active medication condition and followed as outpatients until 24 weeks post-randomization. Assessment visits will occur weekly. Participants whose induction onto their assigned study medication is delayed will also attend weekly research visits. Medical management visits will initially occur weekly, transition to every two weeks and then to every four weeks. In order to retain participants in treatment, and consistent with good practice, we permit flexibility with dosing. The window for Visit 1 is -3/+6 days to accommodate induction; however, induction may occur after Visit 1. A +/- 3-day window will be permissible for subsequent weekly visits. For participants who relapse and/or become lost to follow up, a -3/+28 day window is permissible to complete the EOT visit. Participants who relapse will discontinue study medication and weekly research visits, but should be encouraged to attend the week 24 and follow up visits at weeks 28 and 36.

Phase 4: Post Treatment Follow-up (Week 25 through Week 36): Toward the end of the 24-week treatment period, participants will be referred for follow-up care in the community (which could include continuation of medication, if available, indicated, and desired), and follow-up outcomes will be assessed at week 28 and week 36 post-randomization. For participants receiving BUP-NX, who do not wish to continue, or for whom community resources are not available, the study will provide a two-week BUP-NX taper (beginning at the week 24 visit). A -3/+28 day window will be permissible for the scheduled week 28 visit and a +/- 4 week window will be permissible for the scheduled week 36 visit.

1.3 Treatment Initiation

To maximize generalizability, this study has been designed to permit entry of participants throughout opioid detoxification and early abstinence. While XR-NTX can only be administered to individuals who have completed detoxification, the percentage of participants who are randomized early that are able to successfully initiate antagonist therapy is unknown. A risk to this study plan is that a differentially large percentage of individuals may be unable to initiate XR-NTX versus buprenorphine therapy.

1.3.1 Study Data Analysis Modification

Timing of the randomization is important to execution of the design and may also be an important prognostic variable. All cases are classified into one of three groups at the time of randomization, those:
(a) randomized within 24 hours of last (licit or illicit) opioid use;
(b) randomized between 24 and 72 hours following last (licit or illicit) opioid use;
(c) randomized more than 72 hours following last (licit or illicit) opioid use.

Each of these groups represents different clinical scenarios commonly encountered in CTN CTPs. Group (a) represents early decision-making, at such a time as to avoid unnecessary detoxification for those choosing BUP-NX. For group (b), decision-making occurs later during

detoxification, but while participants still need to surmount the detoxification hurdle to begin XR-NTX. Group (c) includes participants who can be readily inducted onto either medication.

Individuals in groups (a) and (b) comprise the early randomizers. A data analysis modification (assessment of whether the early vs. late randomizers have a differential treatment effect and if so, time to relapse will be estimated for early and late randomizers separately) will occur if differential treatment initiation is a problem for early randomizers (i.e., significantly fewer early randomizers are able to complete detoxification and XR-NTX induction. This assessment will occur after the entry of 100 cases randomized early in the detoxification process.

1.4 Database Sources

Completed forms and electronic data will be entered into the data management system in accordance with the CRF Completion Guidelines established by the DSC. Only authorized individuals shall have access to electronic CRFs.

1.5 Randomization

Immediately following the final assessment of eligibility, participants will be randomly assigned to one of the two conditions: XR-NTX or BUP-NX. Random assignment will be on a 1:1 ratio to one of the two conditions. A restricted randomization plan will be used with centralized, automated, randomized block assignments. Randomization will be stratified by two factors, site and pre-detoxification level of opioid use. While there will be important and otherwise uncharacterized differences between sites – including state and local treatment service environments, opioid misuse epidemiology, and patient-level customs regarding treatment, medications, and clinical trial participation – the level of heroin and other opioid use will likely be an important independent predictor of treatment retention and rates of negative urines as has been demonstrated in recent analysis of naltrexone opioid trials(Sullivan et al 2006; Carpenter et al 2009; Brooks et al 2010). The level of opioid use at treatment entry is a binary classification, operationally defined as 6 or more bags (or equivalent) IV heroin per day (≥6 bags/day) over the 7 days prior to entry into the treatment program versus less than 6 bags (or equivalent) IV heroin per day (<6 bags/day) or other routes of administration or other opioids.

Eligible participants will be randomized in a 1:1 ratio to the BUP-NX and XR-NTX arms. The randomization process will be performed by computer at a centralized location. Randomization will be stratified by site and pre-detoxification level of opioid use [6 or more bags (or equivalent) IV heroin per day (≥6 bags/day) over the 7 days prior to entry into the treatment program versus less than 6 bags (or equivalent) IV heroin per day (<6 bags/day) or other routes of administration or other opioids]. The block size chosen will be adequate to ensure approximate treatment balance. The number in each treatment group will never differ by more than a factor of KB/2 where B is the block size and K is the number of strata.

The randomization procedure will be conducted in a centralized process through the Clinical Trials Network (CTN) Data and Statistics Center (DSC). The DSC statistician will generate the randomization schedule using balanced blocks of varying sizes within strata to ensure lack of predictability along with relative equality of assignment across treatment groups. The DSC statistician will review randomization data on a regular basis to ensure that the scheme is being implemented according to plan. A randomization slot, once used, will not be re-allocated. Details of the randomization process are described in a separate Randomization Plan.

1.6 Study Population

Study participants will be approximately 600 treatment-seeking heroin- and/or prescription opioid-dependent volunteers, without chronic pain requiring opioid therapy, who are willing to accept “agonist-based” or “antagonist-based” therapy. Randomization will be stratified by (1)

treatment site, and (2) baseline opioid use (high level use [≥6 bags {or equivalent} IV heroin/day] vs. all others [i.e., <6 bags {or equivalent} IV heroin/day and other routes of administration or other opioids]).

1.6.1 Inclusion Criteria

1. Male or female;
2. 18 years of age and older;
3. Meet DSM-5 criteria for opioid-use disorder (heroin and/or prescription opioids);
4. Have used opioids other than as specifically prescribed within thirty days prior to consent;
5. Seeking treatment for opioid dependence and willing to accept “agonist-based” or “antagonist-based” therapy;
6. In good-enough general health, as determined by the study physician on the basis of medical history, review of systems, physical exam and laboratory assessments, to permit treatment with XR-NTX or BUP-NX;
7. Able to provide written informed consent;
8. Able to speak English sufficiently to understand the study procedures and provide written informed consent to participate in the study;
9. If female of childbearing potential, be willing to practice an effective method of birth control for the duration of participation in the study.

1.6.2 Exclusion Criteria

1. Serious medical, psychiatric or substance use disorder that, in the opinion of the study physician, would make study participation hazardous to the participant or compromise study findings or would prevent the participant from completing the study. Examples include:
   (a) Disabling or terminal medical illness (e.g., uncompensated heart failure, cirrhosis or end-stage liver disease) as assessed by medical history, review of systems, physical exam and/or laboratory assessments;
   (b) Severe, untreated or inadequately treated mental disorder (e.g., active psychosis, uncontrolled manic-depressive illness) as assessed by history and/or clinical interview;
   (c) Current severe alcohol, benzodiazepine, or other depressant or sedative hypnotic use likely to require a complicated medical detoxification (routine alcohol and sedative detoxifications may be included);
2. LFTs (ALT, AST) greater than 5 times upper limit of normal;
3. Suicidal or homicidal ideation that requires immediate attention;
4. Known allergy or sensitivity to buprenorphine, naloxone, naltrexone, polylactide-co-glycolide, carboxymethylcellulose, or other components of the Vivitrol® diluent;
5. Maintenance on methadone at doses of 30mg or greater at the time of signing consent;
6. Presence of pain of sufficient severity as to require ongoing pain management with opioids;
7. Pending legal action or other reasons that might prevent an individual from completing the study;
8. If female, currently pregnant or breastfeeding, or planning on conception;

9. Body habitus that, in the judgment of the study physician, precludes safe intramuscular injection of XR-NTX (e.g., BMI>40, excess fat tissue over the buttocks, emaciation).

2.0 OUTCOMES

2.1 Primary Outcome

The primary outcome measure will be the time to the event, with the event called relapse. By definition individuals are abstinent at the time of randomization. Relapse occurs if the participant is using any non-protocol prescribed opioids regularly starting at day 21 post-randomization or thereafter. Operationally, loss of persistent abstinence is defined as either: (a) four consecutive opioid use weeks, or (b) seven consecutive days of use by self-report. A use week is defined as any week during which a participant self-reports at least one day of use during that week, provides a urine sample positive for non-protocol opioids, or fails to provide a urine sample. Self-report of opioid (heroin or prescription opioids) and other substance use will be ascertained at each weekly study visit using the Time Line Follow-back for each day leading back to the previous visit. Urine will be collected at each study visit and tested for opioids. In the event that a participant reports no use, but their urine test indicates use, then we will regard the week as a use week. Missing urine samples will be classified as positive. The time of the event occurs at the start of the qualifying clinical event period (e.g., first of the 7 consecutive use days or start of the 4 consecutive weeks of use).

2.2 Secondary Outcomes

Table 1: Protocol Secondary Outcomes and Hypotheses

Outcomes	Hypotheses
Proportion successfully inducted onto assigned study medication (binary: did or did not receive first dose of XR-NTX, or achieve maintenance dose of BUP-NX)	BUP-NX will produce higher rate of successful induction than XR-NTX Significance/Rationale: XR-NTX induction requires completion of detoxification, whereas BUP-NX induction only requires onset of withdrawal symptoms. Thus XR-NTX may have more dropouts after randomization but prior to XR-NTX induction.
Adverse Events related to study medications	XR-NTX and BUP-NX will produce equivalent rates of SAEs, and equivalent rates of AEs, though AE pattern will differ somewhat (e.g. injection site reactions with XR-NTX) Significance/Rationale: Careful documentation of SAEs and AEs, including overdose episodes, would be considered essential safety data, and important component of a comparative effectiveness trial.
Opioid abstinence over time while on study medication (Weekly TLFB, confirmed by urine drug screens)	XR-NTX will produce greater opioid abstinence than BUP-NX Significance/Rationale: XR-NTX produces complete blockade of opioid effects, so that during treatment with monthly injections, opioid use can be expected to be minimal. In contrast BUP-NX may not produce complete blockade, or patients may reduce or stop doses for a few days and substitute other opioids (heroin, prescription opioids).

Table 1: Protocol Secondary Outcomes and Hypotheses	
Outcomes	Hypotheses
Alcohol and other drug use, over time (TLFB and UDS)	XR-NTX will be superior to BUP-NX in producing abstinence from alcohol and other drugs Significance/Rationale: Clinical trials show XR-NTX is effective for treatment of alcohol dependence, and naltrexone has some evidence of efficacy for stimulant dependence.
Cigarette smoking (FTND, Tobacco Use Questionnaire, VAS nicotine craving)	XR-NTX will reduce cigarette smoking compared to BUP-NX Significance/Rationale: Naltrexone has been studied as a treatment for nicotine dependence, with some support from clinical trials, although inconsistent. Given high morbidity and mortality associated with nicotine dependence, a comparative advantage of one or the other of these treatments at reducing smoking would be valuable to examine.
Opioid Craving (VAS) over time	XR-NTX will be superior to BUP-NX in reducing opioid craving Significance/Rationale: Krupitsky et al (Lancet 2011) pivotal XR-NTX trial showed, surprisingly, that XR-NTX reduced craving substantially compared to placebo.
Subacute withdrawal symptoms over time (HAM-D, SOWS)	XR-NTX will produce greater severity of subacute withdrawal symptoms than BUP-NX during the first month after randomization, but will be equivalent to BUP-NX in months 2 to 6 Significance/Rationale: Low-grade withdrawal-like symptoms (dubbed “naltrexone flu” by the Columbia group, and consisting typically of insomnia, fatigue, and anorexia, though not drug craving) have been observed in some patients in the 1 to 4 weeks after naltrexone initiation, resolving gradually. Further characterization of this syndrome would be important for developing treatment guidelines.
Problems related to drug abuse (ASI-Lite and EQ-5D)	XR-NTX will be superior to BUP-NX Significance/Rationale: Greater opioid and non-opioid abstinence on XR-NTX will result in fewer problems associated with active drug abuse.

Table 1: Protocol Secondary Outcomes and Hypotheses	
Outcomes	Hypotheses
HIV risk behavior over time (RAB and other HIV risk measures)	XR-NTX and BUP-NX will be equivalent Significance/Rationale: The opioid-dependent population is at high risk for HIV, both from injection drug use and from unsafe sexual practices. Effective treatment for the opioid dependence may reduce HIV risk behavior. Given the high morbidity and mortality associated with HIV, a comparative advantage of one or the other of these treatments would be valuable to examine.
Cognitive function (Trails Making Test Parts A and B, Stroop)	XR-NTX and BUP-NX will be equivalent Significance/Rationale: Some providers and policy-makers are concerned that patients maintained on BUP-NX will have opioid-agonist-related cognitive impairment.

3.0 GENERAL CONSIDERATIONS

3.1 Terminations

There are multiple types of terminations in this study, end of study medication, medical management termination and study termination. Study medication will be discontinued in the event of intolerable side effects, safety concerns preventing further medication treatment (i.e., pregnancy), relapse, or the end of the 24-week active treatment phase. Participants discontinuing medication, but not yet meeting relapse criteria, prior to week 24 will continue within the same study assessment schedule. Participants meeting relapse criteria will discontinue medication, research visits and complete a medical management termination form. All participants who end treatment early (prior to week 21) will be encouraged to attend a visit at week 24 and will be seen in long-term follow-up (weeks 28 and 36). In all cases of treatment discontinuation, the research team will make an effort to arrange for continued community treatment, as appropriate and available, including further XR-NTX and BUP-NX, or methadone maintenance and intensive outpatient psychosocial aftercare. For participants receiving BUP-NX, who do not wish to continue, or for whom community resources are not available, the study will provide a two-week BUP-NX taper, if clinically appropriate.

Dropout from treatment is a typical failure mode for the treatment of opioid dependence with both XR-NTX and BUP-NX. A sensitivity analysis will be performed to examine the impact on the hazard ratio and its confidence limits of alternative endpoint definitions. In particular for the primary endpoint, individuals who withdraw will be considered events if they fail to provide weekly urine specimens. An alternative to the protocol definition which introduces these as censored observations will be examined. The analyses of these events can be complex as standard assumptions (missing at random) may not be plausible.

Other outcome variables (opioid and other substance use over time, craving, mood, etc.) will have missing data due to missed visits and dropout from treatment and from study participation. The generalized linear model, or mixed effects model frameworks that will be used for analyses, works with what data are gathered, and assumes missing data are missing at random. For selected secondary outcome analyses, sensitivity analyses will be considered to examine the stability of estimated treatment effects in the face of departures from the assumption of missing at random.

Aggressive tracking procedures will be put into effect to attempt to locate participants and re-engage them, and to minimize missing data. These procedures will be detailed in the study MOP. The greatest likelihood of violation of the assumption of missing at random derives from dropouts, since participants assigned to XR-NTX may dropout from the study for different reasons than participants assigned to BUP-NX, creating the potential for differential attrition. Differential study attrition for the two treatment groups, where outcome differs between the dropouts is a threat to the validity of the outcome analysis. Minimizing the rate of study dropout and loss to follow-up, through aggressive tracking and follow-up, serves to reduce this threat. At a minimum the data gathered on dropouts can be used to test the assumption of missing at random, by examining whether dropouts from the different treatment assignments have similar or different outcomes.

3.2 Study Modification for Differential Treatment Initiation

To maximize generalizability, this study has been designed to permit entry of participants throughout the opiate detoxification process and early abstinence. At the time the study was designed, it was understood that community-based practice of detoxification and medication induction would vary across sites and across patients within sites. It was further decided that the

protocol would allow this variation in community based practice of detoxification-induction, consistent with the aims of an effectiveness trial to test the medications under real world conditions. It was also anticipated that induction onto BUP-NX would be easier than induction onto XR-NTX for patients who are randomized "early" while opioids are still in their system. This is because BUP-NX can be safely initiated while opioids are still in the system, as long as some signs of withdrawal begin to develop, while for XR-NTX one needs to wait until detoxification is completed. This delay is an opportunity for differential attrition between the 2 study arms. The concern is that a higher induction failure rate on XR-NTX, among those randomized early, will contribute to differences in outcome (time-to-relapse) across the 6 month trial, with induction failure leading to relapse. If this is the case, then the interaction between early vs. late randomization and treatment assignment on the primary outcome (time to relapse) becomes germane.

Therefore, after the entry of 100 "early randomizers" (as defined in Protocol Section 8.3 [or Section 1.5 above]) we will compare the induction success rate in these early randomizers on XR-NTX vs. BUP-NX with a test of difference between proportions. The decision rule has >80% power (alpha=2.5% 1 tail) to identify differences of .25 or greater if the true initiation rate for the BUP-NX is in the expected range (>=.85). If the difference in induction failure rate is statistically significant, then the following plan will be followed:

1. Increase the sample size to end enrollment at such time as 350 late randomizers have been enrolled to increase power to estimate the difference in primary outcome (time-to-relapse) in this late randomizer group. It is projected that at such time the total N will be approximately 600.
2. Amend the data analysis plan to incorporate an interaction term in the analysis model.

3.3 Sample Size and Power Calculations

The therapeutic strategies defined above will be evaluated and compared in a two-arm randomized open-label multi-center trial.

Original Projected Sample Size: 200 per treatment group. N = 400 total.

Data Analysis Modification Projected Total Sample Size: N~600 total sufficient to enroll 350 late randomizers.

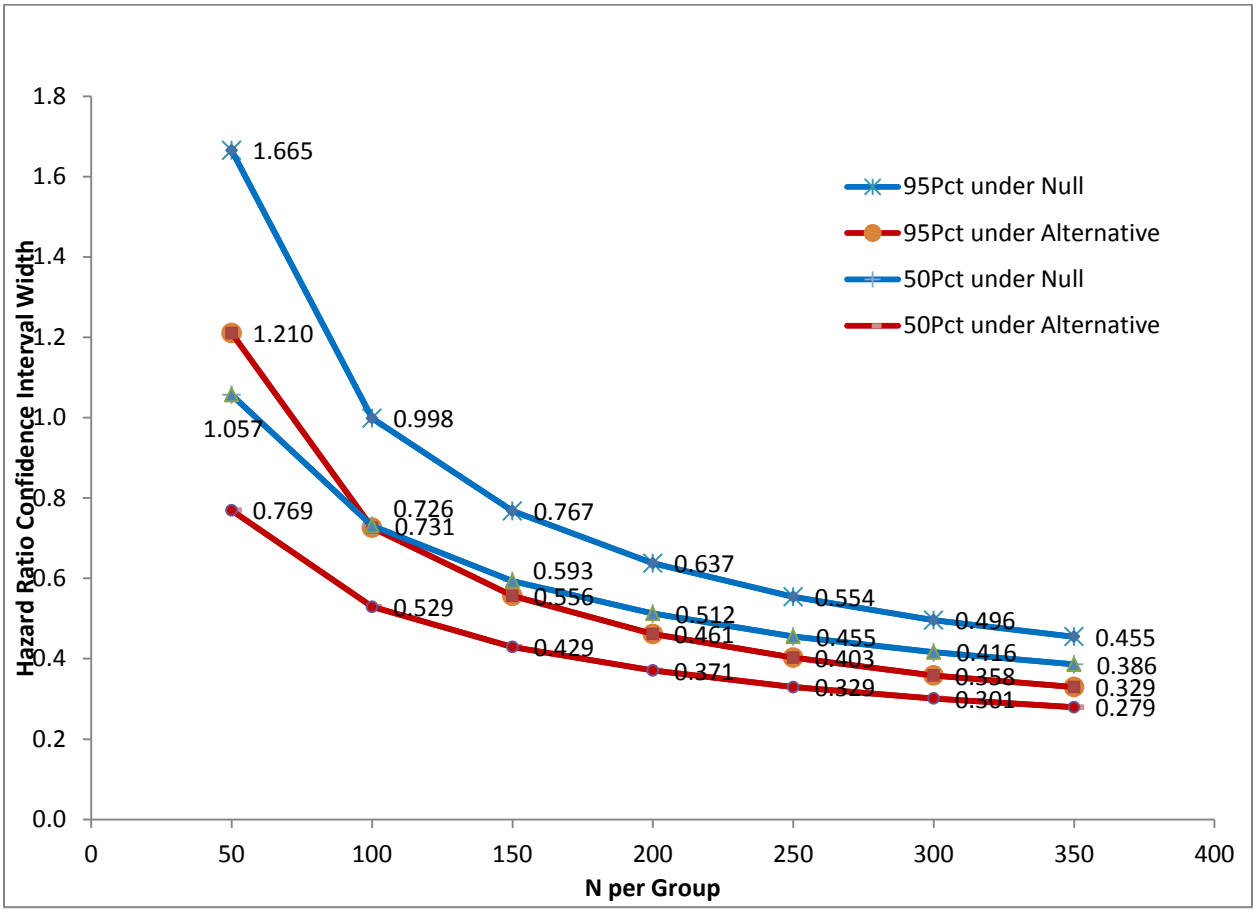
Rationale: The primary outcome is the time to relapse as defined above. Meta-analyses of randomized controlled trials of BUP-NX maintenance treatment for opioid dependence suggest that approximately 50% of patients are retained in BUP-NX treatment with good clinical outcome over 6 months. (Mattick and Kimber 2008). Extended release naltrexone preparations have had few prior randomized comparisons but observations from a recent Russia-based trial evaluating the XR-NTX dose and formulation proposed for this trial had good results with 53% receiving all monthly injections and retained for 6 months. Direct randomized comparison of these approaches has not been performed.

We evaluate the anticipated variability of the primary terminal results by simulating under exponential distributional assumptions with event (relapse) grouping after the first 21 days and using proportional hazards without censoring. Let one treatment have a 6-month success rate of 40% with exponential failure. We use a lower success target than indicated in the above paragraph because the use of the early randomization time point is expected to increase the percentage of participants who are failures. There would be minimal impact on detectable alternatives if a higher 50% success rate was used. From the plot below, we observe that the 95% CI width for the hazard ratio for the 50th percentile of the simulation results under both the null and alternative hypotheses decreases by 31%, 19%, and 14% as the sample size increase

by 50/arm from a base of 50/arm. CI width decreases by 11% when the sample size increases from 200/arm to 250/arm. We have selected 200/arm as subsequent precision improvements with these criteria are close to 10% per 100 sampling units.

Beyond a sample size of 150 to 200 patients per group, further increments in sample size (200 per group, 250 per group, 300 per group, etc.) yield diminishing returns in terms of only relatively small further narrowing of the 95% confidence interval. The rationale for increasing the total sample size to N ~600, in the event of a significant difference in induction success rate among early randomizers, is that given the current ratio of early to late randomizers, N ~600 total will yield approximately 250 early randomizers and 350 later randomizers. 350 late randomizers (N = 175 per treatment group) is close to the 400 (N = 200 per group) originally planned, and will yield a very similar (only slightly wider) 95% confidence interval. This will preserve the intent to achieve a relatively precise estimate of the difference in relapse rates among late randomizers.

Figure 1: Simulation results for the 50th and Upper 95th percentile of the 95% Confidence Interval Widths for the Hazard Ratio, selected sample sizes with lambda=0 and lambda=0.678



The decision theoretic properties of n=200/arm is evaluated further under a decision theoretic approach and using the logrank test. With two-sided alpha = 0.05, N = 400 total participants provides 90% power to detect a hazard ratio of .63 for the second treatment. Table 2 provides additional characterization of power characteristics of the sample size.

Table 2: Detectable Alternatives and Power for 2-tailed 5% level logrank test without censoring Null distribution has a 40% 6 month success rate, N1=N2=200		
Power (%)	Hazard Ratio	6 Month Survival Rate (%) under the Alternative
90.0	.633	56.0
80.0	.678	53.8

Note that inclusion of the baseline level of opioid dependence severity stratification variable in the statistical model as a covariate may increase power and narrow the confidence limits on treatment hazard ratios, should divergent success rates be present in the strata groupings.

Secondary analyses of moderators of treatment effect are important to trial sample size selection. With approximately 200 XR-NTX cases evenly split between two levels of a classifying variable, we would have 79% power to detect, using a two-tailed 5% level test of a binary endpoint, a 20 percentage point difference between the groups. Thus the selected sample size would be relatively robust in its ability to determine whether there are important differences in therapeutic success rates for major demographic or baseline clinical factors.

3.4 Interim Analysis

The study will undergo safety monitoring by the designated DSMB. Both therapies are standard therapies with regulatory approval for treatment of opiate abuse. The treatment strategies have not been directly compared before and classic interim efficacy monitoring is not planned as both are considered acceptable therapies. An adaptive strategy for addressing substantial differential treatment initiation is described above and in Section 5.2.

3.5 Software

All analyses will be performed utilizing SAS® version 9.3. All statistical tests will be conducted at the 5% Type I error rate (two-sided). 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 multiple testing issues and will interpret results with caution and use confidence intervals where possible.

3.6 Analysis Populations

Each primary and secondary efficacy outcome measure will be analyzed for the intent-to-treat (ITT) and evaluable population. The intent-to-treat principle is that participants will be analyzed in the groups to which they were randomized, regardless of whether they received the randomized study medication. Another analysis population of interest is the as-treated population. The as-treated population will consist of only participants who were inducted onto study medication.

Major differences in the results for the ITT and as-treated populations, if any, will be further explored. While there is every intention to be complete in describing the analyses to be performed, it is not possible to anticipate every contingency, and some adjustments may be required to meet constraints posed by the structure of the data. Constraints such as non-linearity, non-normality, etc. may lead to different but more appropriate approaches to analysis.

3.7 Distributional Assumption Tests

Empirical distributions of all variables will be visually inspected to detect outliers. The underlying proposed statistical methods for each analysis will be examined, primarily through inspection of graphical displays, standardized residuals, or influence diagnostics. Where appropriate,

transformations will be utilized or analyses will be performed utilizing a more appropriate distribution.

4.0 ANALYSES OF DEMOGRAPHIC AND BASELINE DATA

The demographic variables for this study include: gender, age, race, ethnicity, education level, employment status, and marital status. The baseline clinical characteristics include: opioid dependence severity, severity of other substance use, severity of mood/anxiety symptoms, severity of opioid withdrawal symptoms, current/past co-occurring psychiatric disorders, current medical disorders, select genetic markers, history of legal problems, currently under legal supervision (parole, probation or mandated).

Descriptive statistics for baseline and demographic variables will be presented for participants randomized to each of the treatment arms and overall. Descriptive statistics will include N, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum and maximum for continuous variables and proportions and percentages for categorical variables. Since 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 not be conducted. The updated CONSORT statement no longer recommends formal testing of statistical significance of differences between baseline characteristics.

5.0 STATISTICAL ANALYSES

5.1 Timing of Randomization Definitions

The early randomizers are those participants randomized within 72 hours following the last licit or illicit opioid use. The late randomizers are those participants randomized greater than 72 hours following the last licit or illicit opioid use. To determine the timing of randomization, it is necessary to know the day and time (measured using 24 hour clock) of last licit or illicit opioid use. On rare occasions, missing values for one or both of these measures may exist. For primary analysis purposes, if the date of last licit or illicit opioid use is available but the time is not, the participant's time will be imputed to be 00:00. This will impute the longest potential time from randomization. If the date of last licit or illicit use is missing, the participant categorization will be imputed by the predominant proportion of the randomization timing status in that site.

5.2 Differential Treatment Initiation for Early Randomizers Assessment

The study modification assessment will be completed when the 100 participants who have been randomized within 72 hours following his/her last (licit or illicit) opioid use have had at least 21 days post-randomization to be inducted onto study medication. The analysis population for the early randomizers assessment will only consist of the first 100 early randomizers. The timing of the database freeze will ensure that these 100 early randomizers have had at least 21 days post-randomization to be inducted onto study medication.

5.2.1 Induction Status Determination

A participant's induction status will be a binary variable of Yes or No. For the participants randomized to BUP-NX, participants will be defined as inducted onto the study medication if he/she has been dispensed medication as measured on the BUP-NX dose log; otherwise, the participant will be defined as not being inducted onto study medication. In a similar manner, for participants randomized to XR-NTX, participants will be defined as inducted onto the study medication if he/she has received an injection of the study medication. Note, the definition of induction status is not dependent upon the number of days for induction to occur.

5.2.2 Induction Status Analysis

The null hypothesis is:

$$H_0 : p_{XR-NTX} = p_{BUP-NX}$$
$$H_A : p_{XR-NTX} \neq p_{BUP-NX}$$

Where p_{XR-NTX} is the proportion of early randomizer participants in the XR-NTX group who were inducted and p_{BUP-NX} is the proportion of early randomizers participants in the BUP-NX group who were inducted. The Fisher's exact test will be used to determine statistical significance at a significance level of 0.05.

5.3 Primary Outcome

The primary outcome measure will be the time to the event, with the event called relapse. By definition individuals are abstinent at the time of randomization. Relapse occurs if the participant is using any non-protocol prescribed opioids regularly starting at day 21 post-randomization or thereafter. Operationally, loss of persistent abstinence is defined as either: (a) four consecutive opioid use weeks, or (b) seven consecutive days of use by self-report. A use week is defined as any week during which a participant self-reports at least one day of use during that week, provides a urine sample positive for non-protocol opioids, or fails to provide a urine sample.

Self-report of opioid (heroin or prescription opioids) and other substance use will be ascertained at each weekly study visit using the Time Line Follow-back for each day leading back to the previous visit. Urine will be collected at each study visit and tested for opioids. In the event that a participant reports no use, but their urine test indicates use, then we will regard the week as a use week. Missing urine samples will be classified as positive. The time of the event occurs at the start of the qualifying clinical event period (e.g., first of the 7 consecutive use days or start of the 4 consecutive weeks of use).

5.3.1 Primary Outcome Criteria

Relapse assessment starts Day 21 post-randomization with the day of randomization as Day 0 and ends at the Week 24 visit. As noted above, relapse is defined in two ways:

a) Four consecutive opioid use weeks

i) There are three ways that a use week can be established:

(1) Participant self-reports at least one day of use during that week

The self-report of use is measured between the weekly visits and thus does not always include the review of exactly seven days. At the weekly visit, if the previous visit was missed, the participant's daily self-report opioid use is assessed from the start of the current visit window (i.e. the beginning of the window as specified by the protocol calendar, see table below) to the day before the current visit. Conversely, if the previous visit was attended, the participants daily self-report opioid use is assessed from the previous visit attended day to the day before that current visit. Note, only participants self-report collected on or after Day 21 is used in evaluating whether the week is a use week. Thus, if the Week 3 visit is attended on Day 21, there cannot be a use week based on self-reported opioid use.

Table 3: CTN-0051 Protocol Calendar

Visit Number	Target Day	Beginning Window (Days)	End of Window (Days)
00R	00	00	00
01	06	3	12
02	13	10	16
03	20	17	23
04	27	24	30
05	34	31	37
06	41	38	44
07	48	45	51
08	55	52	58
09	62	59	65
10	69	66	72
11	76	73	79
12	83	80	86
13	90	87	93
14	97	94	100
15	104	101	107

Table 3: CTN-0051 Protocol Calendar			
Visit Number	**Target Day**	**Beginning Window (Days)**	**End of Window (Days)**
16	111	108	114
17	118	115	121
18	125	122	128
19	132	129	135
20	139	136	142
21	146	143	149
22	153	150	156
23	160	157	163
24	167	164	195

(2) Participant provides a urine sample positive for non-protocol opioids

The urine drug screen (UDS) is used to assess whether the urine sample is positive for non-protocol opioids. Only UDSs assessed at weekly visits will be used to determine relapse status. UDSs assessed at the inductions that occur prior to Day 21, supplemental induction or end of treatment visits will not be used to assess relapse. Note, any induction UDSs that occur after Day 21 are entered into the weekly visit, and the results are duplicated in the induction visit UDS. Additionally, supplemental UDSs are not expected and should not be entered except for supplemental induction visits. If an out of window visit occurs, the UDS collected at that out of window visit will contribute to the use week calculation of that visit.

For the BUP-NX arm, use for a urine sample is defined as a positive result for any of the following tests: Opiates (2000 ng), Oxycodone (OXY), Methadone (MTD), or Opiates (300 ng). For the XR-NTX arm, use for a urine sample is defined as a positive result for any of the following tests: Opiates (2000 ng), Oxycodone (OXY), Methadone (MTD), Opiates (300 ng) or Buprenorphine (BUP).

(3) Participant fails to provide a urine sample.

UDSs that are not collected, determined to be adulterated or out of the temperature range result in a use week. If the field indicating adulterated or out of temperature range is missing, that UDS would result in a use week. Additionally, missed visits are tracked using the missed visit form. If the missed visit form is completed, that week is designated a use week.

b) Seven consecutive days of use by self-report

The timeline follow back dataset is used to calculate the number of consecutive use days. A use day is defined as values for the opioids mentioned above. The first instance of seven consecutive days of use by self-report will define the participant as relapsed. The first day of the seven consecutive days is defined as the relapse start date.

5.3.2 Determination of the Start of the Clinical Qualifying Event

For the purposes of the primary outcome analyses, the relapse start day will be used. The time of the event occurs at the start of the qualifying clinical event period (e.g., first of the 7 consecutive use days or start of the 4 consecutive weeks of use). If both of the criteria above (a and b) are met, then the earlier of the two relapse start dates will define the day that the relapse criterion met for the purposes of primary outcome analyses.

When a participant's data indicates four consecutive weeks of use, the reason the first week was defined as a use week will be used to determine the start of the qualifying clinical event period. The first use week could be due to either a self-report of at least one day of use, a urine sample positive for non-protocol opioids, failure to provide a urine sample or some combination of these reasons. The following table outlines how the start of the clinical qualifying event will be determined in the case of a participant having four consecutive weeks of use.

Table 4: Determination of the Start of the Clinical Qualifying Event

Reason for First Use Week			Start of the Clinical Event
Missing UDS	Positive UDS	Self-report of at least one day	
*		*	Date of first self-reported use
	*	*	Day of first self-reported use
		*	Day of first self-reported use
	*		Day of positive urine drug screen
*			First study day of the first use week period as defined by the protocol calendar

5.3.3 Primary Outcome Analysis Methods

Since the results of the interim analysis indicated a differential treatment initiation rate assessment, the data analysis modification will be employed. As noted in Section 3.2, if there is a differential treatment initiation rate in the early randomizers group, an interaction term for the treatment by randomization timing variables will be incorporated into the final analysis model.

Data will be analyzed using a Cox proportional hazards model. The model is as follows:

$$\log h(t \mid CUF) = \log h_0(t \mid CUF) + \beta_1 * Treatment + \beta_2 * TIMING + \beta_3 * CTP + \beta_4 * STRATA + \beta_5 * Treatment * TIMING$$

where h is the hazard rate, roughly defined as the probability per time unit that a case that has not relapsed to the beginning of the respective interval will relapse in that interval. Conceptually, it can be thought of as the number of relapse per time units in the respective interval, divided by the average number of non-relapse cases at the mid-point of the interval. The quantity h0 is an arbitrary baseline hazard rate.

The SAS PHREG procedure will perform survival analysis based on the Cox model to estimate the hazard ratio for the treatments. The 95% Wald Confidence limits will be estimated.

The following SAS Code will be used to analyze the data:

```
PROC PHREG;
    CLASS TREATMENT (REF='BUP-NX') TIMING (REF='Late');
    MODEL TIME*STATUS = TREATMENT TIMING CTP STRATA
TREATMENT*TIMING;
    HAZARDRATIO TREATMENT;
RUN;
```

The variables included in the SAS code are described as follows:

- TREATMENT- This variable defines the randomized treatment assignment. (BUP-NX or XR-NTX)
- TIME- Time to relapse
- STATUS- Censoring variable
- CTP- CTP
- STRATA- Randomization Stratification factor pertaining to the baseline opioid severity level classified as <6 bags (Low Severity) or ≥ 6 bags (High Severity).
- TIMING- Binary baseline variable (early vs. later randomization as noted in Section 5.1 defined as either 'Late' or 'Early').

The initial analysis will be the construction of the asymptotic 95% CI for the hazard ratio of the difference between the treatment arms in the time to event distribution for the primary outcome. The study arm success rates with confidence intervals at week 24 and the difference in success rate at that time point and associated confidence intervals will be constructed.

If the data analysis modification is implemented, the binary baseline variable (early vs. later randomization as previously defined) is included in the primary outcome analysis (outcome = time-to-relapse) as a covariate, a priori. The early vs. late randomization covariate by treatment interaction is included in the primary outcome analysis. If the covariate (early vs. late randomization) by treatment interaction is significant at P < .10, then the interaction term is retained in the final model. To characterize the interaction, the effect of treatment assignment (which includes the interaction and the main effect for treatment) (i.e., the difference in time-to-relapse between treatments) is estimated separately in early vs. late randomizers, and these two separate estimates become the primary findings of the study. If the covariate (early vs. late randomization) by treatment interaction is not significant (p>=.10) then the interaction term will be removed from the model and the main effect estimate will be the primary finding of the study. Exploratory analyses will also evaluate whether the primary outcome measure of time-to-relapse is associated with the number of hours between last licit or illicit opioid use and randomization, that is, a continuous measure of the randomization timing. Both linear and non-linear effects will be explored as potential effect modifiers.

The Cox proportional hazard model is based on the following assumptions. First, there is a proportional hazards assumption, such that if an individual has a risk to opioid use at initial time point that is twice as high as that of another individual, then at all later times the risk of opioid use remains twice as high. Secondly, factors such as the way participants are recruited into a study and the determination of relapse remains constant over the period of the study i.e. censoring should be independent of an event (relapse) happening. The proportional hazards assumption will be assessed by testing of the time to relapse variable and the corresponding covariates of interest. If the proportional hazards assumption is not met, the final model will incorporate a time-dependent variable for the non-proportional predictors in the Cox model.

5.4 Secondary Analyses of Primary Outcome Measure

Subsequent analyses will explore the treatment effect as a function of time, stratification variables and other factors that may have differential impact on treatment success. The analyses will first model the time to event primary outcome measure as a function of treatment assignment (XR-NTX vs. BUP-NX), opioid dependence severity stratum, site, and the two way treatment interaction terms (site by treatment and stratum by treatment) in a proportional hazards regression model. The Cox model previously described in the primary outcome analysis can separately incorporate covariates that are fixed (at baseline). The constancy of the relative hazard assumption will be examined via the interaction of treatment and time, and the interaction between treatment and baseline severity will be tested.

If treatment by site interaction is significant, we will further investigate if the interaction is quantitative or qualitative. A quantitative interaction between treatment and site will indicate that the treatment differences are in the same direction across sites but the magnitude differs from site to site, while a qualitative interaction reveals that substantial treatment differences occur in different directions in different sites. As indicated by Gail and Simon (1985), the existence of a quantitative interaction between treatment and site does not invalidate the analysis in pooling data across centers. Hence we will analyze the data ignoring the treatment-by-site interaction. But when there is a qualitative interaction the treatment effect itself would not make any sense and any kind of analysis claiming a common treatment effect will be questionable.

If the stratum by treatment interaction has a p-value <0.10, then this will be taken to indicate differences in strata-specific efficacy. We note that if this interaction is qualitative (i.e., reversal of treatment advantage in the subgroups) this will have important consequences for future treatment and research decisions. We will test the pair-wise differences between XR-NTX and BUP-NX, separately in the low dependence vs. high dependence subgroups, and further examine the differences with an ordinal/continuous dependence covariate. Note that we are not powering the study to detect the interaction; however, given the likelihood that baseline use predicts outcome, or may interact with treatment (Nunes et al 2011), the coefficient of the main effect of treatment in the model is not meaningful in the presence of an interaction with baseline covariates, and that a significant interaction should prompt testing of the region(s) of the baseline covariate where the probability of treatment successes differ (Nunes et al 2011; Pocock et al 2002).

Secondary analyses of the 24 week successes will include screening baseline variables to identify potential subgroups in the treatment groups with differential results.

All participants who were randomized will be included in the primary efficacy analysis. Note that the primary analysis for the time to relapse inference is based on the assumption that all missing UDSs' are positive.

A secondary analysis of the primary outcome measure will also be presented assuming these observations are censored which will allow us to assess robustness of conclusions to the deviation from the MAR missing data assumption. See Section 6.0 for additional details.

Summary statistics for the primary outcome measure will be provided for each CTP.

5.5 Secondary Outcomes

Most secondary outcome analyses will follow a similar form and strategy to that above, with different linear models as appropriate for the form of the secondary outcome variable: dichotomous secondary outcomes will use logistic regression; time-to-event variables will use survival analysis with Cox models; continuous variables or count variables (e.g., bags per day of heroin use) will use mixed effect models depending on the distribution of the outcome (e.g., normal, Poisson, negative binomial, zero-inflated). Repeated measures will have time in the model in addition to treatment and baseline covariates.

For the secondary outcome measures that are continuous a mixed effects model will be used to analyze the data incorporating appropriate covariates. The model for secondary outcomes that are continuous can be explained in matrix form as follows:

$$\mathbf{y} = \mathbf{X}\beta + \mathbf{Z}\mathbf{b} + \varepsilon$$
$$\mathbf{b} \sim N_q(0, \Psi)$$
$$\varepsilon \sim N(0, \sigma^2 I)$$

Where

- $\boldsymbol{y}$ is the N (sample size) × 1 secondary outcome vector.
- **X** is the N × p model matrix for the fixed effects (e.g. Treatment).
- β is the p × 1 vector of fixed-effect coefficients.
- **Z** is the N × q model matrix for the random effects (e.g. Site).
- **b** is the q × 1 vector of random-effect coefficients.
- ε is the N × 1 vector of errors for outcome.
- ψ is the q × q covariance matrix for the random effects.
- $\sigma^2 I$ is the N × N covariance matrix for the errors.

5.5.1 Induction Success

Successful initiation of protocol medication is an important binary outcome that may also be useful to subsequently explain differences in the primary outcome. The induction success outcome will be defined as noted in Section 5.3.1. Data will be analyzed using a logistic regression model. The model will include variables for treatment arm, a continuous measure of the randomization timing and the corresponding interaction term. The continuous measure of randomization timing will be the number of days between randomization and last licit or illicit use of opioids.

5.5.2 Opioid Abstinence

Opioid abstinence will be measured using the TLFB and confirmed by urine drug screens.

5.5.3 Cigarette Smoking

Cigarette smoking is assessed by the FTND, Tobacco Use Questionnaire and visual analog scale for nicotine craving assessments.

The visual analog scale for nicotine craving is assessed at multiple follow-up timepoints and thus a mixed effects model will be used to assess whether there is a treatment effect with respect to the VAS nicotine craving scale.

5.5.4 Opioid Craving

Participants' cravings for opioid craving is documented on visual analog scales (VAS) via scores that range from 0 (no craving) to 100 (most intense craving possible). The VAS assessing opioid craving is completed at each study visit throughout the active treatment phase. A mixed effects model analysis will be conducted with treatment as a covariate.

5.5.5 Subacute Withdrawal Symptoms

Subacute withdrawal symptoms are measured by the HAM-D and the SOWS.

5.5.6 Drug Use Problems

There are two assessments that capture data on drug use problems, the ASI-Lite and the EQ-5D.

The ASI-Lite is derived from the Fifth Edition of the ASI, a structured clinical interview that yields scores for seven areas of functioning typically impacted by addiction, including medical status, employment status, drug use, alcohol use, family status, legal status, and psychiatric status. Opioid use questions, including the main type of opioid used by the participant, whether a prescription opioid or heroin, the onset of the use, the participant's perception of the substance that is most problematic, and their present treatment goal will also be assessed at screening as part of the ASI assessment. The ASI-Lite is completed at baseline, at the end-of-treatment visit (week 24/EOT), and at the week 36/EOS follow-up visit.

The seven areas of functioning measured by the ASI-Lite will be analyzed using a mixed effects model with treatment as a covariate. These seven tests will be performed without adjustment for multiple testing.

5.5.7 HIV Risk Behavior as Assessed by the RAB

The sex risk scale of the RAB, which produces a score ranging from 0-28, will be considered as a continuous response variable, and treatment effect will be analyzed using mixed effects model.

5.5.8 Cognitive Function

The Trails Making test Parts A and B and the Stroop test will be used to assess cognitive function.

5.6 Minority/Gender Analyses

In accordance with NIH guidelines, repeated Cox regression model analyses will be completed to determine whether treatment response was significantly affected by participant minority/gender status using an interaction term for treatment and minority/gender as appropriate.

6.0 MISSING DATA

The primary outcome in this study defines missing urines as positive opioid use. Thus, missing value imputation of the urine drug screens is not necessary for the purposes of the primary outcome.

Dropout from treatment is a typical failure mode for the treatment of opioid dependence with both XR-NTX and BUP-NX. A sensitivity analysis for the primary outcome analysis will be performed to examine the impact on the hazard ratio and its confidence limits of alternative endpoint definitions. In particular for the primary endpoint, individuals who withdraw will be considered events if they fail to provide weekly urine specimens. An alternative to the protocol definition which introduces these as censored observations will be examined. The analyses of these events can be complex as standard assumptions (missing at random) may not be plausible.

Other outcome variables (opioid and other substance use over time, craving, mood, etc.) will have missing data due to missed visits and dropout from treatment and from study participation. The generalized linear model, or mixed effects model frameworks that will be used for analyses, works with what data are gathered, and assumes missing data are missing at random. For selected secondary outcome analyses, sensitivity analyses will be considered to examine the stability of estimated treatment effects in the face of departures from the assumption of missing at random.

7.0 SAFETY ANALYSES

7.1 Physical Examination

The study clinician will complete a physical examination, including blood pressure and heart rate, to ensure that there are no medical concerns regarding participation and to gather baseline information regarding the participant's physical health. During the screening physical exam, a description of the participant's body habitus will be documented and the study clinician will examine the planned injection sites to ensure adequacy for XR-NTX gluteal intramuscular injection of naltrexone with the supplied needle. The physical examination will be performed at screening and will be repeated at the end-of-medication visit (if medication is stopped early) or at the end-of-treatment visit (week 24). The physical exam, blood pressure and/or heart rate may be repeated at MM visits at the discretion of the medical clinician.

7.2 Concise Health Risk Tracking-Self Report (CHRT-SR)

The CHRT-SR (Trivedi 2011) is a 16-item participant self-report assessment of suicidality and related thoughts and behaviors. The scale is designed to quickly and easily track suicidality in a manner consistent with the Columbia Classification Algorithm of Suicide Assessment (C-CASA) S(Posner 2007). The CHRT-SR will be assessed at screening, induction, at subsequent MM visits and at the week 28 and 36/EOS visits. The CHRT-SR will assess high risk suicide ideation by a positive response (Agree or Strongly Agree) on any of the last three questions (thoughts of, thoughts of how and/or a specific plan to commit suicide) and prompt a clinician assessment for suicide risk before leaving the clinic.

7.3 The Hamilton Depression Scale (17 item) (HAM-D)

The 17-item Hamilton Depression Scale (HAM-D) is a clinician-administered instrument, useful for following both depression and suicidal ideation, and also for following typical symptoms of subacute withdrawal (e.g., low appetite, fatigue, poor sleep). For the purpose of this study, adequately trained research staff conduct the Hamilton Depression Scale (HAM-D).

The HAM-D is completed at screening, at weeks 1, 2, 3, 4, 8, 12, 16 and 20, at the end-of-treatment visit (week 24/EOT), and at each follow-up. A score of 1 or more to item 3 (suicidality) prompts a clinician assessment for suicide risk before leaving the clinic. Summaries of the suicidality question are tabulated for the purposes of safety analyses.

The HAM-D score is calculated by summing the first 17 items on the HAM-D form. A sum of 0 to 7 is considered to be normal, 8 to 13 is defined as mild depression, 14 to 18 as moderate depression, 19 to 22 as severe depression, and greater than or equal to 23 is defined as very severe depression.

7.4 Clinical Laboratory Tests

Liver function tests (LFTs, consisting of AST, ALT, albumin and bilirubin) and urine pregnancy test (for females) will be performed to help determine eligibility at screening. Receipt and review of laboratory test results is necessary before confirming eligibility, conducting randomization and starting study medication. Results of LFTs conducted within four weeks prior to randomization (e.g., collected as part of routine detoxification admission) will be acceptable. For participants whose induction onto their assigned study medication is delayed for longer than 2 weeks after randomization, LFTs and urine pregnancy should be repeated prior to start of study medication.

At screening, blood will be collected for HIV antibody, hepatitis C virus (HCV) antibody and hepatitis B surface antigen (HBsAG) and hepatitis B surface antibody (HBsAB) tests. These tests do not determine eligibility and will only be conducted on samples from participants who are randomized. Results of HIV antibody, hepatitis C virus (HCV) antibody and hepatitis B surface antigen (HBsAG) and hepatitis B surface antibody (HBsAB) tests conducted within four

weeks prior to randomization (e.g., collected as part of routine detoxification admission) will be acceptable.

For participants whose induction onto their assigned study medication occurs within 2 weeks of Day 0, LFTs will be repeated at week 4, week 12, and at the end-of-medication visit (if medication is stopped early) or at the end-of-treatment visit (week 24). For participants whose induction onto their assigned study medication occurs more than 2 weeks after day 0, LFTs will be repeated approximately 4 and 12 weeks following induction (a +/- 2 week window for post-induction LFTs is permitted), and at the end-of-medication visit (if medication is stopped early) or at the end-of-treatment visit (week 24). For participants who do not get inducted but continue on study, LFTs need not to be repeated at any of the planned visits with scheduled LFTs.

A laboratory that is accredited by the College of American Pathologists (CAP) or equivalent, and participates in the Clinical Laboratory Improvement Act of 1998 (CLIA) will perform these analyses. The laboratory will provide normal values and proof of lab certifications.

Changes in the liver function test values (alkaline phosphatase, ALT, AST, GGT and total bilirubin) over time and by treatment arm will be considered graphically. A listing of participants with elevated AST and ALT by treatment arm will be presented.

7.4.1 Adverse Events (AEs) and Serious Adverse Events (SAEs)

At each medical management visit the study clinician will assess for AEs and SAEs by asking the study participant, “How have you been feeling since your last visit?” AEs and SAEs may also be spontaneously reported to study staff at any visit following consent. AEs and SAEs suggesting medical or psychiatric deterioration will be brought to the attention of a study clinician for further evaluation and management. Medical management visits will emphasize overdose risk and risk-management; any reported overdose will be recorded as an AE or SAE. AE and SAE reporting will be according to the reporting definitions and procedures outlined in the protocol and in accordance with applicable regulatory requirements.

For the purpose of this study, the following AE will not require reporting in the data system but will be captured in the source documentation as medically indicated:

- Grade 1 (mild) unrelated adverse events

This would typically include mild physical events such as headache, cold, etc., that were considered not reasonably associated with the use of the study drug/intervention.

Events related to the injection of the study medication will be recorded on the Injection Site Abnormality (INA) form and will not be duplicate-reported on an AE form (See Section 7.4 for details on Injection Site examination summaries). Events related to withdrawal symptoms will be captured on the SOWS and HAM-D and will not be duplicate-reported on an AE form. Withdrawal symptoms not captured by the SOWS or HAM-D should be reported as an AE. Events captured on study specific forms (INA, SOWS, HAM-D) will not be recorded separately as an AE, unless they meet the SAE definition. Any of these events that meet the definition of an SAE will be reported on the AE/SAE form set. Any spontaneous reporting of withdrawal symptoms by the participant will be captured on AE form in the following situations: withdrawal symptoms reported at visits without scheduled specific structured questionnaires (SOWS, HAM-D); and withdrawal symptoms not listed in the specific structured questionnaires (SOWS, HAM-D) reported at any visit.

Adverse events (AEs), including serious adverse events (SAEs), will be summarized by body system and preferred term using MedDRA (The Medical Dictionary for Regulatory Activities) version 19.0 or higher. Adverse events will be presented in two ways: (1) the number and proportion of participants experiencing at least one incidence of each event will be presented overall and by treatment group. The incidence of adverse events and serious adverse events by

type will be compared between treatment arms using either Fisher's Exact mid-p-value or Chi-Square analysis as appropriate; and (2) a table displaying the total number of each event will be given overall and by treatment group. Listings of serious adverse events will be given, sorted by treatment, body system and preferred term. Detail in these listings will include severity, relationship to study drug, and action taken as available.

Treatment emergent AEs are defined as AEs occurring after participants have been inducted on study medication. Induction is defined as having had an injection if in the XR-NTX arm or having been dispensed medication if in the BUP-NX arm.

7.5 Injection Site Examination

Appropriately qualified and trained medical personnel will examine the injection site on the next Medical Management visit following the XR-NTX administration. Participants will be asked to immediately report any injection site reactions to study staff for evaluation, monitoring, and possible referral, as needed. Injection site reactions should be documented on the Injection Site Abnormality Log. A detailed listing of injection site abnormalities will be provided.

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Appendix A: Table Shells

Figure 1: Consort Diagram

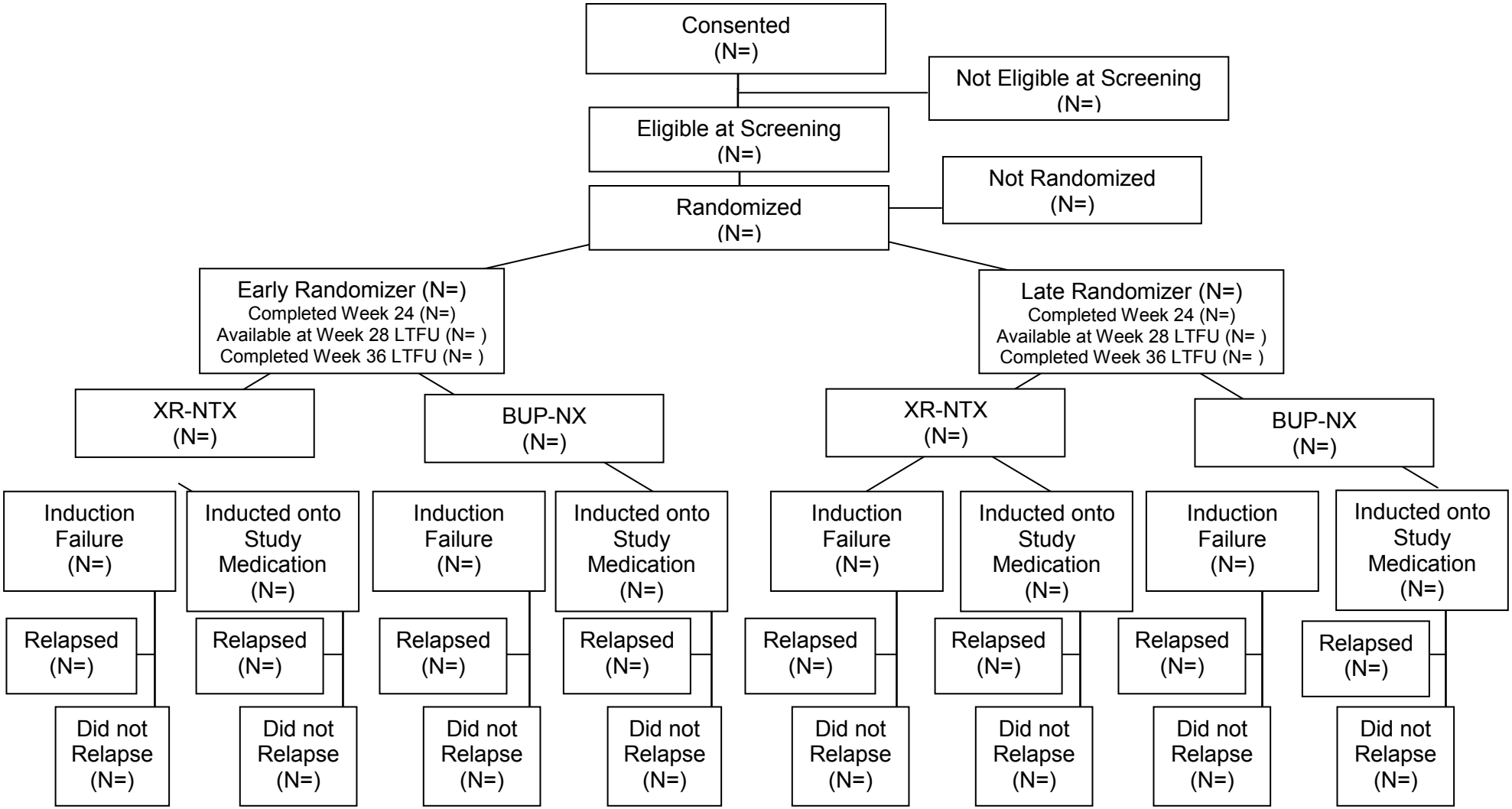
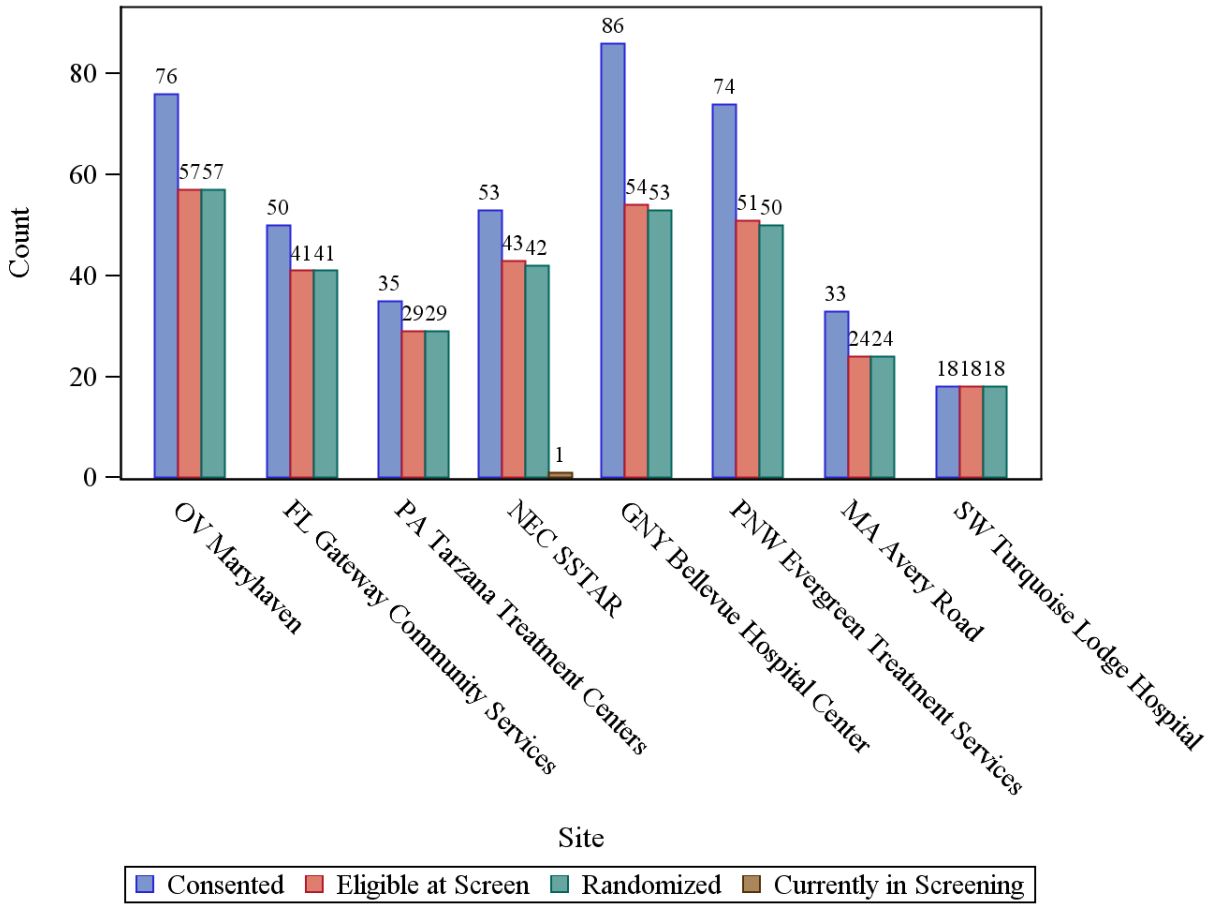
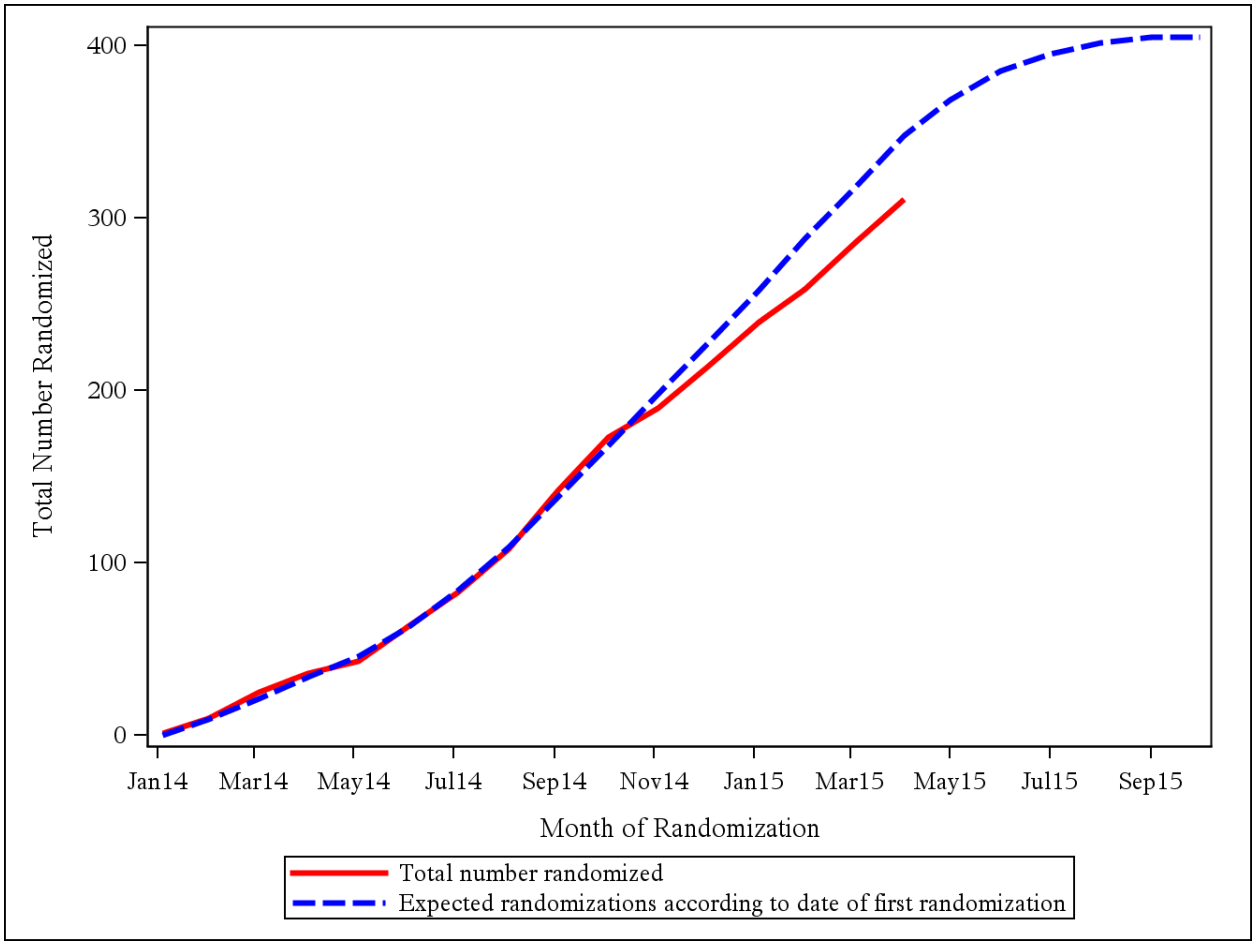


Figure 2: Randomization Status by CTP



Example figure provided.

Figure 3: Overall Expected vs. Actual Randomizations



Example figure provided.

Figure 4A: Early Randomizers Actual Randomizations

Similar Example Figure to Figure 3

Figure 5B: Late Randomizers Actual Randomizations

Similar Example Figure to Figure 3

Table 1: Summary of Consents, Eligible Screens and Randomizations by CTP					
CTP	**Number of Consents**	**Number of Eligible Screens**	**Number Randomized**	**Percent of Consents Randomized**	**Percent of Eligible Screens Randomized**
OV Maryhaven					
FL Gateway Community Services					
PA Tarzana Treatment Centers					
NEC Stanley Street Treatment and Resources (SSTAR)					
GNY Bellevue Hospital Center					
PNW ETS/RCKC					
MA Avery Road					
SW Turquoise Lodge Hospital					
Total					

Table 2: Summary of Screen Failures by CTP									
	OV Maryhaven	**FL Gateway Community Services**	**PA Tarzana Treatment Centers**	**NEC Stanley Street Treatment and Resources (SSTAR)**	**GNY Bellevue Hospital Center**	**PNW ETS/RCKC**	**MA Avery Road**	**SW Turquoise Lodge Hospital**	**Total**
Number of Consented									
Number of Screen Failures									
Eligibility Criteria Violated* (N (%))									
18 years of age or older									
Opioid use disorder									
Opioid use past 30 days									
Willing to accept random assignment									
Agrees to use birth control									
In good-enough health									
Able to provide written informed consent									
Able to speak English/provide consent									
Severe medical, psychiatric, substance use condition									
Has LFTs greater than 5 times upper limit of normal									
Has suicidal or homicidal ideation									
Has allergy									
On methadone maintenance									
Pain requiring opioid tx									
Pending legal action									
Pregnant/breastfeeding									
Inadequate body habitus									

Table 2: Summary of Screen Failures by CTP									
	OV Maryhaven	**FL Gateway Community Services**	**PA Tarzana Treatment Centers**	**NEC Stanley Street Treatment and Resources (SSTAR)**	**GNY Bellevue Hospital Center**	**PNW ETS/RCKC**	**MA Avery Road**	**SW Turquoise Lodge Hospital**	**Total**
Screening Visit Not Completed									
Reasons for Not Completing the Screening Visit (N (%))									
Participant dropped out of CTP									
Participant did not meet eligibility criteria									
Participant did not want research									
Other									
Number and Percentage of Participants Eligible, but not Randomized									
Reasons for Not Being Randomized (N (%))									
Participant dropped out of CTP									
Participant did not meet eligibility criteria									
Participant did not want research									
Other									

* Percentages are calculated based on the denominator of number of ineligibles and the sum may exceed 100% if multiple eligibility criteria are not met for potential participants.

Table 3: Summary of the Timing of Randomization by CTP			
CTP	**# Randomized**	**# of Early Randomizers[1]**	**# of Late Randomizers[1]**
OV Maryhaven			
FL Gateway Community Services			
PA Tarzana Treatment Centers			
NEC Stanley Street Treatment and Resources (SSTAR)			
GNY Bellevue Hospital Center			
PNW ETS/RCKC			
MA Avery Road			
SW Turquoise Lodge Hospital			
Total			

[1] Early randomizers are participants randomized within 72 hours following the last licit or illicit opioid use. Late randomizers are participants randomized greater than 72 hours following the last licit or illicit opioid use.

Table 4: Summary of Participant Study Disposition by Treatment Arm			
	Treatment Arm		
	BUP-NX	XR-NTX	Total
Number of Randomized Participants			
Number Completing Week 24 visit - N (%)			
Number Completing Week 28 visit - N (%)			
Number of Study Completers[1] - N (%)			
Number of Early Terminations - N (%)			
Reasons for Early Termination			
Participant failed to return to clinic and unable to contact			
Participant terminated due to protocol deviation			
Participant terminated due to practical problems (no childcare, transportation, other)			
Participant moved from area			
Participant incarcerated			
Participant terminated due to AE/SAE			
Participant terminated for other clinical reasons			
Participant had a significant psychiatric risk (suicidal, homicidal, psychotic)			
Participant withdrew consent			
Participant deceased			
Participant terminated for other reason			

[1] Study completion is defined based on the Study Termination form and means that the subject completed the Week 36 visit.

Table 5: Randomization by CTP and Stratification Factor				
CTP	**Opioid Severity Level[1]**	**BUP-NX (N=)**	**XR-NTX (N=)**	**Total (N=)**
OV Maryhaven	Low Severity			
	High Severity			
FL Gateway Community Services	Low Severity			
	High Severity			
PA Tarzana Treatment Centers	Low Severity			
	High Severity			
NEC Stanley Street Treatment and Resources (SSTAR)	Low Severity			
	High Severity			
GNY Bellevue Hospital Center	Low Severity			
	High Severity			
PNW ETS/RCKC	Low Severity			
	High Severity			
MA Avery Road	Low Severity			
	High Severity			
SW Turquoise Lodge Hospital	Low Severity			
	High Severity			
Total	Low Severity			
	High Severity			

Table 5a: Randomization by CTP and Stratification Factor for Early Randomizers				
CTP	**Opioid Severity Level[1]**	**BUP-NX (N=)**	**XR-NTX (N=)**	**Total (N=)**
OV Maryhaven	Low Severity			
	High Severity			
FL Gateway Community Services	Low Severity			
	High Severity			
PA Tarzana Treatment Centers	Low Severity			
	High Severity			
NEC Stanley Street Treatment and Resources (SSTAR)	Low Severity			
	High Severity			
GNY Bellevue Hospital Center	Low Severity			
	High Severity			
PNW ETS/RCKC	Low Severity			
	High Severity			
MA Avery Road	Low Severity			
	High Severity			
SW Turquoise Lodge Hospital	Low Severity			
	High Severity			
Total	Low Severity			
	High Severity			

[1] To compute the opioid severity level, if the primary opioid of use in the last 7 days was not heroin or the route of administration is not IV-injection, then the participant is categorized in the low severity group. For IV heroin users where the quantity is not provided in bags but in dollars, bags are estimated as the dollar amount/10 rounded to the nearest integer.

Table 5b: Randomization by CTP and Stratification Factor for Late Randomizers				
CTP	**Opioid severity level[1]**	**BUP-NX (N=)**	**XR-NTX (N=)**	**Total (N=)**
OV Maryhaven	Low Severity			
	High Severity			
FL Gateway Community Services	Low Severity			
	High Severity			
PA Tarzana Treatment Centers	Low Severity			
	High Severity			
NEC Stanley Street Treatment and Resources (SSTAR)	Low Severity			
	High Severity			
GNY Bellevue Hospital Center	Low Severity			
	High Severity			
PNW ETS/RCKC	Low Severity			
	High Severity			
MA Avery Road	Low Severity			
	High Severity			
SW Turquoise Lodge Hospital	Low Severity			
	High Severity			
Total	Low Severity			
	High Severity			

[1] Number of bags is assigned a 0 if the primary opioid of use in the last 7 days was not heroin or the route of administration is not IV-injection. For IV heroin users where the quantity is not provided in bags but in dollars, bags are estimated as the dollar amount/10 rounded to the nearest integer.

Table 6: Summary of Study Medication Induction by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Induction Status			
Induction failure			
Inducted onto study medication			
Reasons for Induction Failure			
Participant could not tolerate detoxification			
Participant failed naloxone challenge			
Participant failed to provide a negative urine sample			
Participant left prior to induction			
Participant rejected treatment assignment			
Participant met criteria for relapse			
Participant reached end of induction window			
Time to Study Medication Induction (days)			
Mean			
SD			
Median			
Min			
Max			

Table 7: Summary of Induction Status for the Groups of Interest				
	BUP-NX (N=)		XR-NTX (N=)	
	Inducted N (%)	Not Inducted N (%)	Inducted N (%)	Not Inducted N (%)
Total				
Randomization Timing Status				
Early Randomizers				
Late Randomizers				
Opioid Severity Level[1]				
Low Severity				
High Severity				
Randomization Timing Status by Opioid Severity Level				
Early Randomizers and Low Severity				
Early Randomizers and High Severity				
Late Randomizers and Low Severity				
Late Randomizers and High Severity				
Baseline Preference[2]				
Preferred Neither Treatment				
BUP-NX Preference				
XR-NTX Preference				
Preferred Either Treatment				

[1] Number of bags is assigned a 0 if the primary opioid of use in the last 7 days was not heroin or the route of administration is not IV-injection. For IV heroin users where the quantity is not provided in bags but in dollars, bags are estimated as the dollar amount/10 rounded to the nearest integer.

[2] Baseline preference is captured on the Motivation for Participating, Attitudes Regarding Study Medication form. The two questions to address preference are “I would prefer to receive Buprenorphine-Naloxone (Suboxone)” and “I would prefer to receive Naltrexone monthly injections” with responses to each on a 1 -5 scale of agreement with 1 indicating Strongly Disagree and 5 indicating Strongly Agree. If a participant indicates agreement or strong agreement, he/she will be deemed as having preferred that treatment. If the participant indicated agreement for both questions, he/she will be categorized as preferred either.

Table 8: Summary of Early Medication Terminations* by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Number of Early Medication Terminations - N (%)			
Reasons for Early Medication Termination			
Participant became pregnant			
Participant feels study treatment no longer necessary, not working			
Participant became incarcerated			
Participant withdrew consent			
Participant moved from area			
Participant deceased			
Participant met criteria for relapse			
Participant unable to tolerate side effects			
Participant continued to experience intolerable side effects after a dose reduction			
Contraindicated concomitant medication			
Participant refused, non-specific			
Participant left study and never returned			
Clinical deterioration: new onset of psychiatric or medical condition			
Physical illness or condition that precludes taking study medication			
Participant feels study treatment no longer necessary, cured			
Other			

*Note: Only participants inducted onto study medication are assessed for early medication termination.

Table 9: Summary of Baseline Characteristics by Treatment Arm			
Characteristic	**BUP-NX (N=)**	**XR-NTX (N=)**	**Total (N=)**
Gender			
Missing			
Male			
Female			
Participant chose not to answer			
Age (Mean(Std))			
Age			
Missing			
< 18			
18 - < 25			
25 - < 35			
35 - < 45			
45 - < 55			
55 - < 65			
65 - < 75			
75+			
Ethnicity			
Not Hispanic or Latino			
Hispanic or Latino			
Missing			
Participant chose not to answer			
Race			
Missing			
American Indian or Alaska Native			
Asian			
Black or African American			
Native Hawaiian or Pacific Islander			
White			
Other			
Multiracial			
Unknown			
Participant chose not to answer			

Table 9: Summary of Baseline Characteristics by Treatment Arm			
Characteristic	**BUP-NX (N=)**	**XR-NTX (N=)**	**Total (N=)**
Education completed			
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			
Professional school degree			
Doctoral degree			
Don't know			
Refused			
Marital status[1]			
Married			
Widowed			
Divorced			
Separated			
Never married			
Living with partner			
Refused			
Don't know			
Employment			
Working now			
Only temporarily laid off, sick leave, or maternity leave			
Looking for work, unemployed			
Retired			
Disabled permanently or temporarily			
Keeping house			
Student			
Other			

[1] As defined on the DEM form.

Table 10: Summary of Baseline Moderators by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
IV Use			
Yes			
No			
Primary Opioid Used in the 7 Days Prior to Detox Admission			
Buprenorphine			
Opioid Analgesics			
Methadone			
Heroin			
Missing			
Cost per Day for Primary Opioid (dollars)			
Mean			
SD			
Median			
Min			
Max			
Usual Living Arrangements (past 3 years)[1]			
With sexual partner and children			
With sexual partner alone			
With children alone			
With parents			
With family			
With friends			
Alone			
Controlled environment			
No stable arrangements			
Not answered			
Any Friends and/or Family Members with Alcohol Problems			
Yes			
No			
Any Friends and/or Family Members that Use Heroin and/or Other Illicit Opioids			
Yes			
No			
Any Friends and/or Family Members that Use Illicit Drugs and/or Non-prescribed Drugs			
Yes			
No			
If I receive BUP-NX I am sure that I will take it every day for the next 6 months.			
Strongly disagree			

Table 10: Summary of Baseline Moderators by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Disagree			
Neutral			
Agree			
Strongly Agree			
If I receive XR-NTX I am sure that I will get an injection every month for the next 6 months.			
Strongly disagree			
Disagree			
Neutral			
Agree			
Strongly Agree			
Ever Heroin Use (Lifetime use based on ASI collected at Baseline)			
Yes			
No			
Current Heroin Use (Past 30 day use based on ASI collected at Baseline)			
Yes			
No			
Ever Prescription Opioid Use (Lifetime use based on ASI collected at Baseline)			
Yes			
No			
Current Prescription Opioid Use (Past 30 day use based on ASI collected at Baseline)			
Yes			
No			
Current Age			
Mean			
SD			
Median			
Min			
Max			
Age at Onset of Any Opioid Use			
Mean			
SD			
Median			
Min			
Max			
Duration of Opioid Use (Current age minus Age at onset of any opioids based on Baseline ASI)			
Mean			
SD			

Table 10: Summary of Baseline Moderators by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Median			
Min			
Max			
First Treatment Status[2]			
Yes			
No			
Past Treatment Successful[3]			
Yes			
No			
Any Stimulants Use			
Yes			
No			
Any Sedatives Use			
Yes			
No			
Any Alcohol Heavy Drinking Days[4]			
Yes			
No			
Any Cannabis Use			
Yes			
No			
HAM-D Score (Baseline)			
Mean			
SD			
Median			
Min			
Max			
ASI Psychiatric Domain Composite Score (Baseline)			
Mean			
SD			
Median			
Min			
Max			
Any History of Psychiatric Disorders from Medical History[5]			
Yes			
No			
Discomfort Level of Past Opioid Withdrawal (Scale of 0 to 10)			

Table 10: Summary of Baseline Moderators by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Mean			
SD			
Median			
Min			
Max			
SOWS Score at Baseline			
Mean			
SD			
Median			
Min			
Max			

[1] Based on the ASI Family/Social Relationships section.
[2] The first treatment status is defined based on the participants response to the Opiate Treatment History provided on the MHX form. If the subject indicated No for the history of any treatments, then this is his/her first episode of treatment.
[3] Past treatment successful is only tabulated for those who were previously treated.
[4] Heavy Drinking days is defined as a day that a man has 5 or more drinks or a woman has 4 or more drinks.
[5] The following psychiatric disorders are collected on the Medical History: Anxiety or panic disorder, Attention Deficit Hyperactivity Disorder, Bipolar Disorder, Major Depressive Disorder, Schizophrenia, Suicidal ideation, Suicidal behavior, Homicidal ideation, Homicidal behavior, Violent behavior, Psychotic episodes, or other psychiatric disorder. If the subject responded Yes to any of those psychiatric disorders, he/she is categorized as Yes to having had a psychiatric disorder.

Table 11: Summary of Treatment Exposure* by Treatment Arm								
CTP	**Participants Randomized to BUP-NX**	**Expected Days (Buprenorphine Arm)**	**Actual Days Taken (Buprenorphine Arm)**	**Buprenorphine Exposure Percentage**	**Participants Randomized to XR-NTX**	**Expected Vivitrol Injections**	**Actual Vivitrol Injections**	**Vivitrol Exposure Percentage**
OV Maryhaven								
FL Gateway Community Services								
PA Tarzana Treatment Centers								
NEC Stanley Street Treatment and Resources								
GNY Bellevue Hospital Center								
PNW ETS/RCKC								
MA Avery Road								
SW Turquoise Lodge Hospital								
Overall								

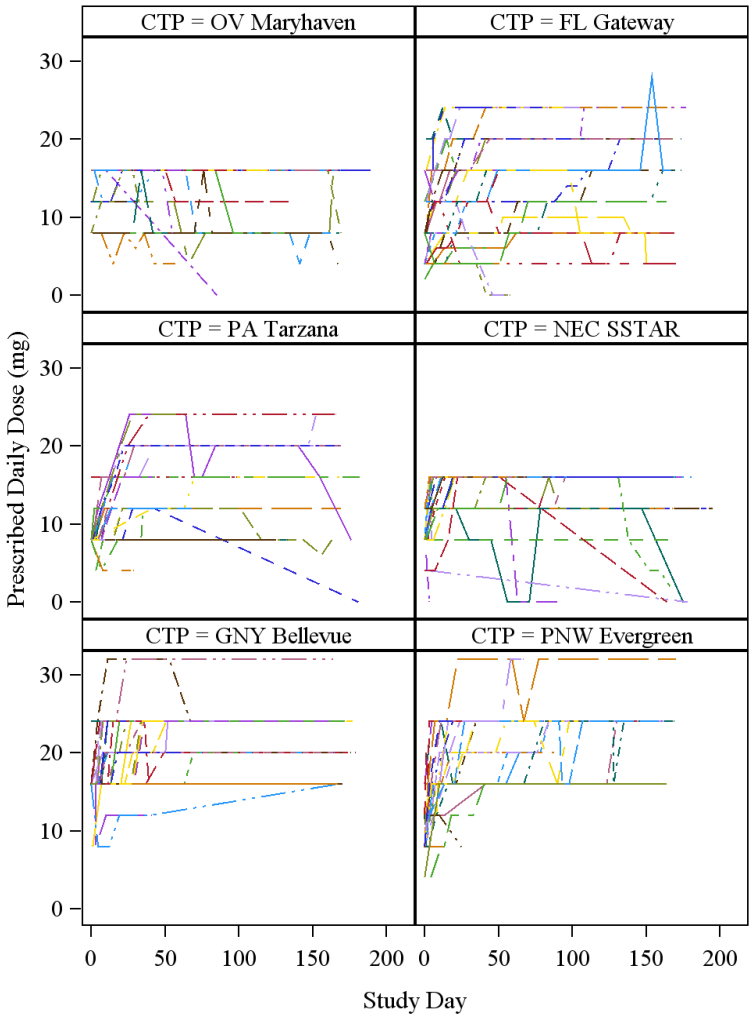
*Treatment Exposure is calculated only for participants who have been inducted onto study medication.
The time period for treatment exposure begins at induction and ends at the onset of the relapse event or at the end of the study treatment period, whichever comes first.

Table 12: Summary of Vivitrol Injections and Injection Intervals by CTP									
	OV Maryhaven	**FL Gateway Community Services**	**PA Tarzana Treatment Centers**	**NEC Stanley Street Treatment and Resources (SSTAR)**	**GNY Bellevue Hospital Center**	**PNW ETS/RCKC**	**MA Avery Road**	**SW Turquoise Lodge Hospital**	**Total**
Number of Participants Randomized to Vivitrol									
Number of Injections									
1									
2									
3									
4									
5									
6									
7									
Injection Intervals (days)[1]									
N									
Mean									
SD									
Median									
Min									
Max									

[1] Injection intervals are defined as time between two consecutive injections. To have an injection interval, participants must have at least two injections. Participants with more than two injections will have multiple injection intervals included.

Table 13: Summary of BUP-NX Prescribed Daily Dose by CTP									
	OV Maryhaven	**FL Gateway Community Services**	**PA Tarzana Treatment Centers**	**NEC Stanley Street Treatment and Resources (SSTAR)**	**GNY Bellevue Hospital Center**	**PNW ETS/RCKC**	**MA Avery Road**	**SW Turquoise Lodge Hospital**	**Total**
Number of Participants Randomized to BUP-NX									
Maximum Prescribed Daily Dose Across all Visits									
N									
Mean									
SD									
Median									
Min									
Max									
Minimum Prescribed Daily Dose Across all Visits									
N									
Mean									
SD									
Median									
Min									
Max									

Figure 6: Participant-level Prescribed Daily Dose of Buprenorphine



Example figure provided.

Table 14: Availability of Primary Outcome by Treatment Arm (Day 21 – Day 167*)								
Treatment Arm	**Participants Randomized**	**Number of UDS Collected**	**Number of UDS Expected**	**Percentage of UDS Collected**	**Number of TLFB Days Collected**	**Number of TLFB Days Expected**	**Percentage of TLFB Days Collected**	**Availability of Primary Outcome****
BUP-NX								
XR-NTX								
Total								

*Day 167 or the last day of the relapse event, whichever occurs first, for participants who have been inducted onto study medication.

**The Availability of Primary Outcome is the average of the percentage of expected TLFB days collected and percentage of expected UDS collected.

Table 15: Summary of Primary Outcome (Relapse) by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Relapse Status[1]			
Yes			
No			
Time to Relapse[2] (days)			
Mean			
SD			
Median			
Min			
Max			
Percentage of Opioid Use Days based on TLFB[3] (Day 0-21 post-randomization) (%)			
Mean			
SD			
Median			
Min			
Max			
UDS Result at Randomization (Day 0)			
Positive for non-prescribed Opioids			
Negative for non-prescribed Opioids			
Missing			
UDS Result at Week 1 (Day 3-12)			
Positive for non-prescribed Opioids			
Negative for non-prescribed Opioids			
Missing			
UDS Result at Week 2 (Day 10-16)			
Positive for non-prescribed Opioids			
Negative for non-prescribed Opioids			
Missing			
UDS Result at Week 3 (Day 17-23)			
Positive for non-prescribed Opioids			
Negative for non-prescribed Opioids			
Missing			

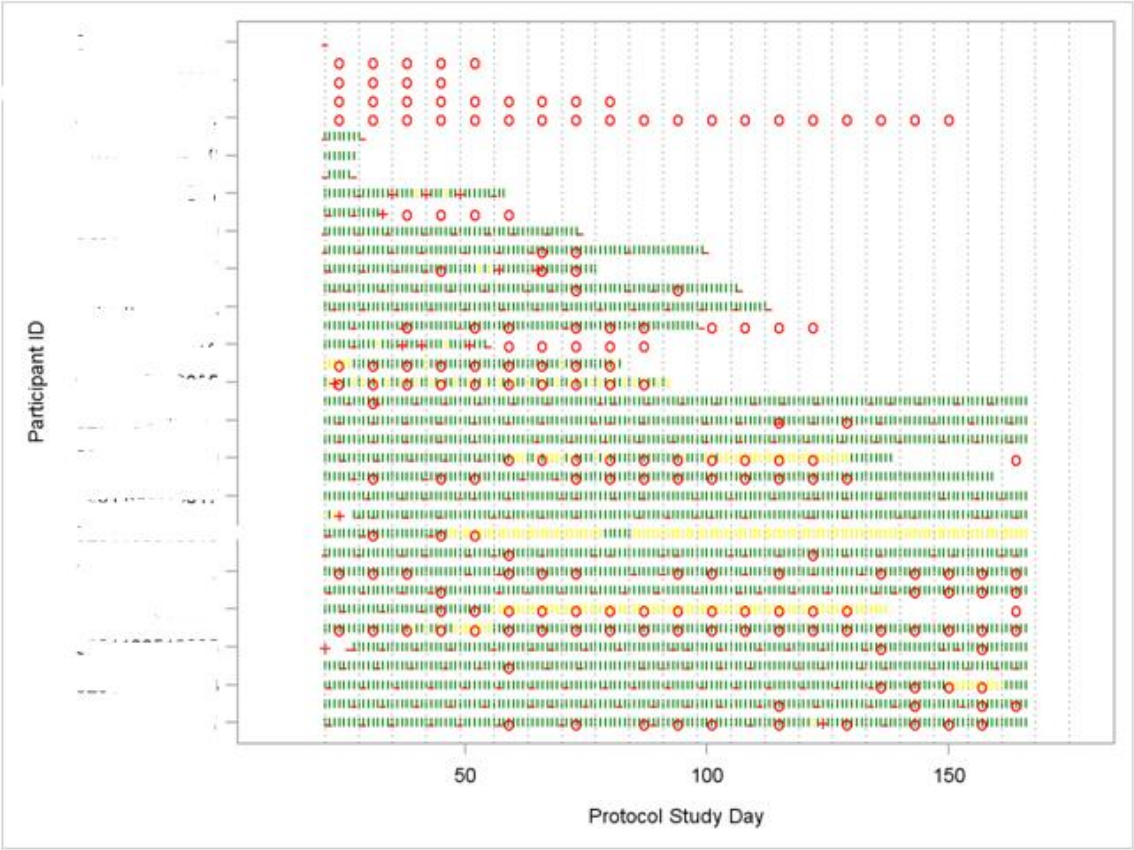
[1] A participant is defined as not having relapsed if by the Week 24 visit, the participant did not meet any of the relapse criteria.
[2] Time to relapse summary statistics are only summarized for subjects who met the relapse criteria.
[3] Participants do not provide TLFB data while in detox.

Figure 5A: TLFB and UDS for Day 0 to Day 21Figure 5A: UDS for Day 0 to Day 21- Treatment=BUP-NX

Figure 5B: UDS for Day 0 to Day 21- Treatment=XR-NTX

Figure 5C: TLFB for Day 0 to Day 21- Treatment=BUP-NX

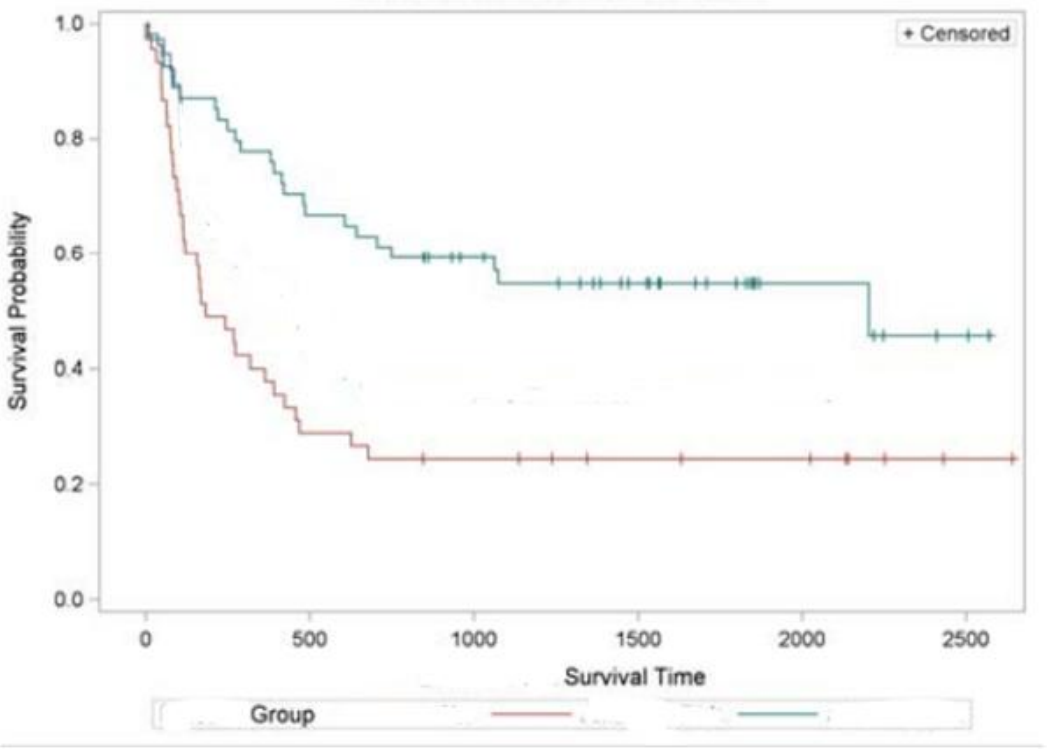
Figure 5D: TLFB for Day 0 to Day 21- Treatment=XR-NTX



Separate figures will be generated for TLFB and UDS and additionally separate for each treatment arm. Each row in the figure would correspond with a participants TLFB and UDS results only from Day 0 to Day 21. The legend would indicate that the green vertical dashes indicate no illicit opioid use on TLFB whereas the yellow vertical dashes indicate illicit opioid use. The red +, - and o values indicate UDS results of positive for non-protocol defined opioids, negative for non-protocol defined opioids and missing UDS results respectively. The figure colors will be modified to accommodate color blind readers.

Figure 6: Kaplan-Meier Plots of Time to Relapse by Treatment Arm

Example Kaplan-Meier figure provided below.



The x-axis for the Time to Relapse Kaplan-Meier Plots will be measured in days. Separate curves on the same plot will be defined as the treatment arms. Censored observations will be represented using a + sign.

Table 16: Summary of Primary Outcome (Time to Relapse[1]) for Groups of Interest						
	BUP-NX (N=)			XR-NTX (N=)		
	N	Mean (STD)	Median (Min, Max)	N	Mean (STD)	Median (Min, Max)
Randomization Timing Status						
Early Randomizers						
Late Randomizers						
Opioid Severity Level						
Low Severity						
High Severity						
Randomization Timing Status by Opioid Severity Level						
Early Randomizers and Low Severity						
Early Randomizers and High Severity						
Late Randomizers and Low Severity						
Late Randomizers and High Severity						
Inducted onto Study Medication						
Baseline Preference[2]						
Preferred Neither Treatment						
BUP-NX Preference						
XR-NTX Preference						
Preferred Either Treatment						
Baseline Motivation[3]						
Motivated for Neither Treatment						
BUP-NX Motivated						
XR-NTX Motivated						
Motivated for Both Treatments						

[1] Time to relapse summary statistics are only summarized for subjects who met the relapse criteria.
[2] Baseline preference is captured on the Motivation for Participating, Attitudes Regarding Study Medication form. The two questions to address preference are “I would prefer to receive Buprenorphine-Naloxone (Suboxone)” and “I would prefer to receive Naltrexone monthly injections” with responses to each on a 1 -5 scale of agreement with 1 indicating Strongly Disagree and 5 indicating Strongly Agree. If a participant indicates agreement or strong agreement, he/she is deemed as having preferred that treatment. If the participant indicated agreement for both questions, he/she is categorized as preferred either.
[3] Baseline motivation is captured on the Motivation for Participating, Attitudes Regarding Study Medication form. The two questions to address motivation are “If I receive Buprenorphine-Naloxone (Suboxone) I am sure that I will take it every day for the next 6 months.” and “If I receive Naltrexone I am sure that I will get an injection every month for the next 6 months” with responses to each on a 1 -5 scale of agreement with 1 indicating Strongly Disagree and 5 indicating Strongly Agree. If a participant indicates agreement or strong agreement, he/she is deemed as being motivated. If the participant indicated agreement for both questions, he/she is categorized as Motivated for Both Treatments.

Figure 7: Kaplan-Meier Plots of Time to Relapse by Randomization Timing Status and Treatment Arm

Example Kaplan-Meier figure provided in Figure 6.

Four separate curves for each treatment arm and randomization timing status will be plotted on one figure.

Figure 8: Kaplan-Meier Plots of Time to Relapse by Opioid Severity Level and Treatment Arm

Example Kaplan-Meier figure provided in Figure 6.

Four separate curves for each treatment arm and opioid severity level will be plotted on one figure.

**Figure 9: Kaplan-Meier Plots of Time to Relapse
by Randomization Timing, Opioid Severity Level and Treatment Arm**

Example Kaplan-Meier figure provided in Figure 6.

Four separate curves for each treatment arm, opioid severity level and randomization timing will be plotted on one figure.

Table 17: Summary of Primary Outcome (Relapse) by CTP									
	OV Maryhaven (N=)	**FL Gateway Community Services (N=)**	**PA Tarzana Treatment Centers (N=)**	**NEC Stanley Street Treatment and Resources (SSTAR) (N=)**	**GNY Bellevue Hospital Center (N=)**	**PNW ETS/RCKC (N=)**	**MA Avery Road (N=)**	**SW Turquoise Lodge Hospital (N=)**	**Total (N=)**
Relapse Status									
Yes									
No									
Time to Relapse[1] (days)									
Mean									
SD									
Median									
Min									
Max									
Percentage of Opioid Use Days based on TLFB[2] (Day 0-21 post-randomization) (%)									
Mean									
SD									
Median									
Min									
Max									
UDS Result at Randomization (Day 0)									
Positive for non-prescribed Opioids									
Negative for non-prescribed Opioids									
Missing									
UDS Result at Week 1 (Day 3-12)									
Positive for non-prescribed Opioids									
Negative for non-prescribed Opioids									
Missing									
UDS Result at Week 2 (Day 10-16)									
Positive for non-prescribed Opioids									

Table 17: Summary of Primary Outcome (Relapse) by CTP									
	OV Maryhaven (N=)	**FL Gateway Community Services (N=)**	**PA Tarzana Treatment Centers (N=)**	**NEC Stanley Street Treatment and Resources (SSTAR) (N=)**	**GNY Bellevue Hospital Center (N=)**	**PNW ETS/RCKC (N=)**	**MA Avery Road (N=)**	**SW Turquoise Lodge Hospital (N=)**	**Total (N=)**
Negative for non-prescribed Opioids									
Missing									
UDS Result at Week 3 (Day 17-23)									
Positive for non-prescribed Opioids									
Negative for non-prescribed Opioids									
Missing									

[1] Time to relapse summary statistics are only summarized for subjects who met the relapse criteria.
[2] Participants do not provide TLFB data while in detox.

Table 18: Summary of Relapse Status[1] for the Groups of Interest				
	BUP-NX (N=)		**XR-NTX (N=)**	
	Relapsed N (%)	Not Relapsed N (%)	Relapsed N (%)	Not Relapsed N (%)
Total				
Randomization Timing Status				
Early Randomizers				
Late Randomizers				
Opioid Severity Level				
Low Severity				
High Severity				
Randomization Timing Status by Opioid Severity Level				
Early Randomizers and Low Severity				
Early Randomizers and High Severity				
Late Randomizers and Low Severity				
Late Randomizers and High Severity				
Inducted onto Study Medication				

[1] A participant is defined as not having relapsed if by the Week 24 visit, the participant did not meet any of the relapse criteria.

Table 19: Summary of Percent Days of Illicit Opioid Use[1] for Groups of Interest

	BUP-NX (N=)			XR-NTX (N=)		
	N	Mean (STD)	Median (Min, Max)	N	Mean (STD)	Median (Min, Max)
Randomization Timing Status						
Early Randomizers						
Late Randomizers						
Opioid Severity Level						
Low Severity						
High Severity						
Randomization Timing Status by Opioid Severity Level						
Early Randomizers and Low Severity						
Early Randomizers and High Severity						
Late Randomizers and Low Severity						
Late Randomizers and High Severity						
Inducted onto Study Medication						

[1] Percent days of illicit opioid use is calculated based on TLFB (only illicit use is provided) starting on Day 21 up until the day of relapse and is calculated as the number of opioid use divided by the total number of days in that time frame. Note, if the subject relapses immediately on Day 21, the percent days of opioid use is 100%. Missing TLFB days are defined as opioid use days.

Table 20: Summary of Abstinent Days[1] for Groups of Interest						
	BUP-NX (N=)			**XR-NTX (N=)**		
	N	Mean (STD)	Median (Min, Max)	N	Mean (STD)	Median (Min, Max)
Randomization Timing Status						
Early Randomizers						
Late Randomizers						
Opioid Severity Level						
Low Severity						
High Severity						
Randomization Timing Status by Opioid Severity Level						
Early Randomizers and Low Severity						
Early Randomizers and High Severity						
Late Randomizers and Low Severity						
Late Randomizers and High Severity						
Inducted onto Study Medication						

[1] Abstinent days are calculated based on TLFB starting on Day 21 up until the day of relapse and will be calculated as the number of days where opioids were not used. Missing TLFB days are defined as non-abstinent days.

Table 21: Summary of Number of Visits 'Present and Clean'[1] for Groups of Interest						
	BUP-NX (N=)			**XR-NTX (N=)**		
	N	Mean (STD)	Median (Min, Max)	N	Mean (STD)	Median (Min, Max)
Randomization Timing Status						
Early Randomizers						
Late Randomizers						
Opioid Severity Level						
Low Severity						
High Severity						
Randomization Timing Status by Opioid Severity Level						
Early Randomizers and Low Severity						
Early Randomizers and High Severity						
Late Randomizers and Low Severity						
Late Randomizers and High Severity						
Inducted onto Study Medication						

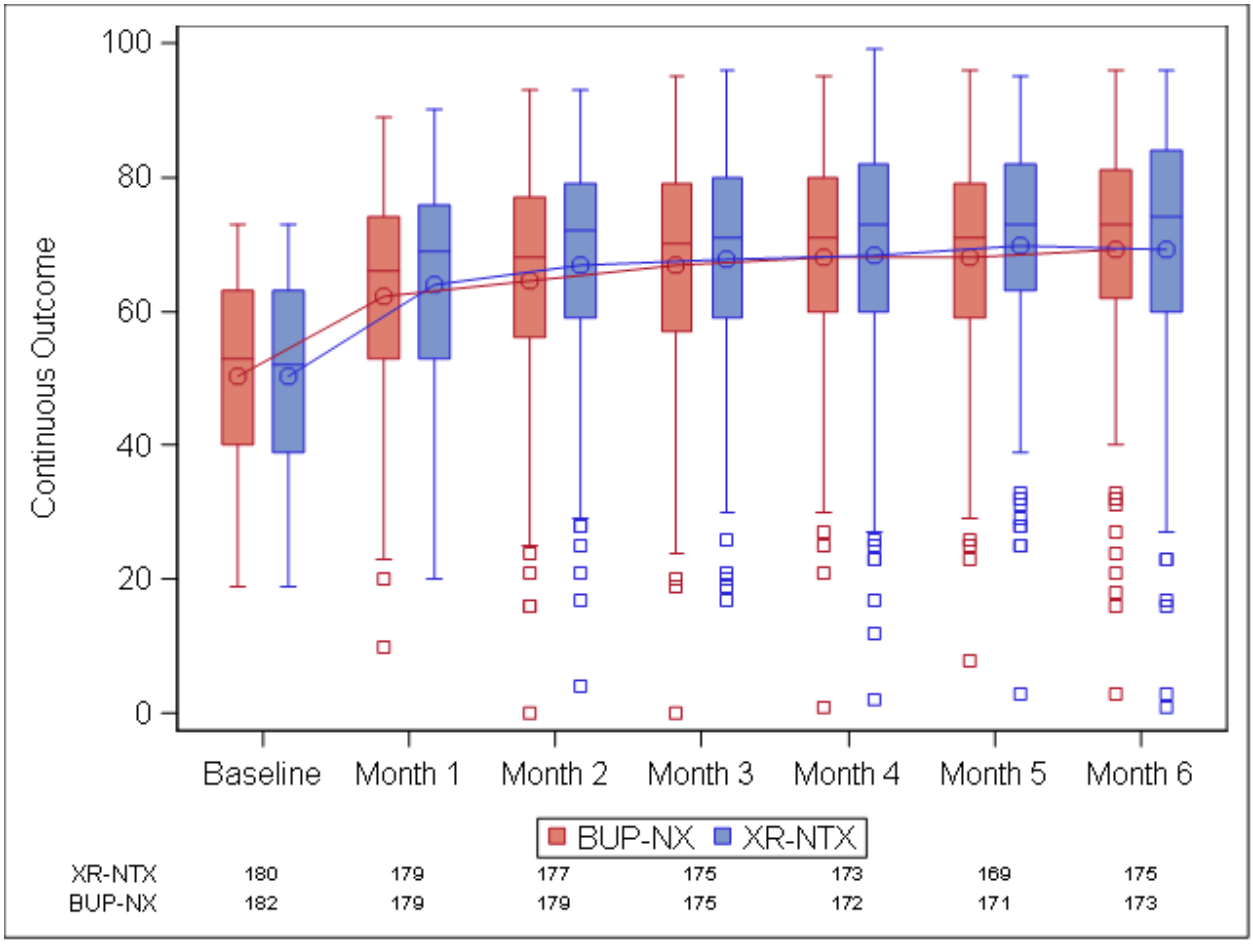
[1] Number of Visits 'Present and Clean" is based on the UDS results evaluated starting at Day 21 and up until the point of relapse. A UDS result which is within temperature range and deemed to be unadulterated and is not positive for non-protocol prescribed opioids is categorized as present and clean. A complete number of UDS results 'Present and Clean" is defined for each participant.

Table 22: Summary of Number Completing 24 Weeks of Treatment[1] for the Groups of Interest				
	BUP-NX (N=)		**XR-NTX (N=)**	
	Completed 24 Weeks of Treatment N (%)	Didn't Complete 24 Weeks of Treatment N (%)	Completed 24 Weeks of Treatment N (%)	Didn't Complete 24 Weeks of Treatment N (%)
Total				
Randomization Timing Status				
Early Randomizers				
Late Randomizers				
Opioid Severity Level[1]				
Low Severity				
High Severity				
Randomization Timing Status by Opioid Severity Level				
Early Randomizers and Low Severity				
Early Randomizers and High Severity				
Late Randomizers and Low Severity				
Late Randomizers and High Severity				
Baseline Preference[2]				
Preferred Neither Treatment				
BUP-NX Preference				
XR-NTX Preference				
Preferred Either Treatment				
Inducted onto Study Medication				

[1] A participant is defined as completing 24 weeks of treatment if he/she received XR-NTX in Week 20-24 or was dispensed BUP-NX during Week 20-24.

Table 23: Summary of Trails A and B by Treatment Arm																		
	Treatment Arm																	
	BUP-NX (N=)						XR-NTX (N=)						Total (N=)					
	Week 0	Week 4	Week 8	Week 16	Week 24	EOT	Week 0	Week 4	Week 8	Week 16	Week 24	EOT	Week 0	Week 4	Week 8	Week 16	Week 24	EOT
Trails A																		
N																		
Mean																		
SD																		
Median																		
Min																		
Max																		
Trails B																		
N																		
Mean																		
SD																		
Median																		
Min																		
Max																		

Figure 10: Boxplots of Trails A by Treatment Arm



Example figure provided.

Figure 11: Boxplots of Trails B by Treatment Arm

See example figure provided above for details.

Table 24: Summary of Stroop Color and Word Scores by Treatment Arm																		
	Treatment Arm																	
	BUP-NX (N=)						XR-NTX (N=)						Total (N=)					
	Week 0	Week 4	Week 8	Week 16	Week 24	EOT	Week 0	Week 4	Week 8	Week 16	Week 24	EOT	Week 0	Week 4	Week 8	Week 16	Week 24	EOT
Word Score																		
N																		
Mean																		
SD																		
Median																		
Min																		
Max																		
Color Score																		
N																		
Mean																		
SD																		
Median																		
Min																		
Max																		
Color-Word Score																		
N																		
Mean																		
SD																		
Median																		
Min																		
Max																		

Figure 12: Boxplots of Stroop Word Score by Treatment Arm

See example box plot figure provided above.

Figure 13: Boxplots of Stroop Color Score by Treatment Arm

See example box plot figure provided above.

Figure 14: Boxplots of Stroop Color-Word Score by Treatment Arm

See example figure provided above.

Table 25: Summary of Subacute Withdrawal per HAM-D Items by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
HAM-D Score – Week 0			
N			
Mean			
SD			
Median			
Min			
Max			
HAM-D Score – Week 1			
N			
Mean			
SD			
Median			
Min			
Max			
HAM-D Score – Week 2			
N			
Mean			
SD			
Median			
Min			
Max			
HAM-D Score – Week 3			
N			
Mean			
SD			
Median			
Min			
Max			
HAM-D Score – Week 4			
N			
Mean			
SD			
Median			
Min			
Max			

Table 25: Summary of Subacute Withdrawal per HAM-D Items by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
HAM-D Score – Week 8			
N			
Mean			
SD			
Median			
Min			
Max			
HAM-D Score – Week 12			
N			
Mean			
SD			
Median			
Min			
Max			
HAM-D Score – Week 16			
N			
Mean			
SD			
Median			
Min			
Max			
HAM-D Score – Week 20			
N			
Mean			
SD			
Median			
Min			
Max			
HAM-D Score – Week 24			
N			
Mean			
SD			
Median			
Min			
Max			

Figure 15: Boxplots of HAM-D Score by Treatment Arm

See example figure provided above for details.

Table 26: Summary of Subacute Withdrawal per SOWS Items by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
SOWS Score – Week 0			
N			
Mean			
SD			
Median			
Min			
Max			
SOWS Score – Week 1			
N			
Mean			
SD			
Median			
Min			
Max			
SOWS Score – Week 2			
N			
Mean			
SD			
Median			
Min			
Max			
SOWS Score – Week 3			
N			
Mean			
SD			
Median			
Min			
Max			
SOWS Score – Week 4			
N			
Mean			
SD			
Median			
Min			
Max			
SOWS Score – Week 8			
N			
Mean			

Table 26: Summary of Subacute Withdrawal per SOWS Items by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
SD			
Median			
Min			
Max			
SOWS Score – Week 12			
N			
Mean			
SD			
Median			
Min			
Max			
SOWS Score – Week 16			
N			
Mean			
SD			
Median			
Min			
Max			
SOWS Score – Week 20			
N			
Mean			
SD			
Median			
Min			
Max			
SOWS Score – Week 24			
N			
Mean			
SD			
Median			
Min			
Max			

Figure 16: Boxplots of SOWS Score by Treatment Arm

See example figure provided above for details.

Table 27: Summary of Opioid Craving Items by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
VAS Score – Week 0			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 1			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 2			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 3			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 4			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 5			
N			
Mean			
SD			

Table 27: Summary of Opioid Craving Items by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Median			
Min			
Max			
VAS Score – Week 6			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 7			
N			
Mean			
SD			
Median			
Min			
Max			
Max			
VAS Score – Week 8			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 9			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 10			
N			
Mean			
SD			
Median			
Min			
Max			

Table 27: Summary of Opioid Craving Items by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
VAS Score – Week 11			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 12			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 13			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 14			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 15			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 16			
N			
Mean			
SD			

Table 27: Summary of Opioid Craving Items by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Median			
Min			
Max			
VAS Score – Week 17			
N			
Mean			
SD			
Median			
Min			
Max			
Max			
VAS Score – Week 18			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 19			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 20			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 21			
N			
Mean			
SD			
Median			
Min			
Max			

Table 27: Summary of Opioid Craving Items by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
VAS Score – Week 22			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 23			
N			
Mean			
SD			
Median			
Min			
Max			
VAS Score – Week 24			
N			
Mean			
SD			
Median			
Min			
Max			

Figure 17: Boxplots of VAS Score by Treatment Arm

See example figure provided above for details.

Table 28: Summary of Self-Reported Alcohol Use by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Week 0			
Alcohol Use in the Past 30 Days – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 1			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 2			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 3			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			

Table 28: Summary of Self-Reported Alcohol Use by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Heavy Drinking Days[1] – N (%)			
Week 4			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 5			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 6			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 7			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			

Table 28: Summary of Self-Reported Alcohol Use by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Max			
Heavy Drinking Days[1] – N (%)			
Week 8			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 9			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 10			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 11			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			

Table 28: Summary of Self-Reported Alcohol Use by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 12			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 13			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 14			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 15			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			

Table 28: Summary of Self-Reported Alcohol Use by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 16			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 17			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 18			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 19			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			

Table 28: Summary of Self-Reported Alcohol Use by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 20			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 21			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 22			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 23			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			

Table 28: Summary of Self-Reported Alcohol Use by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			
Week 24			
Alcohol Use Within Visit Window – N (%)			
Drinks per Day			
N			
Mean			
SD			
Median			
Min			
Max			
Heavy Drinking Days[1] – N (%)			

[1]A heavy drinking day is defined as 4 or more drinks for females and 5 or more for males.

Table 29: Summary of Self-Reported Other Drug Use by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Week 0			
Number of Available Participants			
Any Substance Use in the Past 30 Days – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 1			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 2			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 3			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 4			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 5			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 6			
Number of Participants Available			

Table 29: Summary of Self-Reported Other Drug Use by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 7			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 8			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 9			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 10			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 11			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 12			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			

Table 29: Summary of Self-Reported Other Drug Use by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 13			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 14			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 15			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 16			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 17			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 18			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			

Table 29: Summary of Self-Reported Other Drug Use by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Week 19			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 20			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 21			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 22			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 23			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			
Week 24			
Number of Participants Available			
Any Substance Use Within Visit Window – N (%)			
Cannabis Use – N (%)			
Cocaine Use – N (%)			
Stimulant Use – N (%)			

Table 30: Summary of Self-Reported Tobacco Use by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Week 0			
Cigarettes per Day in Past 30 Days – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 1			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 2			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 3			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 4			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 5			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 6			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			

Table 30: Summary of Self-Reported Tobacco Use by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
11-20			
21-30			
31 or more			
Week 7			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 8			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 9			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 10			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 11			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 12			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			

Table 30: Summary of Self-Reported Tobacco Use by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
Week 13			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 14			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 15			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 16			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 17			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 18			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 19			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			

Table 30: Summary of Self-Reported Tobacco Use by Treatment Arm			
	Treatment Arm		
	BUP-NX (N=)	XR-NTX (N=)	Total (N=)
11-20			
21-30			
31 or more			
Week 20			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 21			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 22			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 23			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			
Week 24			
Cigarettes per Day Within Visit Window – N (%)			
10 or less			
11-20			
21-30			
31 or more			

Table 31: Summary of Problems Related to Drug Abuse by Treatment Arm									
	Treatment Arm								
	BUP-NX (N=)			XR-NTX (N=)			Total (N=)		
	Week 0	Week 24	Week 36	Week 0	Week 24	Week 36	Week 0	Week 24	Week 36
ASI-Lite: Drug/Alcohol Use Composite Score									
N									
Mean									
SD									
Median									
Min									
Max									
ASI-Lite: Family/Social Relationships Composite Score									
N									
Mean									
SD									
Median									
Min									
Max									
ASI-Lite: General Information Composite Score									
N									
Mean									
SD									
Median									
Min									
Max									
ASI-Lite: Legal Status Composite Score									
N									
Mean									
SD									
Median									
Min									
Max									
ASI-Lite: Medical Status Composite Score									
N									
Mean									
SD									

Table 31: Summary of Problems Related to Drug Abuse by Treatment Arm									
	Treatment Arm								
	BUP-NX (N=)			XR-NTX (N=)			Total (N=)		
	Week 0	Week 24	Week 36	Week 0	Week 24	Week 36	Week 0	Week 24	Week 36
Median									
Min									
Max									
ASI-Lite: Psychiatric Status Composite Score									
N									
Mean									
SD									
Median									
Min									
Max									
EuroQoL Questionnaire Composite Score									
N									
Mean									
SD									
Median									
Min									
Max									

Table 32: Summary of HIV Risk by Treatment Arm												
	Treatment Arm											
	BUP-NX (N=)				XR-NTX (N=)				Total (N=)			
	Week 0	Week 12	Week 24	Week 36	Week 0	Week 12	Week 24	Week 36	Week 0	Week 12	Week 24	Week 36
Number of Times Participant had Penetrative Sex (vaginal or anal sex) in the Past 30 Days												
N												
Mean												
SD												
Median												
Min												
Max												
Number of Times Participant had Penetrative Sex (vaginal or anal sex) without a Condom in the Past 30 Days												
N												
Mean												
SD												
Median												
Min												
Max												

Table 33: Summary of Treatment Emergent* Adverse Events by Treatment Arm			
	BUP-NX (N=)	**XR-NTX (N=)**	**Total (N=)**
Number of Participants with Treatment Emergent Adverse Events			
Number of Treatment Emergent Adverse Events			
Severity of Treatment Emergent Adverse Event			
Grade 1-Mild			
Grade 2-Moderate			
Grade 3-Severe			
Relationship of Treatment Emergent Adverse Event			
Not Related			
Related			

*Note: Treatment emergence is defined as any adverse event that occurred after the study day of induction for those participants inducted onto study medication.

Table 34: Summary of Treatment Emergent* Serious Adverse Events by Treatment Arm			
	BUP-NX (N=)	**XR-NTX (N=)**	**Total (N=)**
Number of Participants Inducted			
Number of Participants with a Treatment Emergent Serious Adverse Event			
Number of Treatment Emergent Serious Adverse Events			
Type of Treatment Emergent Serious Adverse Event			
Death			
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			
Severity of Treatment Emergent Serious Adverse Event			
Grade 1-Mild			
Grade 2-Moderate			
Grade 3-Severe			
Relationship of Treatment Emergent Serious Adverse Event			
Not Related			
Related			

*Note: Treatment emergence is defined as any adverse events that occurred after the study day of induction for those participants inducted onto study medication.

Table 35: Summary of Treatment Emergent* MedDRA Coded Adverse Events by Treatment Arm			
System Organ Class/ Preferred Term (MedDRA v19.0 or higher)	**BUP-NX (N=)**	**XR-NTX (N=)**	**Total (N=)**
Participants with at least one treatment emergent adverse event			
Gastrointestinal disorders			
Constipation			
Vomiting			
Diarrhoea			
Nausea			
Toothache			
Abdominal pain upper			
Abdominal pain			
Glossitis			
Oral mucosal erythema			
Abdominal discomfort			
Glossodynia			
Gingival swelling			
Dyspepsia			
Abdominal pain lower			
Oral discomfort			
Mouth ulceration			
Lip swelling			
Psychiatric disorders			
Suicidal ideation			
Insomnia			
Anxiety			
Depression			
Depressed mood			
Suicide attempt			
Self injurious behavior			
Panic attack			
Depression suicidal			
Delirium			
Anhedonia			
Alcohol withdrawal syndrome			
Agitation			
Restlessness			
Psychotic disorder			
Paranoia			

Table 35: Summary of Treatment Emergent* MedDRA Coded Adverse Events by Treatment Arm			
System Organ Class/ Preferred Term (MedDRA v19.0 or higher)	**BUP-NX (N=)**	**XR-NTX (N=)**	**Total (N=)**
Mania			
Loss of libido			
Hypomania			
Affective disorder			
Drug abuse			
Nervous system disorders			
Headache			
Somnolence			
Syncope			
Migraine			
Dizziness			
Seizure			
Carpal tunnel syndrome			
Tremor			
Restless legs syndrome			
Paraesthesia			
Lethargy			
Hypoaesthesia			
Formication			
Facial paresis			
Burning sensation			
Sedation			
Sciatica			
Ageusia			
Loss of consciousness			
Infections and infestations			
Bronchitis			
Upper respiratory tract infection			
Cellulitis			
Influenza			
Abscess limb			
Pneumonia			
Urinary tract infection			
Sinusitis			
Gastroenteritis			
Eye infection			
Bursitis infective			

Table 35: Summary of Treatment Emergent* MedDRA Coded Adverse Events by Treatment Arm			
System Organ Class/ Preferred Term (MedDRA v19.0 or higher)	**BUP-NX (N=)**	**XR-NTX (N=)**	**Total (N=)**
Aspergilloma			
Acarodermatitis			
Tooth abscess			
Subcutaneous abscess			
Abscess neck			
Nasopharyngitis			
Muscle abscess			
Lung infection			
Kidney infection			
Injection site abscess			
Hepatitis viral			
Groin abscess			
Gingival abscess			
Gastroenteritis viral			
Injury, poisoning and procedural complications			
Overdose			
Laceration			
Contusion			
Limb injury			
Ligament sprain			
Eye contusion			
Muscle strain			
Joint injury			
Joint dislocation			
Head injury			
Tooth injury			
Tooth fracture			
Burns third degree			
Tendon injury			
Skin abrasion			
Road traffic accident			
Periorbital haematoma			
Nerve injury			
Multiple fractures			
Lower limb fracture			
Avulsion fracture			
Limb crushing injury			

Table 35: Summary of Treatment Emergent* MedDRA Coded Adverse Events by Treatment Arm			
System Organ Class/ Preferred Term (MedDRA v19.0 or higher)	**BUP-NX (N=)**	**XR-NTX (N=)**	**Total (N=)**
Musculoskeletal and connective tissue disorders			
Back pain			
Arthralgia			
Myalgia			
Joint swelling			
Neck pain			
Musculoskeletal pain			
Pain in extremity			
Muscle contracture			
Arthritis			
Temporomandibular joint syndrome			
General disorders and administration site conditions			
Chest pain			
Peripheral swelling			
Oedema peripheral			
Fatigue			
Drug withdrawal syndrome			
Chills			
Asthenia			
Pyrexia			
Pain			
Local swelling			
Feeling jittery			
Investigations			
Transaminases increased			
Hepatic enzyme increased			
White blood cell count decreased			
Liver function test increased			
Blood urine present			
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
Rash			
Pruritus			
Urticaria			
Ecchymosis			
Cold sweat			
Alopecia			
Acne			

Table 35: Summary of Treatment Emergent* MedDRA Coded Adverse Events by Treatment Arm			
System Organ Class/ Preferred Term (MedDRA v19.0 or higher)	**BUP-NX (N=)**	**XR-NTX (N=)**	**Total (N=)**
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
Cough			
Rhinorrhoea			
Epistaxis			
Throat tightness			
Sinus congestion			
Respiratory depression			
Nasal congestion			
Asthma			
Eye disorders			
Vision blurred			
Eye irritation			
Dry eye			
Diplopia			
Amaurosis fugax			
Metabolism and nutrition disorders			
Decreased appetite			
Dehydration			
Hyponatraemia			
Hypokalaemia			
Gout			
Vascular disorders			
Hot flush			
Hypertension			
Renal and urinary disorders			
Nephrolithiasis			
Urinary retention			
Pollakiuria			
Haematuria			
Dysuria			

Table 35: Summary of Treatment Emergent* MedDRA Coded Adverse Events by Treatment Arm			
System Organ Class/ Preferred Term (MedDRA v19.0 or higher)	**BUP-NX (N=)**	**XR-NTX (N=)**	**Total (N=)**
Reproductive system and breast disorders			
Vaginal discharge			
Menstruation delayed			
Breast mass			
Breast discharge			
Hepatobiliary disorders			
Hepatic failure			
Cholecystitis			
Surgical and medical procedures			
Tooth extraction			
Cardiac disorders			
Tachycardia			
Social circumstances			
Victim of crime			
Product issues			
Device deployment issue			
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			

*Note: treatment emergence is defined as any adverse events that occurred after the study day of induction for those participants inducted onto study medication.

Table 36: Summary of Treatment Emergent* MedDRA Coded Serious Adverse Events by Treatment Arm			
System Organ Class/ Preferred Term (MedDRA v19.0 or higher)	**BUP-NX (N=)**	**XR-NTX (N=)**	**Total (N=)**
Participants with at least one treatment emergent serious adverse event			
Psychiatric disorders			
Suicidal ideation			
Suicide attempt			
Self injurious behavior			
Psychotic disorder			
Depression suicidal			
Depression			
Delirium			
Anxiety			
Affective disorder			
Injury, poisoning and procedural complications			
Overdose			
Multiple fractures			
Burns third degree			
Infections and infestations			
Cellulitis			
Abscess limb			
Pneumonia			
Influenza			
Groin abscess			
Gastroenteritis			
Bronchitis			
Nervous system disorders			
Syncope			
Seizure			
Facial paresis			
Respiratory, thoracic and mediastinal disorders			
Respiratory depression			
Asthma			
Musculoskeletal and connective tissue disorders			
Back pain			
Metabolism and nutrition disorders			
Dehydration			
Hepatobiliary disorders			
Hepatic failure			

Table 36: Summary of Treatment Emergent* MedDRA Coded Serious Adverse Events by Treatment Arm			
System Organ Class/ Preferred Term (MedDRA v19.0 or higher)	**BUP-NX (N=)**	**XR-NTX (N=)**	**Total (N=)**
General disorders and administration site conditions			
Chest pain			
Gastrointestinal disorders			
Vomiting			
Eye disorders			
Diplopia			
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			

*Note: treatment emergence is defined as any adverse events that occurred after the study day of induction for those participants inducted onto study medication.

Table 37: Listing of Treatment Emergent* Adverse Events by Treatment Arm

[Serious Adverse Events Noted in Grey]

Treatment Arm = BUP-NX

									MedDRA	
CTP	Participant ID	AE Description	Onset date	Severity of AE	Relatedness	Outcome	Resolution Date	AE Associated With	Preferred Term	System Organ Class

Note: MedDRA v19.0 or higher.
*Note: treatment emergence is defined as any adverse events that occurred after the study day of induction for those participants inducted onto study medication.

Table 38: Listing of Non-Treatment Emergent Adverse Events in Randomized Participants by Treatment Arm

[Serious Adverse Events Noted in Grey]

Treatment Arm = BUP-NX

									MedDRA	
CTP	Participant ID	AE Description	Onset date	Severity of AE	Relatedness	Outcome	Resolution Date	AE Associated With	Preferred Term	System Organ Class

Note: MedDRA v19.0 or higher.
*Note: treatment emergence is defined as any adverse events that occurred after the study day of induction for those participants inducted onto study medication.

Table 38: Listing of Non-Treatment Emergent Adverse Events in Randomized Participants by Treatment Arm

[Serious Adverse Events Noted in Grey]

Treatment Arm = XR-NTX

									MedDRA	
CTP	Participant ID	AE Description	Onset date	Severity of AE	Relatedness	Outcome	Resolution Date	AE Associated With	Preferred Term	System Organ Class

Note: MedDRA v19.0 or higher.
*Note: treatment emergence is defined as any adverse events that occurred after the study day of induction for those participants inducted onto study medication.

Table 39: Listing of Non-Treatment Emergent Adverse Events Among Screen Failures

[Serious Adverse Events noted in Grey]

									MedDRA	
CTP	**Participant ID**	**AE Description**	**Onset date**	**Severity of AE**	**Relatedness**	**Outcome**	**Resolution Date**	**AE Associated With**	**Preferred Term**	**System Organ Class**

Note: MedDRA v19.0 or higher.

SAE Narratives

Table 40: Listing of Serious Adverse Events by Treatment Arm

Treatment Arm = BUP-NX

									MedDRA	
CTP	Participant ID	AE Description	Onset date	Severity of AE	Relatedness	Outcome	Resolution Date	AE Associated With	Preferred Term	System Organ Class

Note: MedDRA v19.0 or higher.

Table 40: Listing of Serious Adverse Events by Treatment Arm

Treatment Arm = XR-NTX

									MedDRA	
CTP	Participant ID	AE Description	Onset date	Severity of AE	Relatedness	Outcome	Resolution Date	AE Associated With	Preferred Term	System Organ Class

Note: MedDRA v19.0 or higher.

Table 41: Listing of Deaths by Treatment Arm Treatment Arm=BUP-NX						
					MedDRA	
CTP	**Participant ID**	**AE Description**	**Onset date**	**Relatedness**	**Preferred Term**	**System Organ Class**

Note: MedDRA v19.0 or higher.

Table 41: Listing of Deaths by Treatment Arm Treatment Arm=XR-NTX						
					MedDRA	
CTP	**Participant ID**	**AE Description**	**Onset date**	**Relatedness**	**Preferred Term**	**System Organ Class**

Note: MedDRA v19.0 or higher.

Table 42 Listing of Participants with HAM-D and/or CHRT Assessment Question Responses Indicating Potential Suicidality by Treatment Arm

Treatment Arm = BUP-NX

				HAM-D Assessment	CHRT Assessment		
CTP	**Participant ID**	**Date of Assessment**	**Study Day**	**Suicide**	**I have been having thoughts of killing myself**	**I have thoughts about how I might kill myself**	**I have a plan to kill myself**
OV Maryhaven							
FL Gateway Community Services							
PA Tarzana Treatment Centers							
NEC Stanley Street Treatment and Resources (SSTAR)							
GNY Bellevue Hospital Center							
PNW ETS/RCKC							
MA Avery Road							
SW Turquoise Lodge Hospital							
OV Maryhaven							
FL Gateway Community Services							
PA Tarzana Treatment Centers							
NEC Stanley Street Treatment and Resources (SSTAR)							
GNY Bellevue Hospital Center							
PNW ETS/RCKC							
MA Avery Road							
SW Turquoise Lodge Hospital							

Refer to figures for details regarding the color-coding.

Table 42 Listing of Participants with HAM-D and/or CHRT Assessment Question Responses Indicating Potential Suicidality by Treatment Arm

Treatment Arm = XR-NTX

				HAM-D Assessment	CHRT Assessment		
CTP	**Participant ID**	**Date of Assessment**	**Study Day**	**Suicide**	**I have been having thoughts of killing myself**	**I have thoughts about how I might kill myself**	**I have a plan to kill myself**
OV Maryhaven							
FL Gateway Community Services							
PA Tarzana Treatment Centers							
NEC Stanley Street Treatment and Resources (SSTAR)							
GNY Bellevue Hospital Center							
PNW ETS/RCKC							
MA Avery Road							
SW Turquoise Lodge Hospital							
OV Maryhaven							
FL Gateway Community Services							
PA Tarzana Treatment Centers							
NEC Stanley Street Treatment and Resources (SSTAR)							
GNY Bellevue Hospital Center							
PNW ETS/RCKC							
MA Avery Road							
SW Turquoise Lodge Hospital							

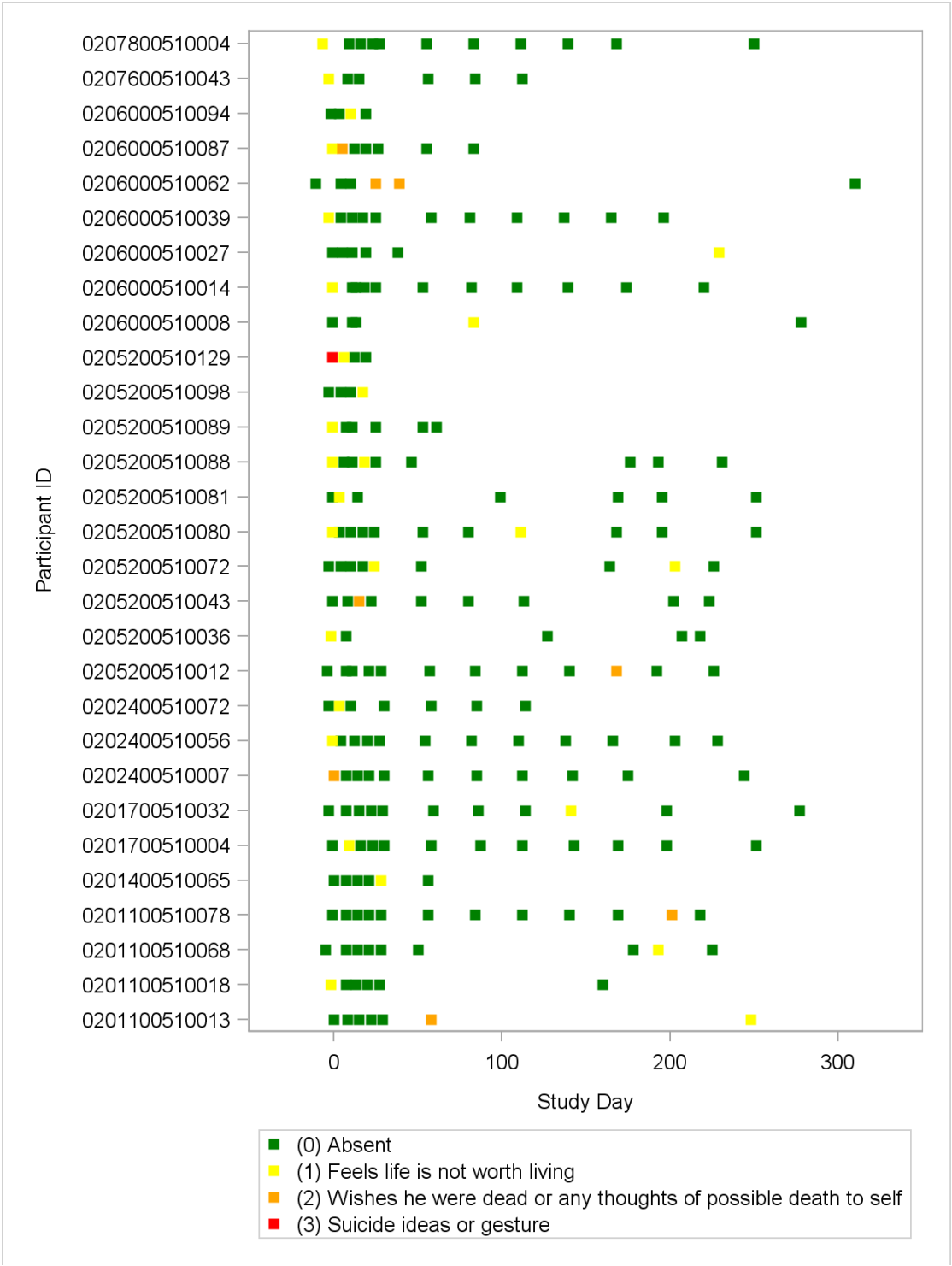
Refer to figures for details regarding the color-coding.

Table 43: Summary of Participants with Reponses Indicating Potential Suicidality by Treatment Arm			
	BUP-NX (N=)	**XR-NTX (N=)**	**Total (N=)**
Number of Participants who endorsed suicidal ideation on CHRT at Screening			
Number of Participants who endorsed suicidal ideation on CHRT at any Follow-up Visit			
Number of Participants who endorsed suicidal ideation[1] on HAM-D[1] at Screening			
Number of Participants who endorsed suicidal ideation on HAM-D at any Follow-up Visit			
Number of Participants who ever endorsed a suicide attempt[2] on the HAM-D at any Follow-up Visit			
Number of Participants with AE's MedDRA-coded as either Suicide attempt, Suicidal Ideation, Self injurious behavior or Depression suicidal			

[1] Indicated as a response of 1 or higher to the HAM-D Suicide Question.
[2] Indicated as a response of 4 on the HAM-D Suicide Question

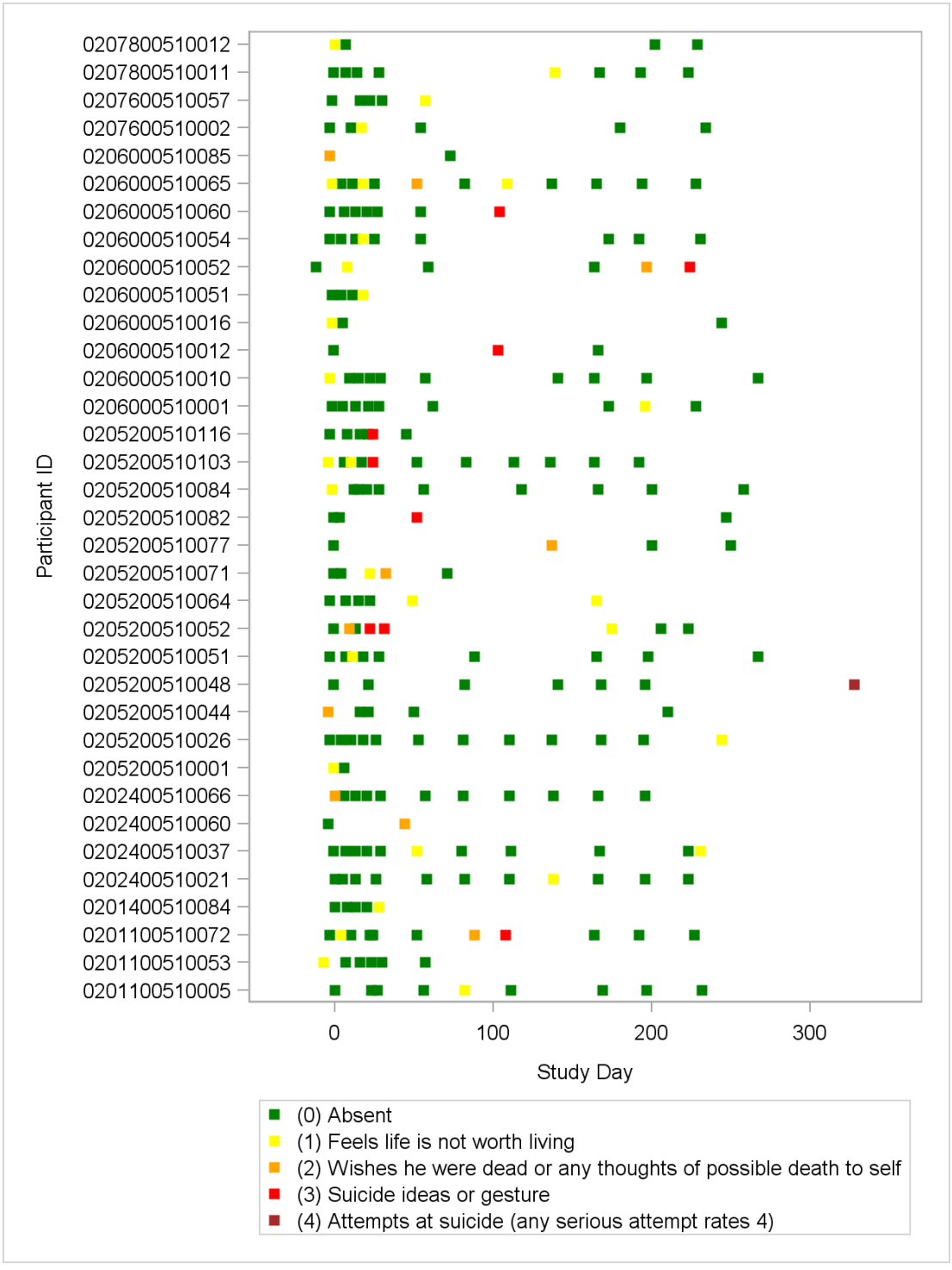
Figure 18: Participant-level Plot of HAM-D Question 3: Suicide by Treatment Arm

Figure 18A: Treatment Arm = BUP-NX



Example figure provided. The figure colors will be modified to accommodate color blind readers.

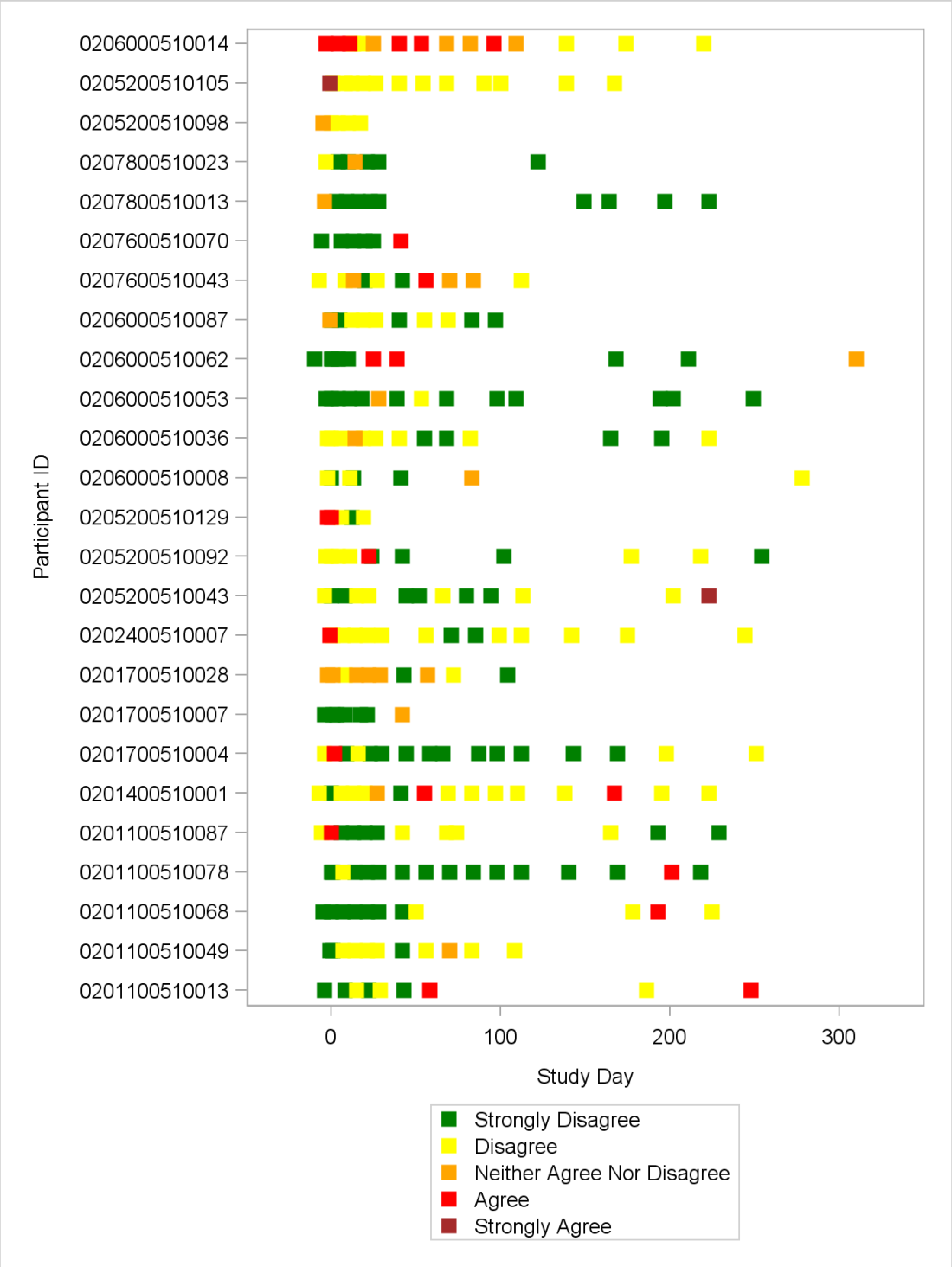
Figure 18B: Treatment Arm = XR-NTX



Example figure provided. The figure colors will be modified to accommodate color blind readers.

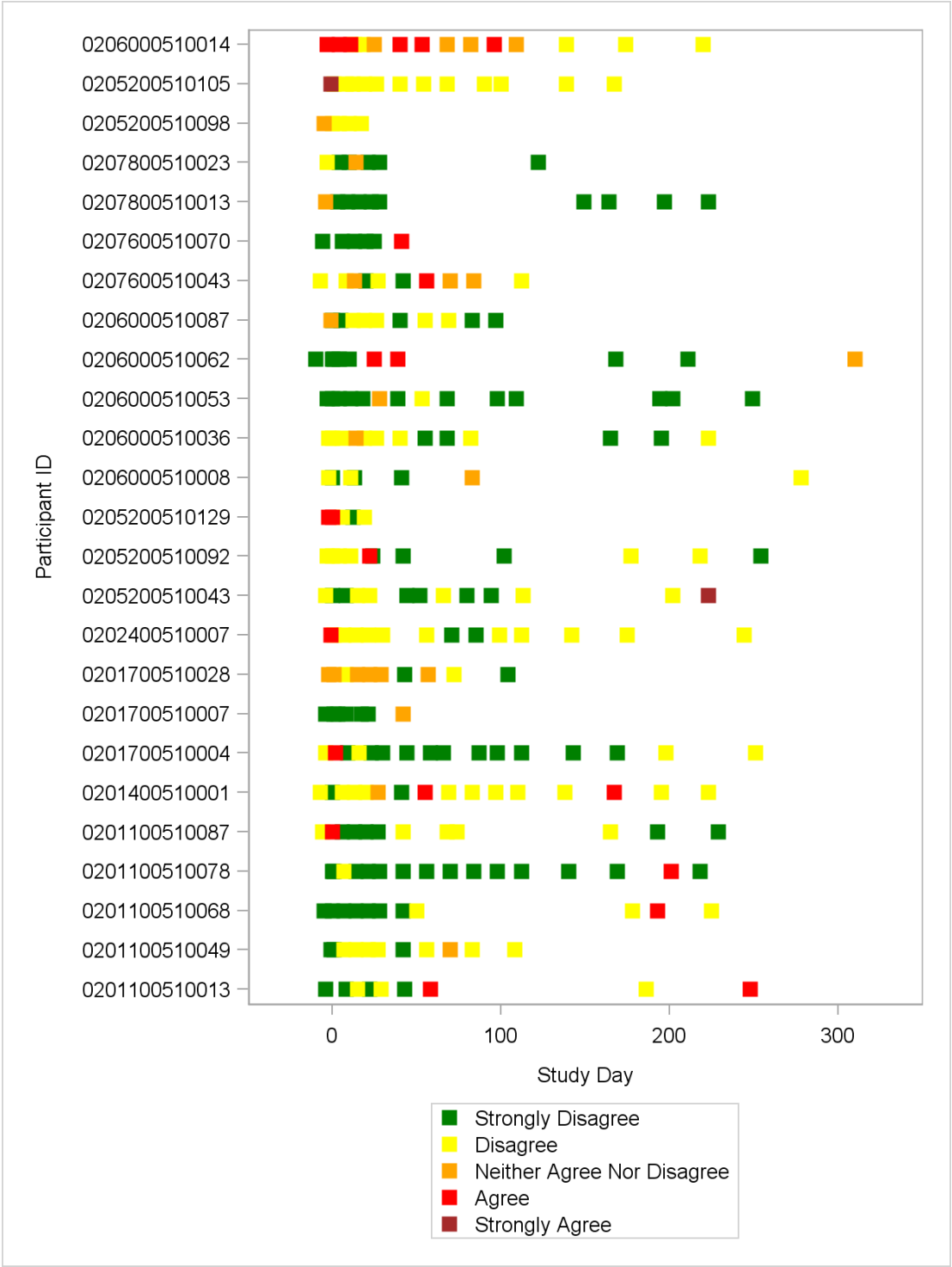
Figure 19: Participant-level Plot of CHRT Question 14: I have been having thoughts of killing myself, by Treatment Arm

Figure 19A: Treatment Arm = BUP-NX



Example figure provided. The figure colors will be modified to accommodate color blind readers.

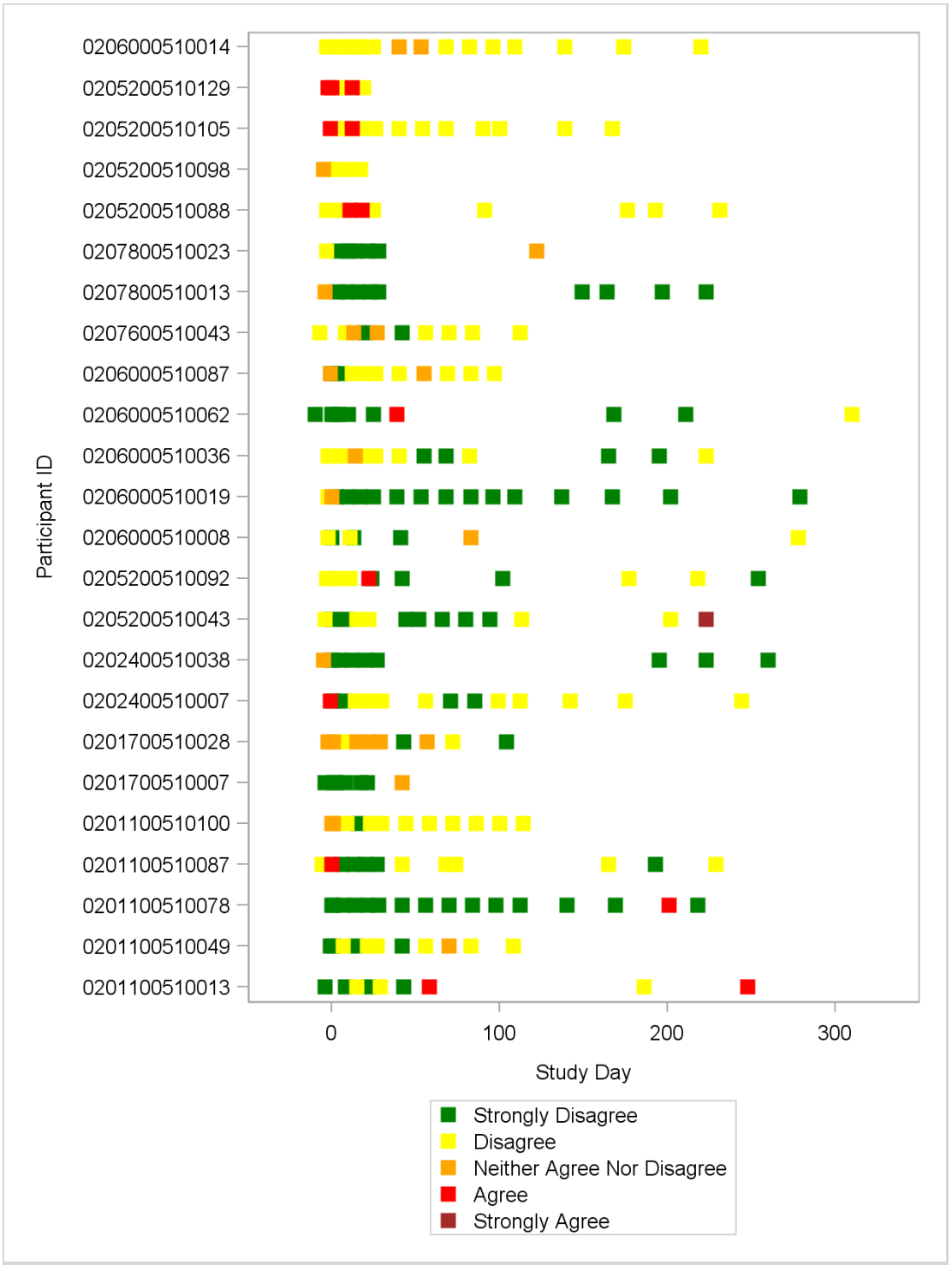
Figure 19B: Treatment Arm = XR-NTX



Example figure provided. The figure colors will be modified to accommodate color blind readers.

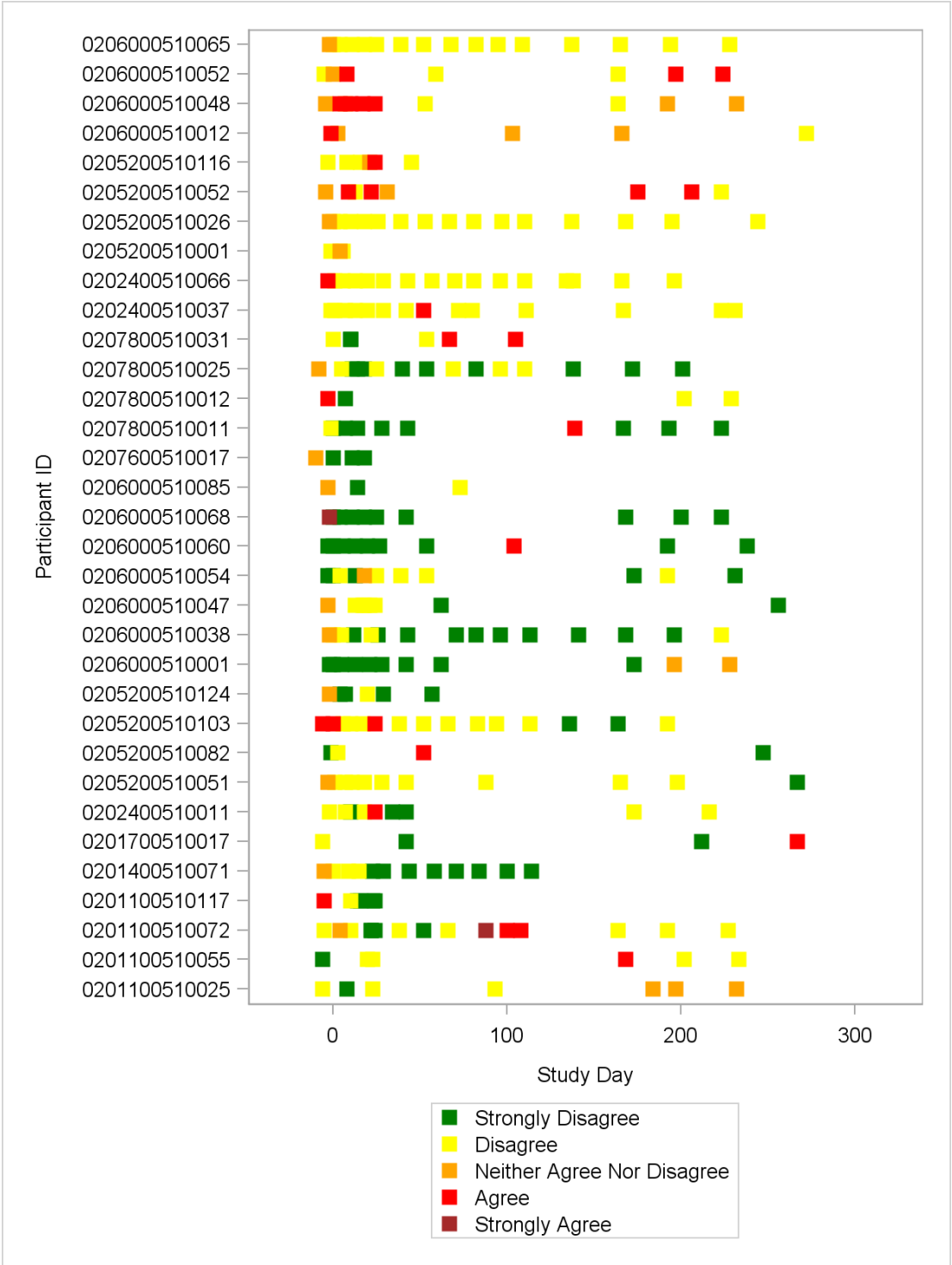
Figure 20: Participant-level Plot of CHRT Question 15: I have been having thoughts of how I might kill myself, by Treatment Arm

Figure 20A: Treatment Arm = BUP-NX



Example figure provided. The figure colors will be modified to accommodate color blind readers.

Figure 20B: Treatment Arm = XR-NTX



Example figure provided. The figure colors will be modified to accommodate color blind readers.

Figure 21: Participant-level Plot of CHRT Question 16: I have a plan to kill myself, by Treatment Arm

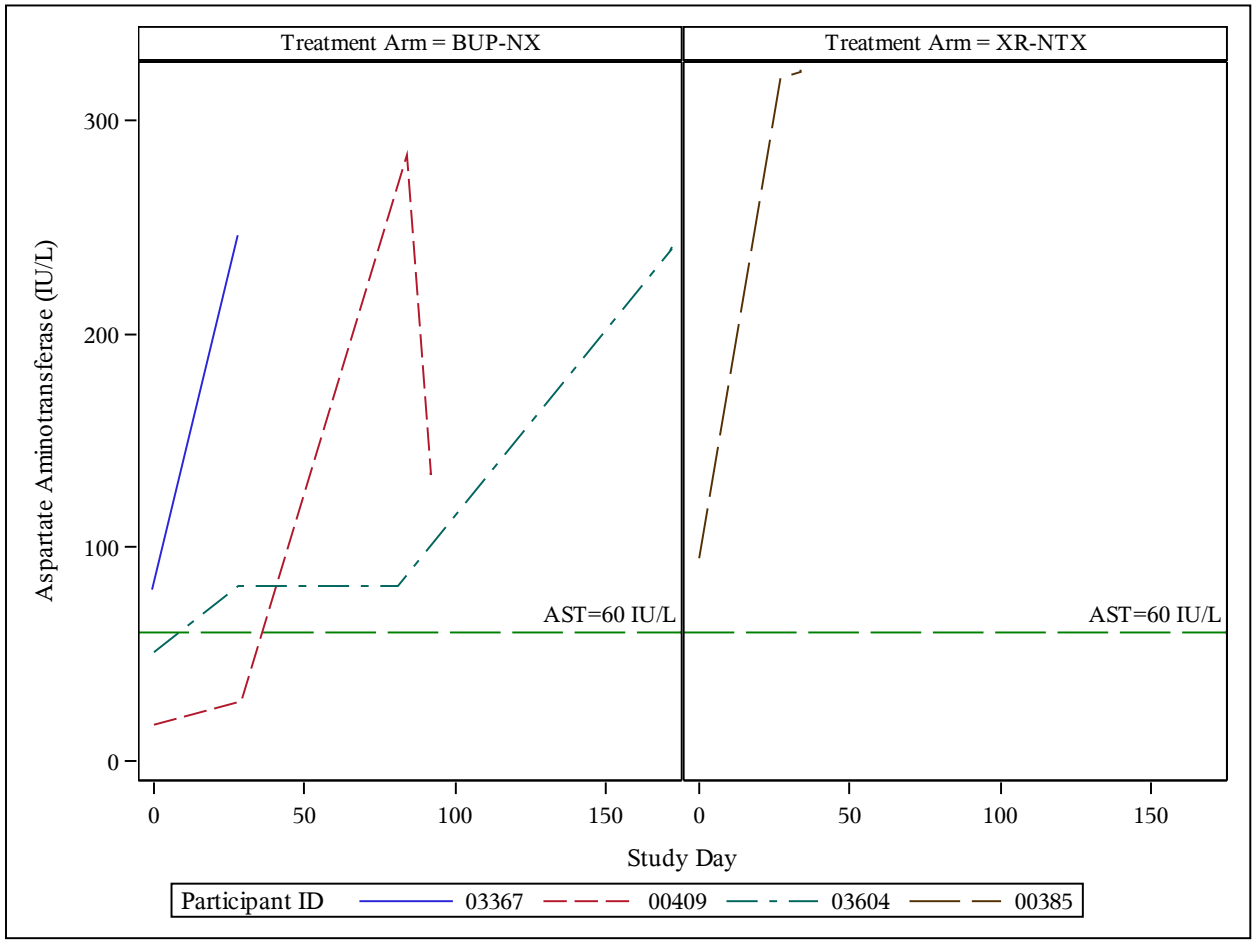
Figure 12A: Treatment Arm = BUP-NX

Example figure provided. The figure colors will be modified to accommodate color blind readers.

Figure 12B: Treatment Arm = XR-NTX

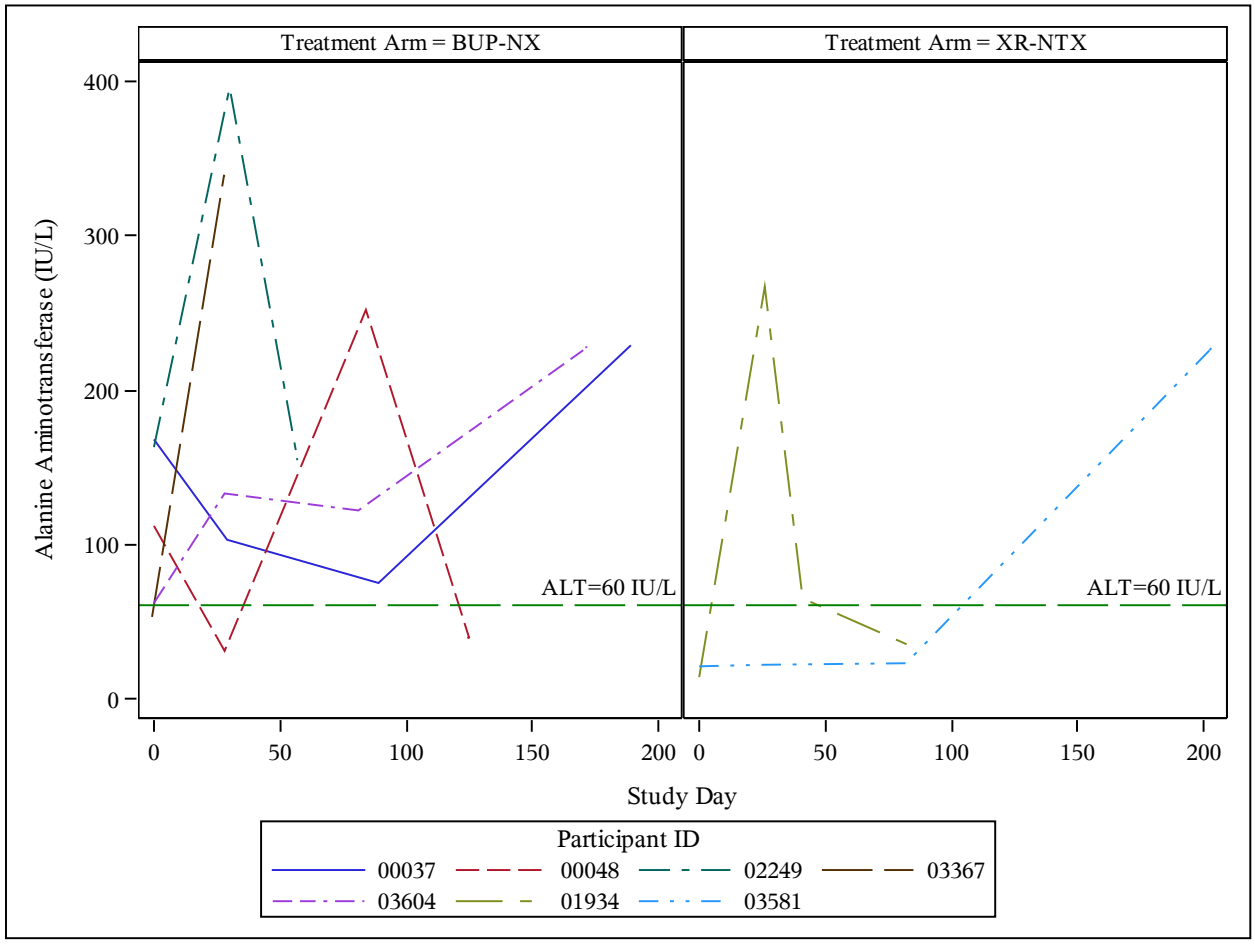
Example figure provided. The figure colors will be modified to accommodate color blind readers.

Figure 22: Participant-level Trajectories for Participants with Aspartate Aminotransferase > 225 IU/L by Treatment Arm



Example figure provided.

Figure 23: Participant-level Trajectories for Participants with Alanine Aminotransferase > 225 IU/L by Treatment Arm



Example figure provided.

Table 44: Listing of Liver Function Tests for ALT and AST exceeding 45 IU/L by Treatment Arm							
Treatment Arm=BUP-NX							
CTP	**Participant ID**	**Date of Labs**	**Study Day**	**Baseline Aspartate Aminotransferase (IU/L)**	**Follow-up Aspartate Aminotransferase (IU/L)**	**Baseline Alanine Aminotransferase (IU/L)**	**Follow-up Alanine Aminotransferase (IU/L)**
Treatment Arm=XR-NTX							
CTP	**Participant ID**	**Date of Labs**	**Study Day**	**Baseline Aspartate Aminotransferase (IU/L)**	**Follow-up Aspartate Aminotransferase (IU/L)**	**Baseline Alanine Aminotransferase (IU/L)**	**Follow-up Alanine Aminotransferase (IU/L)**

Yellow highlighted cells indicate liver function test results greater than 45 IU/L. Red highlighted cells indicate liver function tests results greater than 225 IU/L.

Table 45: Summary of Injection Site Abnormalities by CTP									
	OV Maryhaven	**FL Gateway Community Services**	**PA Tarzana Treatment Centers**	**NEC Stanley Street Treatment and Resources (SSTAR)**	**GNY Bellevue Hospital Center**	**PNW ETS/ RCKC**	**MA Avery Road**	**SW Turquoise Lodge Hospital**	**Total**
Number of Participants Randomized to XR-NTX									
Number of Participants with Injection Site Abnormality									
Number of Injection Site Abnormalities Reported									
Type of Injection Site Abnormality									
Pain									
Abscess									
Sterile abscess									
Necrosis									
Cellulitis									
Tenderness									
Induration									
Swelling									
Erythema (redness)									
Bruising									
Pruritus									
Nodule									
Hematoma									
Other									
Severity of Injection Site Abnormality									
Mild									
Moderate									
Severe									

Table 46: Listing of Injection Site Abnormalities

CTP	Participant ID	Date of Injection	Injection Number	Event Start Date	Event Resolution Date	Abnormal Event	Severity	Treatment

Appropriately qualified and trained medical personnel examine the injection site on the next Medical Management visit following the Vivitrol administration.

Table 47: Summary of Withdrawal Symptoms (SOWS Composite Score) at Induction by Treatment Arm		
	Treatment Arm	
SOWS Composite Score	**BUP-NX (N=)**	**XR-NTX (N=)**
SOWS Composite Score Before Induction		
N		
Mean		
SD		
Median		
Min		
Max		
SOWS Composite Score after Naloxone Challenge		
N	N/A	
Mean	N/A	
SD	N/A	
Median	N/A	
Min	N/A	
Max	N/A	
SOWS Composite Score After Induction		
N		
Mean		
SD		
Median		
Min		
Max		
Change in SOWS Composite Score between post Naloxone Challenge SOWS and after induction SOWS		
N	N/A	
Mean	N/A	
SD	N/A	
Median	N/A	
Min	N/A	
Max	N/A	
Change in SOWS Composite Score*		
N		
Mean		
SD		

Table 47: Summary of Withdrawal Symptoms (SOWS Composite Score) at Induction by Treatment Arm		
	Treatment Arm	
SOWS Composite Score	BUP-NX (N=)	XR-NTX (N=)
Median		
Min		
Max		

At the induction visit for the XR-NTX group, the SOWS is administered three times, the first time within the hour prior to the naloxone challenge, the second time 10-30 minutes following the naloxone challenge, and the third time 1-3 times following the XR-NTX injection. At the induction visit for the BUP-NX group, the SOWS is administered twice, the first time within the hour prior to the BUP-NX dosing and the second time 1-3 hours following dosing.

The SOWS is a 16-item questionnaire with a maximal score of 4 per item (0=absent, 4=extremely) for a maximal composite score of 64.

*Change in SOWS Composite Score is calculated as the SOWS Composite Score after induction minus the SOWS Composite Score before induction. Thus, a negative value indicates symptoms improvement whereas a positive value indicates worsening.

Table 48: Listing of Pregnancies by Treatment Arm Treatment Arm=BUP-NX						
CTP	**Participant ID**	**Date of Randomization**	**Date Staff Aware**	**Action Taken with Study Drug**	**Pregnancy Outcome**	**Date of Pregnancy Outcome**

Table 48: Listing of Pregnancies by Treatment Arm Treatment Arm=XR-NTX						
CTP	**Participant ID**	**Date of Randomization**	**Date Staff Aware**	**Action Taken with Study Drug**	**Pregnancy Outcome**	**Date of Pregnancy Outcome**

Live Birth Narratives

Table 49: Summary of Protocol Deviations in Randomized Participants, by Treatment Arm			
	BUP-NX (N=)	**XR-NTX (N=)**	**Total (N=)**
Number of randomized participants with protocol deviations			
Total number of protocol deviations			
Number of major protocol deviations			
Type of major protocol deviation – N (%)			
Medication dosing errors (protocol specified dose not dispensed)			
Breach of Confidentiality			
Safety assessment (e.g. labs, ECG, clinical referral to care) not conducted per protocol			
Stratification error			
Unauthorized assessments and/or procedures conducted prior to obtaining informed consent			
Medication dispensed to ineligible participant			
Participant use of protocol prohibited medication			
Type of minor protocol deviation – N (%)			
Study assessments not completed/followed as per protocol			
Biologic specimen not collected/processed as per protocol			
AE/SAE reported out of protocol specified reporting timeframe			
Protocol required visit/assessment not scheduled or conducted			
Study medication management - Other			
Study procedures/assessments - Other			
AE not reported			
Laboratory assessments - Other			
Non IRB approved/outdated/obsolete informed consent documents used			
Informed consent process not properly conducted and/or documented			
Informed consent procedures - Other			
Invalid/incomplete informed consent form			

Table 49: Summary of Protocol Deviations in Randomized Participants, by Treatment Arm			
	BUP-NX (N=)	**XR-NTX (N=)**	**Total (N=)**
Adverse event - Other			
Other significant deviations			
Inclusion/exclusion criteria - Other			
AE/SAE not elicited, observed and/or documented as per protocol			
Randomization procedures - Other			
Study behavioral intervention was not provided/performed as per protocol			

Table 50: Summary of Protocol Deviations Among Screen Failures	
	Total (N=)
Number of screen failures	
Number of screen failures with protocol deviations	
Total number of protocol deviations	
Number of major protocol deviations	
Type of major protocol deviation – N (%)	
Participant use of protocol prohibited medication	
Breach of Confidentiality	
Type of minor protocol deviation – N (%)	
Non IRB approved/outdated/obsolete informed consent documents used	
Study assessments not completed/followed as per protocol	
Biologic specimen not collected/processed as per protocol	
Invalid/incomplete informed consent form	
Informed consent process not properly conducted and/or documented	
Other significant deviations	

Table 51: Listing of Protocol Deviations in Randomized Participants by Deviation Category

Deviation Category=Informed Consent Procedures

Major protocol deviations are highlighted in grey

CTP	Participant ID	Treatment Arm	Date of Deviation	Days from Site Endorsement	Date Entered in AdvEDC	Level of Deviation	Deviation Type	Description	Plan to Prevent Recurrence	IRB Reporting Required?

Table 51: Listing of Protocol Deviations in Randomized Participants by Deviation Category

Deviation Category=Laboratory Assessments

Major protocol deviations are highlighted in grey

CTP	Participant ID	Treatment Arm	Date of Deviation	Days from Site Endorsement	Date Entered in AdvEDC	Level of Deviation	Deviation Type	Description	Plan to Prevent Recurrence	IRB Reporting Required?

Table 51: Listing of Protocol Deviations in Randomized Participants by Deviation Category

Deviation Category=Study Procedures/assessments

Major protocol deviations are highlighted in grey

CTP	Participant ID	Treatment Arm	Date of Deviation	Days from Site Endorsement	Date Entered in AdvEDC	Level of Deviation	Deviation Type	Description	Plan to Prevent Recurrence	IRB Reporting Required?

Table 51: Listing of Protocol Deviations in Randomized Participants by Deviation Category

Deviation Category=Adverse Event

Major protocol deviations are highlighted in grey

CTP	Participant ID	Treatment Arm	Date of Deviation	Days from Site Endorsement	Date Entered in AdvEDC	Level of Deviation	Deviation Type	Description	Plan to Prevent Recurrence	IRB Reporting Required?

Table 51: Listing of Protocol Deviations in Randomized Participants by Deviation Category

Deviation Category=Randomization Procedures

Major protocol deviations are highlighted in grey

CTP	Participant ID	Treatment Arm	Date of Deviation	Days from Site Endorsement	Date Entered in AdvEDC	Level of Deviation	Deviation Type	Description	Plan to Prevent Recurrence	IRB Reporting Required?

Table 51: Listing of Protocol Deviations in Randomized Participants by Deviation Category

Deviation Category=Study Medication Management

Major protocol deviations are highlighted in grey

CTP	Participant ID	Treatment Arm	Date of Deviation	Days from Site Endorsement	Date Entered in AdvEDC	Level of Deviation	Deviation Type	Description	Plan to Prevent Recurrence	IRB Reporting Required?

Table 52: Listing of Protocol Deviations among Screen Failures by Deviation Category

Deviation Category=Informed Consent Procedures

CTP	Participant ID	Date of Deviation	Days from Site Endorsement	Date Entered in AdvEDC	Level of Deviation	Deviation Type	Description	Plan to Prevent Recurrence	IRB Reporting Required?

Table 52: Listing of Protocol Deviations Among Screen Failures by Deviation Category

Deviation Category=Study Procedures/Assessments

CTP	Participant ID	Date of Deviation	Days from Site Endorsement	Date Entered in AdvEDC	Level of Deviation	Deviation Type	Description	Plan to Prevent Recurrence	IRB Reporting Required?

Table 52: Listing of Protocol Deviations Among Screen Failures by Deviation Category

Deviation Category=Other Significant Deviations

CTP	Participant ID	Date of Deviation	Days from Site Endorsement	Date Entered in AdvEDC	Level of Deviation	Deviation Type	Description	Plan to Prevent Recurrence	IRB Reporting Required?