Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD

Protocol Identifying Number: AS140026-A5
Principal Investigator: Lori Davis, MD
Co-Principal Investigator: Ismene Petrakis, MD

IND/IDE Sponsor: Not applicable; Exempt from IND

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Version Number: 7.0/July 19, 2021

Section	Substantive Changes (v6, 6/19/2020 to v7, 7/19/2021)
Summary	Expanded recruitment area for Tuscaloosa site to include Central Alabama VA Healthcare System (CAVAHS)
Summary	Updated to 37-month study period that includes ~32-month enrollment period.
2.3.1, 3, 4.1, 4.2.2, 7.1.1, 7.3.4, 7.3.7, 10.2, and 10.4.3	Restarted the psychophysiologic assessments. • Removed where protocol states "psychophysiologic assessments on HOLD due to COVID-19." • Changed psychophysiologic assessments to highly encouraged but optional. o Procedures should not be a barrier to recruitment o Participant payments for these procedures should provide incentive for participation.
1 and 6.1	• Closed enrollment at Wayne State/Detroit site o Dr. Norrholm remains co-investigator (for purposes of the psychophysiologic assessments)
7.3.7	COVID-19 Safety Precautions section was updated to allow for flexibility for sites to follow local policies as both vaccination and infection rates evolve.
7.5	Updated the prohibited medications to: • Lamotrigine removed from the prohibited medication list. o There is no medical contraindication to combining lamotrigine with study medications; thus, removing an unnecessary barrier to enrollment. • Quetiapine removed from the prohibited medication list. o There is no medical contraindication to combining lamotrigine with study medications; thus, removing an unnecessary barrier to enrollment. • Atomoxetine removed from the prohibited medication list. o ADHD treatment medication, but not a stimulant; thus, removing an unnecessary barrier to enrollment. Since all scenarios for concomitant medication use cannot be anticipated, we have added this statement so that exceptions can be made without causing a protocol deviation: *"Due to the potential drug: drug interactions (e.g., opiates) or confounding therapeutic effects (e.g., naltrexone or acamprosate), participants may not use the medications listed in the table below, unless authorized by PASA medical monitor and approved by the lead PIs."*
5.2	Clarified exclusion # 7 criteria wording: • Version 6: '….including seizures (other than childhood febrile seizures),….' • Version 7: '….including **seizure disorder** (other than childhood febrile seizures),…..'

5.2 and 7.2.1	<u>Changed exclusion criteria # 8 (wording regarding ALT and AST upper limit of normal (ULN)):</u> • Version 6: ALT or ASTs >3x ULN = exclusion criteria *"aspartate aminotransferase and/or alanine aminotransferase > 3 times upper limit of normal"* • Version 7: ALT or AST >5x ULN = exclusion criteria *"aspartate aminotransferase and/or alanine aminotransferase > 5 times upper limit of normal"* This patient population has transiently high ALT and AST levels due to heavy alcohol use. This criterion has caused delay in treatment in several cases to date, due to having to wait and repeat baseline labs. Thus, the threshold of 3x ULN is an unnecessary barrier to randomization. <u>Added procedure:</u> • If baseline ALT or AST is between 3x to 5x ULN o Recheck ALT and AST at Week 4 visit: ▪ If ALT or AST >4x ULN, PI may consider discontinuing the study medication if clinically indicated. o Recheck ALT and AST at Week 8 visit: ▪ If ALT or AST >3x ULN, PI may consider discontinuing the study medication if clinically indicated. • The PI may consult with the medical monitor as needed.
5.3 and 7.3.1	Changed compensation per visit based on the optional psychophysiologic assessments and telehealth visits.

Table of Contents

LIST OF ABBREVIATIONS

ADS	Alcohol Dependence Scale
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AOD	Accounting of Disclosure
APN	Advanced Practice Nurse
ASP	Acoustic Startle Pulse
AST	Aspartate Aminotransferase
AUD	Alcohol Use Disorder
BrAC	Breathalyzed alcohol concentration
BIS	Barratt Impulsivity Scale
BMP	Basic metabolic panel
BVAMC	Birmingham VA Medical Center
BUN	Blood urea nitrogen
BUP	Buprenorphine
CAPS-5	Clinician Administered PTSD Scale for DSM-5
CBC	Complete Blood Count
CDMRP	Congressionally Directed Medical Research Program
CFR	Code of Federal Regulations
CGI-S/CGI-I	Clinical Global Impression-Severity & Clinical Global Impression-Improvement
CIWA-Ar	Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CoC	Certificate of Confidentially
Co-I	Co-Investigator
CO2	Carbon dioxide
COWS	Clinical Opiate Withdrawal Scale
CPRS	Computerized Patient Record System
CREEF	Connecticut Research & Education Foundation
CRC	Clinical Research Coordinator
CS	Conditioned Stimulus
C-SSRS	Columbia-Suicide Severity Rating Scale
DAQ	Desire of Alcohol Questionnaire
DCC	Data Coordinating Center
D/C	Discontinued
dL	Deciliter
DoD	Department of Defense
DSM-5	Diagnostic and Statistical Manual-5th Edition
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EMG	Electromyography
FDA	Food and Drug Administration
FPS	Fear-Potentiated Startle
FU	Follow-Up

FY	Fiscal Year
g	Grams
GABA	Gamma-Aminobutyric Acid
GCP	Good Clinical Practice
GGT	gamma-GTP
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GOR	Grants Officer Representative
GSC	Government Steering Committee
GSR	Galvanic skin response
H&P	History and Physical
HCT	Hematocrit
HGB	Hemoglobin
HIPPA	Health Insurance Portability and Accountability Act of 1996
HR	Heart rate
hr	Hour
Hz	Hertz
IATA	International Air Transport Association (IATA)
ICH	International Council for Harmonization
IM	Intramuscular
IND	Investigational New Drug Application
IOM	Institute of Medicine
IRB	Institutional Review Board
KOR	Kappa opioid receptor
kg	Kilograms
LFTs	Liver function tests
LEC-5	Life Events Checklist for DSM-5
LOC	Loss of Consciousness
LSI	Local Site Investigator
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MD	Doctor of Medicine
mEq	Milliequivalent
mg	Milligrams
MINI-5	Mini-International Neuropsychiatric Interview for DSM-5
ml	Milliliters
MM	Medical management
MMRM	Mixed-Effect Model of Repeated Measure
MOP	Manual of Procedures
msec	Millisecond
NA	Noise alone
NDA	New Drug Application
N/A	Not Applicable
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIH	National Institute of Health
NIMH	National Institute of Mental Health
NTX	Naltrexone

OCDS	Obsessive Compulsive Drinking Scale
OSU-TBI	Ohio State University Traumatic Brain Injury Identification Method (Short Form)
PASA	Pharmacotherapies for Alcohol and Substance Abuse Consortium
PCL-5	PTSD Checklist for DSM-5
PEth	Phosphatidyl ethanol
PharmD	Pharmacist with a Doctorate Degree
PHQ-9	Patient Health Questionnaire
PI	Principal Investigator
PLC	Placebo
PO4	Phosphate
PSI	Pounds per square inch
PTSD	Post-Traumatic Stress Disorder
RCS	Records Control Schedule
RBC	Red blood cell count
RCT	Randomized Controlled Trial
RN	Registered Nurse
RSA	Respiratory sinus arrhythmia
SAE	Serious adverse event
SCL	Skin conductance level
SCR	Skin conductance response
SIP	Short Inventory of Problems
SL	Sublingual
SNRI	Serotonin and norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
T	Telephone visit
TLFB	Timeline Follow Back
TRD	Treatment Resistant Depression
TREAC	Tuscaloosa Research & Education Advancement Corporation
TSH	Thyroid Stimulating Hormone
TVAMC	Tuscaloosa VA Medical Center
ULN	Upper Limit of Normal
UP	Unanticipated Problem
USPS	United States Postal Service
VA	Veteran’s Administration
VACT	VA Connecticut Healthcare System
VR	Virtual reality
VR-12	Veterans RAND 12-item Health Survey
WBC	White blood cell count
WHO	World Health Organization
XR	Extended release
XR-NTX	Extended-release injectable naltrexone

STATEMENT OF COMPLIANCE:

All key personnel, defined as all individuals responsible for the design and conduct of this trial, will complete Human Subjects Protection Training. The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

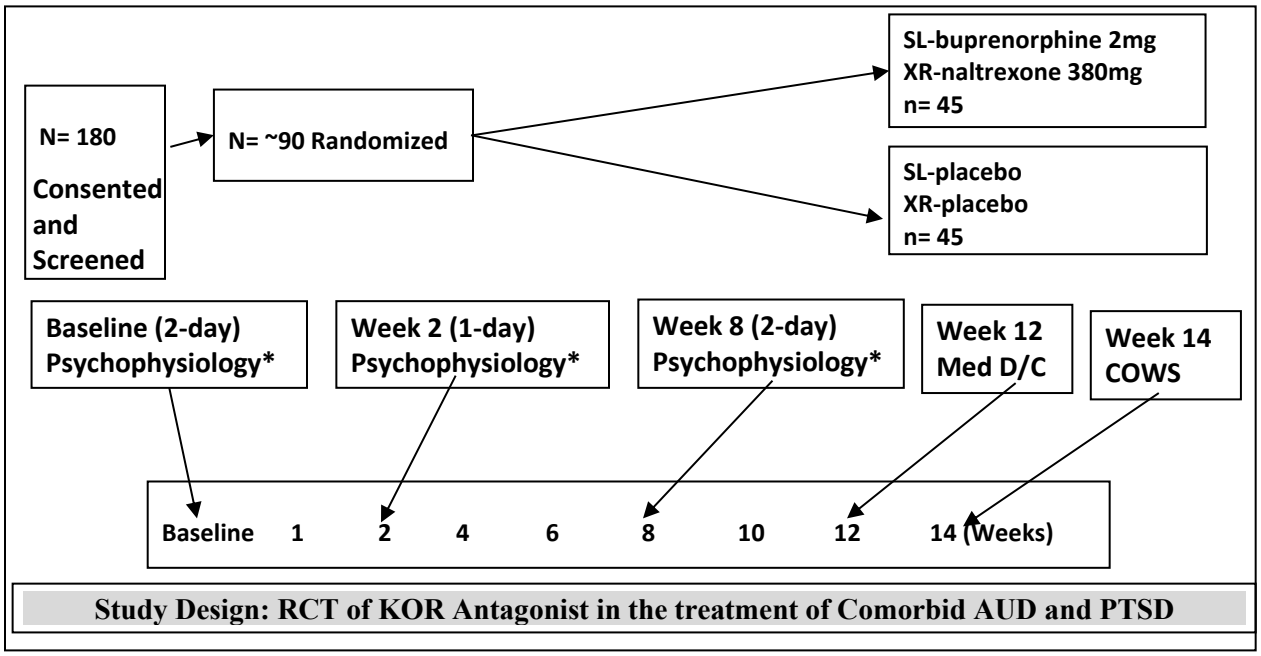
- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21CFR Part 11, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312)
- ICH E2, E3, E6, E8 and E9

PROTOCOL SUMMARY

Title:	Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD
Objectives:	Evaluate the efficacy and physiological effects of sublingual buprenorphine (SL-BUP; Subutex) combined with extended-release injectable naltrexone (XR-NTX; Vivitrol) in the treatment of comorbid alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD)
Endpoint	Primary endpoint is improved AUD+PTSD outcomes at 8 weeks, in patients with comorbid AUD and PTSD
Population:	Treatment-seeking veterans, non-veterans, and service members with comorbid AUD and PTSD screened, enrolled, and randomized to the two treatment groups. With respect to sample size, the goal is to obtain at least 90 participants randomized to either of the two retained arms (XR-NTX/2mgBUP arm or PLACEBO arm). Recruitment will occur over a 32-month enrollment period. If this goal is met with time left in the enrollment period, sites will be allowed to randomize additional participants but will not exceed the original planned sample size of 135 randomized participants.
Phase:	Phase II Randomized Controlled Trial (RCT)
Number of Sites enrolling participants:	**2 sites:** 1. Tuscaloosa: Tuscaloosa Research & Education Advancement Corporation (TREAC)/Tuscaloosa VA Medical Center (TVAMC) a. Recruitment area to include catchment area for Tuscaloosa, Birmingham, and Central Alabama VA Healthcare System (CAVHS) 2. West Haven: Connecticut Research & Education Foundation (CREEF) / VA Connecticut Healthcare System (VACT)

Description of Study Agent:	Sublingual buprenorphine, which acts as an antagonist at kappa and partial agonist of the mu receptors, combined with extended-release injectable naltrexone, which blocks the mu receptor, yields a pharmacologically net effect of kappa opioid receptor (KOR) antagonism. Concurrent use of naltrexone diminishes the potential of buprenorphine misuse.
Study Duration:	37-month study period that includes ~32-month enrollment period
Participant Duration:	14 weeks from the time of randomization

SCHEMATIC OF STUDY DESIGN



*Psychophysiologic assessments are optional to not be a barrier to enrollment or randomization.

1 KEY ROLES

- **Lori L. Davis, MD (Co-Principal Investigator); Tuscaloosa Research & Education Advancement Corporation (TREAC)/Tuscaloosa VA Medical Center (TVAMC)**

Dr. Davis is a Clinical Professor of Psychiatry at the University of Alabama School of Medicine and the Associate Chief of Staff for Research at the TVAMC. As a PTSD clinical researcher and Study Chair of the VA Cooperative Study Program #589, she is well-suited for the role of Co-Principal Investigator for this multisite randomized controlled trial. She has 24 years of VA clinical research experience under continuous peer-reviewed funding, including pivotal work in psychopharmacologic and vocational rehabilitation treatments Veterans with posttraumatic stress disorder (PTSD). Dr. Davis is currently collaborating with Dr. Kathleen Brady as the local site investigator for a study on mindfulness-based relapse prevention in Veterans with addictions. Her work on the NIMH-funded STAR*D study focused on secondary analysis of the comorbidity of depression and substance use disorders, predictors of treatment response, and outcomes. Dr. Davis has led several multisite placebo-controlled drug studies for the treatment of PTSD and is highly regarded by the field for her leadership in PTSD clinical trials. For this reason, she was a member of the 2017 VA-DoD Clinical Practice Guidelines for the Treatment of PTSD workgroup.

- **Ismene Petrakis, MD (Co-Principal Investigator); VA Connecticut Research & Education Foundation (VACREEF) / VA Connecticut Healthcare System (VACT)**

Dr. Petrakis is a Professor of Psychiatry at Yale school of Medicine, and the Chief of Psychiatry at VACT Healthcare System. She serves as co-PI and is instrumental in the design of the methods, implementation, clinical management, integration and interpretation of the findings based on her past research and clinical experience. Over the past 20 years, her research focus has been on understanding and developing treatments for alcohol dependence particularly in those with psychiatric comorbidity, and in understanding the underlying neurobiology of alcohol use disorders. This work informed the randomized clinical trials that she has conducted in patients with alcohol dependence and comorbid mental illness. This work includes the first study to evaluate naltrexone in individuals with schizophrenia and studies evaluating other medications approved to treat alcohol dependence by the Food and Drug Administration (FDA) in patients with psychiatric comorbidity. More recently, Dr. Petrakis has also explored different pharmacologic options for veterans with alcohol dependence with comorbid PTSD. This includes the largest study to date of prazosin in Veterans with alcohol dependence and comorbid PTSD.

- **Seth Norrholm, PhD (Co-investigator/Subject Matter Expert, Wayne State University); fear-potentiated startle testing**

Dr. Norrholm is a translational neuroscientist who studies trauma-, stressor-, and anxiety-related disorders in combat and civilian populations. The primary objective of his work is to develop “bench-to-bedside” clinical research methods to inform therapeutic interventions for PTSD and the disorders with which it is co-morbid. The most effective treatments for PTSD involve exposure therapy, a clinical analog to laboratory fear extinction, and as such there is a compelling need to further study these processes. Dr. Norrholm has developed a conditioned fear extinction paradigm using fear-potentiated startle (FPS); a methodology that has the potential to be an effective outcome measure for PTSD treatment as well as an index of fear recovery. His work is and has been supported by funding from the VA Clinical Science R&D, NATO, the Brain and Behavior Foundation (formerly NARSAD), the Congressionally Directed Medical Research Program through the Department of Defense (CDMRP/DoD), and the Emory University Research Committee. Dr. Norrholm and his collaborators have recently established a Human Psychophysiology of Emotion Laboratory that brings together cutting-edge psychophysiological techniques to study the neurobiology of fear, anxiety, and depression. These collaborations are focused on the interaction between genetic and environmental risk factors that mediate vulnerability to developing PTSD, PTSD symptom severity, and treatment outcome, with a focus on the identification of intermediate phenotypes.

2 INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

2.1 BACKGROUND

Alcohol use disorder (AUD) affects 18 million Americans and is highly prevalent in U.S. service members and among military Veterans. AUD has a large detrimental impact on society.[1,2] One important comorbid condition for individuals with AUD is PTSD. PTSD has a past year and lifetime prevalence of 4.7% and 6.1%, respectively.[3] The odds of having PTSD are 30% greater for those with a lifetime AUD than those with no lifetime AUD.[4] Taken from the other direction, those with lifetime PTSD are at greater risk of having an AUD (20% increased risk) compared to those without PTSD.[12] Comorbidity is associated with many detrimental outcomes including significant social instability, disability, and more severe symptoms, higher rates of relapse, suicidal behaviors, and medical complications.[5, 6] Currently, there are only four FDA–approved medications (disulfiram, oral and long-acting injectable naltrexone, and acamprosate) to treat AUD and two FDA-approved medications (sertraline and paroxetine) to treat PTSD. Despite a growing body of research in this area,[7] there is no medication with clear evidence of efficacy in AUD-PTSD comorbidity and there are no FDA-approved medications to treat these disorders when they co-occur.[15] New treatment strategies are urgently needed. This study addresses the substantial deficit in pharmacologic treatments for comorbid AUD and PTSD.

2.2 SCIENTIFIC RATIONALE

The use of medication that result in kappa opioid receptor (KOR) antagonism represents a novel potential treatment for Veterans and Service Members with comorbid AUD and PTSD. Endogenous opioid systems in the brain are involved in regulation of mood, stress modulation, and cravings.[1] Kappa opioid receptors are densely localized in limbic and cortical areas comprising the brain reward system, which play a role in modulating stress and in promoting addictive behaviors.[2,3] Endogenous dynorphins, called k-selective opioid peptides, are released during the stress response and contribute to the anxiogenic and dysphoric responses to the stressful experience.[4] Further, the KOR dynorphin system impacts stress-induced drug and alcohol seeking behavior.[8] In animal models of alcohol dependence, KORs are implicated in the excessive alcohol consumption, particularly during withdrawal. KOR antagonists block the actions of endogenous dynorphins and block the stress-induced reinstatement of extinguished cocaine- and ethanol-seeking behaviors in animals. Studies for animal models of cocaine dependence have shown promise for using a combination of buprenorphine and naltrexone, without producing opioid dependence.[9]

KOR antagonists may be beneficial in the treatment of addictions,[5] PTSD,[6] and major depressive disorder.[6-8] An example includes a short-acting potent KOR antagonist with selectivity over other opioid receptors (CERC-501) which has demonstrated antidepressant-like effects in animal models of depression and been shown to reduce ethanol self-administration in alcohol-preferring rats.[10] CERC-501 is currently unavailable for additional studies due to its being purchased by another pharmaceutical company that is pursuing its use in major depression as the first approved indication.

Another medication that acts as a net KOR antagonist is ALKS-5461, which is a combination drug formulation of buprenorphine and samidorphan. Buprenorphine acts as an antagonist at kappa and partial agonist of the mu receptors and samidorphan is a mu opioid receptor antagonist, resulting in a pharmacologically net effect of kappa-opioid receptor antagonism (i.e., the same mechanism of action as the combination approach proposed in this application). The combination drug binds with high affinity to opioid receptors with low net intrinsic signaling activity. ALKS-5461 is intended to support opioid tone in the brain regions with impaired endogenous activity and dampen opioid tone in upregulated regions. In a recent study, adjunctive ALKS-5461 significantly reduced depression scores compared to placebo in patients with treatment resistant depression.[11] Following a positive phase II trial, ALKS-5461 was granted Fast Track Designation by the FDA for treatment resistant depression (TRD) in October 2013.[12] In 2014, two of three core phase II trials showed that ALKS-5461 at daily doses of 0.5mg/0.5mg and 2mg/2mg were safe and well-tolerated but, disappointingly, the trials failed to meet their primary efficacy endpoints, due in part to an unusually strong placebo effect. However, some endpoints trended towards efficacy for 2mg/2mg/d and a statistically significant signal on the depression endpoint. In a sequential parallel comparison design study (stage 1 double-mask placebo-controlled parallel comparison with higher proportion of patients randomized to placebo than to active drug and those patients who meet placebo nonresponse are re-randomized in stage 2 to drug or placebo), the 2mg/2mg and 8mg/8mg doses of ALKS 5461 were tested in patients with TRD.[20] **The 2/2 dose was significantly better that placebo across the three depression outcomes.** Although there was significant improvement in the 8mg/8mg dosage, it did not achieve statistical significance. The medication was well tolerated and there was no evidence of opioid withdrawal on treatment discontinuation. Three additional Phase 3 studies showed efficacy ALKS-5461 2mg/2mg in participants with TRD maintained on their selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI) or bupropion.

Alkermes is currently seeking approval of ALKS-5461 as adjunctive treatment of TRD, which makes the timing for assessing this compound in AUD+PTSD studies potentially problematic. While initially interested in partnering with us, Alkermes leadership decided to forego testing ALKS 5461 in AUD+PTSD at this time due to priorities related in their current FDA new drug application (NDA). Alkermes is willing to continue to partner with us by providing the long-acting injectable naltrexone and placebo for this proposal.

The combination of buprenorphine, which acts as an antagonist at kappa and partial agonist of the mu receptors, and naltrexone, which blocks the mu receptor, yields a pharmacological net effect of a KOR antagonist, and thus, is an excellent alternative study medication to ALKS-5461 and CERC-501. Several clinical trials have been conducted safely and effectively using buprenorphine combined with naltrexone, including one in patients with comorbid cocaine and opioid use disorders.[13] Buprenorphine alone has been evaluated for antidepressant effects in 41 studies, most of which were conducted in comorbid opioid dependence, but several were not.[14] There is clinical evidence that buprenorphine is effective in attenuating some PTSD symptoms among those with opioid use disorder.[15] The use of buprenorphine in a non-opioid dependent population has ethical implications given its risk of addiction, which has led to the idea to

combine it with naltrexone in order mitigate the potential for misuse. Further, preclinical studies suggest KOR antagonism is important for drinking behavior, stress induced reinstatement of drug and alcohol consumption. For these reasons, there is substantial interest in the development of KOR antagonists for indications such as AUD and PTSD and the combination of buprenorphine and naltrexone allows for a proof-of-concept study until a formulated KOR-antagonist becomes commercially available.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 POTENTIAL RISKS

Naltrexone for extended-release injectable suspension (XR-NTX; Vivitrol) is FDA-indicated for the treatment of alcohol dependence, so participants in this study may have direct benefit from this treatment. XR-NTX is not a controlled substance.

Sublingual buprenorphine (SL-BUP) is FDA-indicated for the treatment of opioid dependence. SL-BUP is a Schedule III narcotic under the Controlled Substances Act. The use of SL-BUP in a non-opioid dependent population has a risk of misuse or abuse. Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. However, to mitigate the potential for misuse, dependency, and withdrawal, buprenorphine can be combined with XR-NTX, a medication that blocks the mu receptor involved in psychogenic properties of buprenorphine.

XR-NTX can antagonize the effects of opioids via competitive inhibition of opioid receptors, which raises the concern that the combination of SL-BUP and XR-NTX will make SL-BUP less effective. This would be a risk for individuals who are using opiates or SL-BUP on a regular basis prior to starting XR-NTX, (i.e., the addition of XR-NTX may precipitate opioid withdrawal symptoms). For this reason, this study excludes patients who have recent opioid use or opioid use disorders, and opiates are not allowed to be concurrently taken during the study. XR-NTX is contraindicated in patients receiving opioid analgesics and in patients with current physiologic opioid dependence, acute opiate withdrawal, acute hepatitis or liver failure, and previous hypersensitivity reaction to XR-NTX. Patients with these contraindications are not eligible to participant in this study.

The CURB study[16] evaluated low dose and high dose SL-BUP added to XR-NTX in participants recovering from current cocaine use disorder and past year (not recent) opioid use or dependence and whom did not necessarily have a diagnosis of PTSD. In the publication of its results, Ling et al (2016) provide an extensive table of the reported and related adverse events, with a breakdown of causal relationship and type of adverse events comparing placebo, low dose and high dose SL-BUP added to XR-NTX. The study found no significant differences in numbers of adverse events or serious adverse events by treatment arm and there were no significant adverse events related to induction onto XR-NTX. None of the serious adverse events were deemed by the medical monitor as study-related[16].

In the current study, XR-NTX is administered as a long-acting injectable, the protective pharmacologic properties are present for the full duration of treatment with SL-BUP, thereby eliminating the risk that the participant will become psychologically or physically addicted to SL-BUP. In addition, we are using low dose SL-BUP (Note: the dose is lower than 16mg dose used in CURB study). At the end of the study XR-NTX is gradually eliminated from the body. Thus, a pharmacologic taper is not needed for either XR-NTX or SL-BUP. Participants should not experience withdrawal symptoms, but to be conservative, they are followed by the investigators for an additional two weeks to monitor the participants for any adverse events related to discontinuation. To be cautious and thorough, the investigators assess for signs and symptoms of opioid withdrawal at the end of the study.

The study uses low dose of buprenorphine (2mg daily) which is usually the target of a taper when stopping treatment in a patient on medication-assisted therapy for opioid use disorders. Withdrawal is highly unlikely with these low doses after 12 weeks of treatment, especially when used in combination with naltrexone. The potential for withdrawal is mitigated by naltrexone. Withdrawal from low dose buprenorphine in patients with non-opioid use disorders is not described in the literature. Case reports of discontinuation of higher dose (12mg to 20 mg daily) buprenorphine indicate that mild opiate withdrawal symptoms last 1 to 2 days and did not require opioid medication or other medication. Psychosocial intervention is recommended, and the lengthy withdrawal regimens might prolong withdrawal symptoms unnecessarily.

The investigators have designed the study to include two weeks (from Week 12 to Week 14) to monitor the patient for drug discontinuation or withdrawal symptoms. The investigators will treat emergent psychological symptoms with psychosocial support and physical symptoms with the appropriate treatments, such as metoclopramide for nausea, NSAIDs for pain, clonidine for opioid-like withdrawal symptoms, and loperamide for diarrhea. Three to five days after Week 12 discontinuation of medication, the research nurse will call participant to check on emergent adverse symptoms

A caution that is included in the informed consent stating that in a situation when analgesia may be required in a patient who has received full blocking doses of XR-NTX, consideration should be given to regional analgesia, conscious sedation with a benzodiazepine, use of non-opioid analgesics, or general anesthesia. If opioid analgesia is required, the amount of opioid needed may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged. In this case, a rapidly acting opioid analgesic that minimizes the duration of respiratory depression is preferred. XR-NTX can also diminish the benefit from opioid-containing cough, cold, and antidiarrheal preparations, which is listed as a warning in the informed consent. These warning are standard when treating patients with XR-NTX.

Side effects of XR-NTX that led to more discontinuation of treatment compared to placebo include the following: pain, tenderness, induration or pruritus at the site of the injection (3%), nausea (2%), headache (1%), and suicide-related events (0.3%). Other known non-serious side effects that differ from placebo include nausea (29% vs 11%), vomiting (12% vs 6%), diarrhea (13% vs 10%), abdominal pain (11% vs 8%), injection site reactions (65% vs 50%), arthralgia/arthritis (9% vs 5%), muscle cramps (5% vs 1%), rash (6% vs 4%), headache (21% vs

18%) dizziness (13% vs 4%), somnolence/sedation (5% vs 1%), and appetite decrease (11% vs 3%). XR-NTX has the capacity to cause hepatocellular injury when given in excessive doses (the margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be five-fold. XR-NTX does not appear to be a hepatoxin at the recommended doses used in this study.

SL-BUP is contraindicated in patients who have had prior hypersensitivity to any formulation of buprenorphine. Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol). Buprenorphine, particularly when taken by the IV route, in combination with benzodiazepines or other CNS depressants (including alcohol), has been associated with significant respiratory depression and death. Many, but not all post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines involved misuse by self-injection. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other CNS depressant drugs. For these reasons, participants are not allowed to take concomitant benzodiazepines or CNS depressant drugs (i.e., neuroleptics or sedating anticonvulsants) during the study. In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary. Patients should be warned of the potential danger of self-administration of benzodiazepines or other depressants while under treatment with SL-BUP. SL-BUP should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression). Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. For this reason, patients with severe liver disease or liver failure are excluded, and liver enzymes are measured at baseline and endpoint. SL-BUP may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during treatment induction and dose adjustment. Patients should be cautioned about driving or operating hazardous machinery until they are reasonably certain that buprenorphine therapy does not adversely affect his or her ability to engage in such activities. SL-BUP is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when SL-BUP sublingual tablet is given concurrently with agents that affect CYP3A4 activity. The concomitant use of SL-BUP sublingual tablet with CYP3A4 inhibitors (e.g., azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors) should be monitored and may require dose-reduction of one or both agents.

Adverse events most commonly observed during clinical trials and post-marketing experience for SL-BUP compared to placebo are headache (29% vs 22%), nausea (14% vs 11%), vomiting, hyperhidrosis, constipation (8% vs 3%), signs and symptoms of withdrawal (18% vs 37%, i.e.,

greater in placebo group), insomnia (21% vs 16%), and pain (18% vs 19%). The dose used in this study is lower and may yield fewer side effects.

Although the virtual reality exposure may evoke physiologic reactivity (increased heart rate and skin conductance; alcohol craving), it is not at the level of overt PTSD symptom provocation. The psychophysiological studies* are well tolerated. This protocol has been utilized in previously published studies in both active service member and veteran populations. The virtual reality environments have been reported by military personnel, past and present, as capable of evoking trauma-related memories and physiological responses but not to be re-traumatizing.

*Psychophysiologic assessments are optional so as to not be a barrier to enrollment or randomization.

2.3.2 POTENTIAL BENEFITS

Extended-release naltrexone is FDA approved for the treatment of alcohol dependence, as well as for the prevention of relapse to opioid dependence, following opioid detoxification. Thus, naltrexone may directly benefit the participants in this study and help them to reduce or stop the use of alcohol. As described in a report of outcomes from the Vivitrol's Cost and Treatment Outcomes Registry, XR-NTX has been used effectively and safely.[17]

As described in the section above, SL-BUP has antidepressant effects and may help attenuate the symptoms of PTSD.

When added to XR-NTX, SL-BUP may further potentiate the anti-craving effects and reduce alcohol use and this combination may reduce symptoms of PTSD. Reducing alcohol use may also be a factor in reduction of PTSD symptoms and conversely, reduced PTSD symptoms may lower the participants' tendency to self-medicate with alcohol.

Another benefit of the study is that knowledge to be gained can help guide treatment for patients with comorbid AUD and PTSD in the future.

3 OBJECTIVES AND SPECIFIC AIMS

The objective of this study is to evaluate the efficacy and physiological effects of sublingual buprenorphine (SL-BUP; Subutex) combined with extended-release injectable naltrexone (XR-NTX; Vivitrol) in the treatment of comorbid AUD and PTSD.

Aim 1: To evaluate the efficacy of SL-BUP + XR-NTX in the treatment of comorbid moderate-to-severe AUD and PTSD based on a response in both AUD and PTSD outcomes.

Aim 2a: Examine the baseline association between fear extinction and PTSD symptom severity in participants with comorbid AUD and PTSD.

Aim 2b: Examine the baseline association between Psychophysiological Reactivity to a Trauma-Relevant Stimuli and PTSD symptom severity.

Aim 2c: Examine the baseline association between Psychophysiological Reactivity to Alcohol-Cues Stimuli and measures of alcohol craving.

Aim 3: Examine the association of baseline fear extinction*, stress reactivity*, and treatment outcomes.

Aim 4: Examine whether the degree of change from baseline to 2-week psychophysiological measures are associated with AUD and PTSD outcomes at Week 8. An early indication of signal detection can be used in the future to enhance precision medicine treatment decisions.

*Psychophysiologic assessments are optional so as to not be a barrier to enrollment or randomization.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This randomized, double-mask, placebo-controlled, multi-site study evaluates the efficacy of SL-BUP combined with XR-NTX in the treatment of comorbid AUD and PTSD. In addition to the primary clinical outcomes for AUD and PTSD, pre- and post-treatment psychophysiological correlates of fear and alcohol craving include 1) measures of the extinction of fear-potentiated startle and 2) measures of psychophysiological reactivity to trauma stimuli and alcohol cues.

Recruitment is based on convenience sampling of treatment-seeking veterans, nonveterans, and active duty service members. Upon contact with a potential participant, the study team member describes the study and reviews initial eligibility criteria (prescreening under an approved HIPAA waiver). Persons meeting initial criteria are given a consent form to read and discuss with research team members, family and/or providers. Persons who provide written informed consent are scheduled for an initial screening and baseline visit.

Following screening and baseline visits, eligible patients are randomization to receive one of two treatments in a double-mask fashion for 12 weeks.

- **Treatment A (SL-BUP 2mg and XR-NTX 380mg) or**
- **Treatment B (SL-PLC and XR-PLC)**.

The treatment allocation ratio for the treatment vs. placebo (PLC) regimens is **1:1** and is stratified by site, presence of concomitant antidepressants, and gender using a random permuted block scheme with variable block size.

The optional psychophysiological studies are conducted at baseline (2-day testing), Week 2 (1-day testing), and Week 8 (2-day testing). The participants are assessed for outcomes on Weeks 1, 2, 4, 6, 8, 10, and 12. Primary and secondary efficacy endpoints are at Week 8. At Week 8, participants remain on the assigned drug or placebo for an additional 4 weeks to allow for a 12-week endpoint. Study medication is discontinued at Week 12 and participants return at Week 14 for evaluation of withdrawal side effects.

All Adverse Events occurring during the clinical trial are collected at each visit, documented, and reported by the PI according to the specific procedures detailed in Section 8.

4.2 ENDPOINTS

4.2.1 PRIMARY ENDPOINT

Primary Hypothesis: Compared to the PLC group, a proportionally higher number of participants will respond to treatment with SL-BUP + XR-NTX, as defined as decrease ≥ 8 points on the Clinician Administered PTSD Scale for DSM-5 (CAPS-5) **and** reduction ≥1-shift in World Health Organization (WHO) risk levels of alcohol use disorder, as assessed on the Timeline Follow-Back (TLFB)[18] from baseline to Week 8. **The primary efficacy endpoint** is a reduction of both AUD and PTSD symptoms, such that lowering both will be coded success and any other outcome will be failure. All group comparisons will be made.

As a complement to the primary hypothesis, we will also examine each of the components individually. Compared to PLC group, SL-BUP + XR-NTX will significantly reduce PTSD symptoms, as measured by the change in CAPS-5 over an 8-week treatment period. Compared to PLC group, SL-BUP + XR-NTX will be more effective in decreasing heavy alcohol use at 8 weeks. This outcome is the percent of heavy drinking days (defined as *>4 standard drinks/sessions for men and >3 standard drinks/sessions for women)* as assessed by the TLFB.

4.2.2 SECONDARY ENDPOINTS

Secondary outcomes examined both between group and over time include:

- Examine association between baseline psychophysiological measures, severity of PTSD and AUD, and treatment outcomes.
- Examine whether SL-BUP + XR-NTX improves psychophysiology measures at Week 8.
- Examine whether the degree of change from baseline to 2-week psychophysiological measures* are associated with AUD and PTSD outcomes at Week 8.

*Psychophysiologic assessments are optional so as to not be a barrier to enrollment or randomization.

Aim 2a Hypotheses: PTSD symptom severity in participants with comorbid AUD and PTSD will be positively associated with an elevated level of fear (“fear load”) during the acquisition and extinction of fear. Participants with comorbid AUD and PTSD will show increased spontaneous recovery of fear as compared to archival data from research participants with no diagnosis of AUD and PTSD.

Aim 2b Hypotheses: Given recently published evidence showing individuals with PTSD characterized by severe, repeated trauma display a hyper-reactive, elevated physiological responses,[19,20] we hypothesize greater PTSD symptoms will be associated with a hyper-reactive stress reactivity, evidenced by an increased skin conductance and trauma-potentiated startle difference scores (max response– baseline).

Aim 2c Hypothesis: Greater AUD craving will be associated with hyper-reactive stress

reactivity, evidenced by increased skin conductance and trauma-potentiated startle difference scores (max response– baseline).

Aim 3 Hypotheses: Compared to PLC group, 2mg SL-BUP + XR-NTX will reduce psychophysiological responses at 8 weeks in patients with comorbid AUD and PTSD. Deficits in fear extinction at pre-treatment baseline will be associated with poorer treatment outcome. Increased physiological responding during trauma-relevant and alcohol cue stimulus at baseline will be associated with poorer treatment outcomes.

Aim 4 Hypotheses: Change from baseline to Week 2 in the psychophysiological reactivity* to trauma-related stimuli will predict the AUD and PTSD outcomes.

4.2.3 EXPLORATORY ENDPOINTS

Exploratory Endpoints: Examine all AUD and PTSD outcomes over time between the SL-BUP + XR-NTX and PLC groups at Week 12. As suggested by the Government Steering Committee, some AUD and PTSD measures were added to the study to harmonize with the Simpson-Saxon study. Changes in these exploratory outcome measures from baseline to Week 8 will be compared against the SL-BUP+XR-NTX and PLC groups.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

To be enrolled in this study, participants *must meet* the following criteria.

1. Male or female, 18 to 70 years of age, capable of reading and understanding English, and able to provide written informed consent (i.e., no surrogate).
2. Current moderate to severe AUD as determined by MINI International Neuropsychiatric Interview for DSM-5 (MINI-5).
3. At least two recent episodes of heavy drinking (>5 standard drinks/sessions for men and >4 standard drinks/sessions for women) over the past 30 days, and heavy drinking pattern defined as 14 drinks per week for women and 21 drinks per week for men for at least 2 of a 4-week interval within the 90 days prior to baseline (i.e., at least Moderate Risk level on WHO category).
4. PTSD diagnosis defined by MINI-5 at screening.
5. Clinician Administered PTSD Scale for DSM-5 (CAPS-5) total score ≥26 **for the past week** at baseline.
6. Females of child-bearing potential must be using medically acceptable birth control (e.g., oral, implantable, injectable, or transdermal contraceptives; intrauterine device; double-barrier method) AND not be pregnant OR have plans for pregnancy or breastfeeding during the study.
7. Must have a CIWA-Ar score of ≤ 8 prior to randomization.
8. Willing and able to refrain from medications thought to influence alcohol consumption (other formulations of naltrexone, disulfiram, acamprosate, topiramate, ondansatron, and baclofen).

9. Willing and able to refrain from psychotropic medications listed in the prohibited medication list (7.5) that includes opioids, stimulants, Alzheimer's medications, most antipsychotics, benzodiazepines/other sedatives and most mood stabilizers.

Notes:

- Participants may continue stable dose of antidepressants, prazosin, and non-benzodiazepine hypnotics and non-benzodiazepine anxiolytics to treat PTSD or insomnia.
- Stable dose is defined as taken for ≥2 months prior to randomization and current dose has been stable for ≥3 weeks prior to randomization and held constant during 12 weeks of study medication.)

5.2 PARTICIPANT EXCLUSION CRITERIA

To be enrolled in this study, participants ***must not meet*** the following criteria.

1. Current diagnosis of DSM-5 bipolar I, schizophrenia, schizoaffective, and/or major depressive disorder with psychotic features (defined by MINI-5 at screening).
2. Increased risk of suicide that necessitates inpatient treatment or warrants therapy excluded by the protocol, and/or current suicidal plan, per investigator clinical judgement, based on interview and defined on the Columbia Suicidality Severity Rating Scale (C-SSRS).
3. Treatment with trauma-focused therapy for PTSD (e.g., Cognitive Processing Therapy, Prolonged Exposure, or EMDR) within two weeks of baseline study visit. Note: Supportive psychotherapy in process for PTSD at time of Screening may be continued.
4. Current diagnosis of severe non-alcohol substance use disorder (except for caffeine and nicotine) during the preceding 1 month, based on participant screening interview.
5. Use of opioids within 2 weeks of baseline or opioid use disorder in the previous 90 days.
6. History of severe traumatic brain injury (TBI) per Ohio State University TBI Identification Method. Note: history of mild or moderate TBI is allowed.
7. Any clinically significant, uncontrolled, or medical/surgical condition that would contraindicate use of SL-BUP + XR-NTX, or limit ability to complete study assessments, including seizure disorders (other than childhood febrile seizures), severe renal insufficiency, significant arrhythmia or heart block, heart failure, or myocardial infarction within the past 2 years, severe thrombocytopenia or hemophilia, severe hepatic failure, complete hearing loss, and/or need for surgery that might interfere with ability to participate.
8. Clinically significant laboratory abnormalities, including a thyroid stimulating hormone (TSH) >1.5 times upper limit of normal, hyperthyroidism, cardiovascular findings QTcF ≥500 msec on electrocardiogram (ECG) or blood pressure >190/110, and aspartate aminotransferase and/or alanine aminotransferase > 5 times upper limit of normal.
9. History of allergic reaction, bronchospasm or hypersensitivity to a naltrexone or buprenorphine.

10. Unable or unwilling to refrain from medications thought to influence alcohol consumption (see inclusion criteria above.)
11. Unable or unwilling to refrain from psychotropic medications on the prohibited medication list; with the exception of stable doses of psychotropics listed on the allowed psychotropic medications list.
12. Persons who are imprisoned, of minor age, diagnosed with dementia, diagnosed with a terminal illness, or otherwise require a surrogate to provide informed consent.

Note: Allowance for elevated liver function enzymes, with close medical monitoring, upon enrollment into this study protocol due to the expected impact of heavy drinking in this study population causing transiently high liver function enzymes.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Multipronged Recruitment Strategy: The recruitment strategies include direct recruitment from the investigator's clinics, social media and news advertisement, self-referral through word-of-mouth interactions with others, and integrated outreach to mental health and primary care outpatient clinics, substance rehabilitation programs, community, and inpatient units. The investigators may use social media, advertisements, and commercial services to advertise the study and outreach to potential participants. Under a HIPAA waiver, IRB-approved letters of invitation can be mailed to prospective participants with a past diagnosis of AUD or PTSD who otherwise might meet eligibility criteria. Rate of enrollment at each site is monitored monthly to make sure sites remain on track, and if enrollment is less than 80% of target, for two or more consecutive months, an action plan is developed and implemented. Sites provide cumulative de-identified pre-screening data to the DCC on a monthly basis. This data will allow for the DCC/PASA Consortium to check both site performance metrics as well as help identify any trends in eligibility criteria that could be causing difficulties in enrolling participants into the study.

Retention Strategies: Adherence and attendance is vital to the success of both treatment and the study. Patient education on study procedures and treatment approaches in the study is the cornerstone. As a primary way to minimize drop-out from the study, the investigators and/or Clinical Research Coordinators (CRC) provide thorough pre-enrollment education for all prospective participants during the informed consent process and confirm the participant's commitment to and feasibility for follow-up. Screening and baseline visits are separate from day of randomization so that any ambivalence can manifest, and participants can back-out prior to randomization. The investigators and CRCs also provide ongoing support and education during the study to reinforce the participants' commitment and resolve logistical barriers to keeping the appointments. Participant burden is kept to a minimum (i.e., small number of assessments and low frequency).

To maximize participant retention, CRCs are trained to have a substantial focus, especially in the first several meetings with participants, on developing a strong alliance, educating them about the study, understanding the importance of adhering to treatment, what is expected of

them as a study participant, and eliciting commitment. The investigators also provide ongoing reinforcement of the patients' commitment to long-term follow-up and medication adherence. The study medication and visits are provided at no cost. The study medication providers emphasize the need to properly adhere to prescribed treatments or to call to revise the treatments if side effects occur or therapeutic effects are lost.

The participant receives a modest payment for each attended visit to offset the inconvenience of the follow-up appointments and transportation costs. The site IRBs have approved similar payments in the past and have not viewed the amount as coercive. Service members cannot be paid while on active duty but may be reimbursed for travel costs. Participants are paid more on the days of the psychophysiological testing since these visits require more time. Participants exiting early are encouraged to undergo Week 12 assessments and are paid Week 12 amount.

After consenting to participate, a urine drug screen and breathalyzer will be conducted at each visit. If the drug screen is positive for opiates at screening or baseline visit and/or if the participant has a breathalyzer level > 0.02 at any visit, the appointment will be canceled and rescheduled, and the participant will not be paid for the canceled appointment. The CRC may reschedule the appointment for a later date. If the urine drug screen is positive for opiates at follow-up visits, the investigator must assess the safety of continuing the participant on study medication, but the visit does not need to be canceled.

Schedule of Participation Payments																
	Screening, Baseline, Week (#) or Telephone (T) Visit															
	Screen	Base-line	1	2	T	4	T	6	T	8	T	10	T	12	T	14
Outcome Visits	**25**	**75**	**25**	**25**		**75**		**25**		**75**		**25**		**50**		**25**
Psychophysiology testing		**50** 2d								**50** 2d						

The above payment schedule offers maximum for study participation of $425 for medication outcomes without psychophysiologic assessments and $525 with psychophysiologic assessments. (Note: There is flexibility for sites to adjust their participation payment amounts, for instance West Haven has a minimum payment amount of $25)

Also, sites can pay for transportation or provide a $25 gas/gift card to offset transportation costs if needed, at the discretion of investigator and TREAC Executive Director.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants may discontinue study treatment or withdraw from participation in the study at any time without cause or reason. Participants may stop study medication but are encouraged to

remain in the study for follow-up assessments. The investigator may discontinue study treatment for a participant or withdraw a participant from the study for one or more of the following reasons:

- The participant's expressed desire to end his/her participation in the study.
    - Note: The participant may choose to stop the study drug but continue in the study for data collection and is thus not withdrawn from the study.
- A clinically significant adverse event (AE), laboratory abnormality, or other medical condition or situation that makes continued participation in the study to be not in the best interest of the participant
- The participant demonstrates an inability to comply with the verbal and written study instructions and/or procedures, (i.e., loses the capacity to provide informed consent)
- The participant exhibits unsafe behaviors (e.g., abusive, aggressive) or becomes suicidal, homicidal, or psychotic, (i.e., at significant risk of harming self or others).
- The participant has an intolerable adverse reaction to a study medication.
- The participant's underlying condition is worsening and needs alternative treatment(s)
- The study is canceled by the PASA Consortium, DoD, or investigators.
- The study is closed by the Data Safety and Monitoring Board (DSMB), Institutional Review Board (IRB), or other oversight committee.
- New information regarding the safety of a study medication emerges that changes the risk benefit profile for a sub-group of participants

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

If an early exit occurs, the reason(s) for early termination is documented and all Week 12 procedures are conducted. A post-study phone call or visit is scheduled with the research team to ensure that the participant has made or scheduled the appropriate follow-up appointments and to address any clinical problems or AEs that may have occurred.

Participants may stop study medication but are encouraged to remain in the study for follow-up assessments. In this case, the participant may attend assessments for data collection or consent to allow for continued follow-up through chart review. If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, then the investigators will not access the participant's medical record or make future contact with the participant. If a study participant withdraws consent for study participation, then the participant is excluded from all future study procedures and treatments. No additional study data is collected from the participant after consent has been withdrawn.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be suspended or prematurely terminated if there is reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, DoD Grants Officer Representative (GOR) for further distribution to the Government Steering Committee (GSC), PASA

Consortium PI (or designee), DSMB, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- A pattern of AEs indicating that the selected dose of SL-BUP + XR-NTX is inappropriate or unsafe
- Determination of unexpected, significant, or unacceptable risk to participants
- New information emerges that suggests the risks are increased beyond an acceptable limit and outweigh benefits
- Significant and recurring protocol violations that threaten the integrity of the study data
- Data that are not sufficiently complete and/or evaluable
- Continuing and ongoing serious noncompliance with human research protections and regulations that warrants study closure
- Determination of futility. While there are no formal assessments of futility for efficacy, the study may be terminated if operationally futile, (e.g., there is an inability to enroll or retain study participants). The study may resume once concerns about safety, protocol compliance, data quality is addressed and satisfy the PASA Consortium, IRB and/or other regulatory agencies.
- Generally, any study suspension that could occur will be based upon review of the study and recommendations made by the DSMB. Details of safety oversight and associated study halting rules are provided in Sections 8.6 and 8.5, respectively.
- A local site that is not performing for one of the reasons above, may be selectively terminated and replaced with a new site.

6 STUDY AGENTS

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

XR-NTX and XR-PLC are donated by Alkermes, Inc; and will be sent by Alkermes to the local site pharmacies.

SL-BUP is purchased by each local site's pharmacy from a manufacturer of generic formulation.

SL-PLC is donated to the study by TONIX Pharmaceuticals; and will be distributed through Tuscaloosa VA pharmacy to the West Haven VA.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

XR-NTX (naltrexone for extended-release injectable suspension, VIVITROL) is supplied as a single use kit containing one 380 mg vial of VIVITROL microspheres, one vial of diluent, one 5-mL syringe, one ½-inch 20-gauge preparation needle, and two 1½-inch 20-gauge administration needles with safety device. VIVITROL microspheres consist of a sterile, off-white to light-tan

powder that is available in a dosage strength of 380-mg naltrexone per vial. Naltrexone is incorporated in 75:25 polylactide-co-glycolide (PLG) at a concentration of 337 mg of naltrexone per gram of microspheres. The diluent is a clear, colorless solution. The composition of the diluent includes carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection.

SL-BUP (sublingual buprenorphine tablet; SUBUTEX) is supplied as an uncoated oval white tablet in counts of 30 tablets per bottle in 2mg/sublingual tablet dosage. SL-BUP contains no naloxone.

SL-PLC is supplied in 40 tablets per bottle that contains 1-gram Sorb-it canister desiccant and polyester coil. The pill is yellow, T debossed on one side, plain on the other side, 4mm diameter x 2.5mm thick.

6.1.3 PRODUCT STORAGE AND STABILITY

Investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under conditions specified on the label until dispensed for participant use or destroyed per instructions from PASA Consortium Leadership and according to local regulations. Product is stored in a limited-access location in the local site VA pharmacies.

The entire dose pack of XR-NTX should be stored in the refrigerator (2 - 8°C, 36 - 46°F). Unrefrigerated, XR-NTX can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration. Do not expose the product to temperatures above 25°C (77°F). XR-NTX should not be frozen.

The SL-BUP and SL-PLC should be stored at 25°C (77°F) and excursions are permitted to 15°-30°C (59°-86°F).

6.1.4 PREPARATION

The XR-NTX microspheres must be suspended in the diluent prior to injection. Parenteral products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. A properly mixed suspension is milky white, does not contain clumps, and moves freely down the wall of the vial.

SL-BUP has no preparation requirements.

6.1.5 DOSING AND ADMINISTRATION

The dose of XR-NTX is 380 mg delivered intramuscularly [gluteal; alternating buttocks for each subsequent injection and documentation of injection site and date in the Computerized Patient Record System (CPRS) source notes] every 4 weeks or once a month by research MD, APN or RN. XR-NTX and XR-PLC must be suspended **only** in the diluent supplied in the dose kit and must be administered with the needle supplied in the dose kit. All components (i.e., the microspheres, diluent, preparation needle, and an administration needle with safety device) are required for administration. A spare administration needle is provided in case of clogging. Do not substitute any other components for the components of the dose kit.

SL-BUP or SL-PLC will be ordered by an investigator/co-investigator with prescribing privileges in the quantity of pills (one per day) needed for the exact number of days until the next scheduled visit (may vary according to patient needs and location, (i.e., can dispense a four-week supply with number of tablets needed until next scheduled visit for the injection). The local pharmacy or research pharmacist dispenses the medication. The medication management provider and/or the research coordinator reviews the medication instructions with the participant. The participant is informed that he/she must bring any unused portion of the study medication to subsequent visits so that the prescriber can issue the correct number of pills to allow for enough supply to last until the next scheduled visit. Also, the participant is informed that if she/he misses a dose, she/he should take the next dose as soon as possible.

If for any reason there is SL-BUP or SL-PLC study medication that will go unused, the participant will place the unused medication in a Take-Away Medication Recovery System tamper-resistant envelope and place in a US postal service mailbox to be sent to a pharmacy destruction service. This can vary by site and may be done at each visit and/or at the end of the study.

6.1.6 ROUTE OF ADMINISTRATION

XR-NTX or XR-PLC should be administered by a health care professional as an intramuscular (IM) gluteal injection, alternating buttocks, using the manufacturer's kits provided.

SL-BUP or SL-PLC is taken sublingually by the participant, (i.e., placed and held under the tongue until it is dissolved); swallowing the tablet reduces the bioavailability of the drug.

6.1.7 DOSE

Pretreatment with oral naltrexone is not required before using XR-NTX. XR-NTX starting dose is 380mg IM every four weeks. The dose is held constant for the duration of the study treatment period.

SL-BUP is started at 2mg daily and the dose is held constant for the duration of the study treatment period.

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

If a participant misses a dose, he/she should be instructed to receive the next dose ASAP.

6.1.9 DURATION OF THERAPY

The duration of therapy is 12 weeks.

6.1.10 TRACKING OF DOSE

XR-NTX or XR-PLC is dispensed by the local site pharmacy and administered by a health care professional in the research clinic. The local site pharmacy keeps record of the electronic order for dispensing the medication and the research clinic provider tracks the administration at time of injection in a research note.

SL-BUP or SL-PLC is dispensed by the local site pharmacy. The local site pharmacy keeps record of the electronic order for dispensing the medication and the clinical research assistant tracks the pill count at the return visits. The participant is instructed to bring any unused medication back to the research clinic at each visit.

6.1.11 DEVICE SPECIFIC CONSIDERATIONS

Not applicable.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

Each local site Pharmacy is responsible for study medication receipt, storage, dispensing, accounting for inventory, and destruction of unused medication. Each local site Pharmacy has standard operational procedures for the handling of research medications and controlled medications that are required to be adhered to for this study.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

Rater Training and CAPS-5 Fidelity Monitoring: An independent rater at each site performs the Timeline Follow Back (TLFB), Clinician Administered PTSD Scale for DSM-5 (CAPS-5), and Columbia Suicide Severity Rating (C-SSR) assessments. The independent rater is kept masked to the treatment assignment and does not assess adverse events (to avoid accidental un-masking) and remains therapeutically neutral (to avoid an inflated placebo response). In consultation with Frank Weathers, Ph.D., all independent raters undergo training and certification by Dr. Davis and Dr. Petrakis prior to assessing study participants. CAPS-5 inter-rater reliability coefficients in the range of 0.90 to 0.95 will be established and repeated annually. The audio-recordings of TLFB and CAPS-5 assessments are sent to the Tuscaloosa research team via a secure data transmission method (shared VA server access) and Tuscaloosa research team sends the recordings on an encrypted disc to Dr. Weathers via chain of custody mail. Dr. Weathers or a trained designee listens to at least 25% of the recordings for consensus scoring and give personalized written feedback to the independent raters. If there is rater-drift, the rater receives additional training from Dr. Davis, Dr. Weathers, and/or Dr. Petrakis. To the extent possible, participants are evaluated by the same independent rater throughout their duration in the study. Back-up raters are trained and certified.

Table below provides a brief description of the study instruments that will be utilized during the course of this study.

Description of Study Instruments
SCREENING or BASELINE (Administered by trained investigator or CRC)
MINI International Neuropsychiatric Interview for DSM-5 (MINI-5)[21] is an updated semi-structured clinician-administered interview for DSM-5 diagnoses. To reduce participant burden, modules B (Suicidality), L (anorexia nervosa), M (bulimia), N (generalized anxiety), P (antisocial) and optional assessment measures will not be collected. **Purpose:** To document current and past psychiatric diagnoses and confirm eligibility criteria for AUD, PTSD and excluded diagnoses; administered by trained local site investigator (LSI), assessor, or CRC.
Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)[22] is an interviewer-driven measure of alcohol withdrawal used to identify withdrawal symptoms requiring medical treatment.
Alcohol Dependence Scale (ADS)[23] is a self-report measure of alcohol dependence that is used as a measure for group differences in severity of alcohol dependence at baseline.
Clinical Opiate Withdrawal Scale (COWS)[24] is an 11-item clinician-administered scale used to rate common signs and symptoms of opiate withdrawal, to make sure participants meet baseline eligibility.
Ohio State University Traumatic Brain Injury Identification Method – Short Form (OSU-TBI)[25,26] is an interviewer-administered questionnaire of history and severity of TBI to characterize sample and determine eligibility.
Barratt Impulsivity Scale (BIS)[27] is a 30-item self-report instrument that uses a 4-point scale for declarative "I" statements meant to be answered quickly that is used to assess the behavioral construct of impulsiveness.
Life Events Checklist for DSM-5 (LEC-5)[28,29] is a self-report that assesses exposure to 16 traumatic events, as a preface to the CAPS-5, to provide an anchor of the index trauma and document category of trauma.
SCREENING, BASELINE, AND FOLLOW-UP (Administered by certified independent assessor)
Timeline Follow Back (TLFB)[30] is a calendar-based method of assessing drinking patterns used to document the frequency and amount of daily alcohol consumption and to categorize the **World Health Organization Risk Levels of Alcohol Use.**
Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[31] is a 30-item structured interview to assess PTSD severity for baseline eligibility (total score ≤26[32]) and outcome of treatment.
Columbia-Suicide Severity Rating Scale (C-SSRS)[33] is clinician-administered interview to measure suicidality and document suicidal behavior used to evaluate recent suicidality, ideation, and suicidal behavior for eligibility at baseline (past two months) and to track emergent suicidality at Week 8.
BASELINE AND FOLLOW-UP INSTRUMENTS
PTSD Checklist for DSM-5 (PCL-5)[34,35] is a 20-item self-report measure that assesses the DSM-5 symptoms of PTSD and is used in confirmatory analysis of change in PTSD symptoms.
Short Inventory of Problems (SIP)[36] measures adverse consequences of alcohol abuse in five areas: Interpersonal, Physical, Social, Impulsive, and Intrapersonal total adverse consequences.
Obsessive Compulsive Drinking Scale (OCDS)[37] measures obsessive and compulsive thoughts related to drinking alcohol and is used as a measure craving for alcohol.
Desire of Alcohol Questionnaire (DAQ)[38] is a self-report measure the assesses (a) desires/intentions to drink, (b) negative reinforcement, and (c) positive reinforcement and ability to control drinking. DAQ scores have been found to increase during cue exposure and after alcohol administration in the laboratory and is used to measure desire/intentions, negative and positive reinforcements for alcohol during the stress reactivity paradigm.
Clinical Global Impression-Severity & Clinical Global Impression-Improvement (CGI-S/CGI-I) [39] are two single-item 7-point clinician-rated scales used to measure global change in severity of illness and status of improvement.
Patient Health Questionnaire (PHQ-9)[40] is a validated 9-item self-report measure of depressive symptoms used to measure change in depression and has one item that is used to monitor suicidality (safety measure).
Veterans RAND 12-Item Health Survey (VR-12)[41] is used to assess functioning domains: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, energy/vitality, social functioning, role limitations due to emotional problems, and mental health.
Adverse Events (AE) are assessed by a research team member at each assessment using Food and Drug Administration (FDA) standards for AE reporting. AEs, SAE are reported to the DSMB, and local IRB.

Psychophysiological Studies*: Local site research personnel are trained by Dr. Norrholm.

*Psychophysiologic assessments are optional to not be a barrier to enrollment or randomization.

Fear Conditioning and Extinction Paradigm (Assessment Time: Preparation 15 min, Acquisition phase 20 min, and Extinction phase: 20 min.) The participant undergoes the two-day psychophysiological assessments, prior to beginning the study medication.

Fear Acquisition: The following method has been used successfully in Dr. Norrholm's previous studies to generate a robust fear response. The unconditioned stimulus (US) is a 250-millisecond blast of air with an intensity of 140 psi directed to the larynx. The conditioned stimuli (CS's) are different colored shapes presented on a computer monitor in front of the participant. The startle probe is presented after six seconds and is followed by the US 500 milliseconds seconds later. The CS+ is paired with the air blast, while the CS- is not. The acquisition session consists of a habituation phase and a conditioning phase with three blocks of four trials of each type (noise alone, (NA), CS+, CS-) in each block.

Fear-potentiated startle is defined as the increase in the magnitude of the acoustic startle response in the presence of a cue that has been paired with an aversive US. Startle responses to a CS stimulus are compared to startle responses to the noise alone. Fear-potentiated startle is calculated by subtracting the startle magnitude to the noise probe alone (termed noise alone or NA trials) from startle in the presence of the CS stimuli and expressed as a difference score. For this reason, trial types are termed NA, CS+ (paired to airblast US), and CS- (not paired to an airblast US). Successful fear conditioning is observed by an increase in startle to the CS+ (paired with an airblast US) as compared to noise alone and a significant difference to the CS+ as compared to the CS- (this is termed CS discrimination).

Fear Extinction: The following method allows us to assess fear extinction and has been used successfully in our previous studies.[49] The extinction session occurs ten minutes after acquisition. Neither the CS+ nor the CS- are paired with the US. The extinction session consists of six blocks of four trials of each type (NA, CS+ (unreinforced), and CS-) in each block.

Extinction Recall: The test of spontaneous recovery of fear occurs 24 hours after fear conditioning and consists of one block of four trials of each type (NA, CS+ (unreinforced), and CS-). This paradigm has been used successfully in healthy volunteers as well as combat Veterans seeking treatment in the Trauma Recovery Program. After completing this test, three unpaired air blasts are delivered during a subsequent session to measure reinstatement effects.

Psychophysiological Reactivity to Trauma-Evoking and Alcohol-Related Stimuli using Virtual Reality (VR) Exposure: (Assessment time: Trauma related reactivity: 8 min and Alcohol cues reactivity: 8 min.)

Participants view a computer-generated VR environment that includes combat-related contexts associated with deployment (e.g., Middle Eastern city, combat scenes, barracks, military vehicles). A second paradigm using computer-generate VR environment for alcohol-related stimuli is subsequently conducted. If the participant is a someone who experienced sexual trauma as the cause of his/her PTSD, he/she will view a high definition video that contains

images or sounds associated with assault in locations such as barracks, latrines, rear seat of a vehicle instead of combat scenes. These contexts do not recreate the assault. A third paradigm for non-combat, non-sexual trauma will be used for civilian participants with non-sexual trauma.

Acoustic Startle Assessment: As described in our prior work, the eye-blink component of the acoustic startle response is measured by electromyography (EMG) recordings of the right orbicularis oculi muscle with two 5-mm Ag/AgCl electrodes filled with electrolyte gel. This is done by scrubbing on the cheek below the eye with a special cleanser and attaching two electrodes to the skin just below the eye. The startle probe is a 108-dB (A) SPL, 40 ms burst of broadband noise with near instantaneous rise time, delivered binaurally through headphones (Model TDH 39, Maico, Inc.). The startle response data is acquired using Biopac MP150 for Windows (Biopac Systems, Inc.). All data are sampled at 1000 Hz and amplified with a gain of 5000 using the EMG module of the Biopac system. The acquired data are filtered, rectified, and smoothed using MindWare software (MindWare Technologies, Ltd.) and exported for statistical analyses. The maximum amplitude of muscle contraction 20–200 ms after the startle probe is used as a measure of the startle response.

Galvanic Skin Response (GSR, Skin Conductance Level): We measure skin conductance reactivity based upon the amount of perspiration on the skin. Two 5-mm Ag/AgCl disposable electrodes filled with isotonic paste are attached to middle phalanges of the second and fourth finger of the non-dominant hand. We assess tonic skin conductance and skin conductance change from baseline during the above-mentioned psychophysiological tasks. The skin conductance level and skin resistance data are acquired at a sampling rate of 1 kHz using the GSR module of the Biopac system. Additionally, skin conductance level (SCL) and skin conductance response (SCR) data are acquired at a sampling rate of 10 Hz using the eSense system connected to a secure, study designated iPad. Two 5 mm Ag/AgCl electrodes filled with isotonic paste are attached to middle phalanges of the second and fourth finger of the non-dominant hand during the Stress Reactivity to Trauma Evoking Stimuli portion of the study. The acquired data are exported for further analyses.

Heart Rate (HR) and Respiration: Heart rate is measured throughout the psychophysiological assessment by attaching two Ag/AgCl electrodes, one below the right clavicle and the other on the left forearm. High frequency heart-rate variability is quantified from spectral analysis of HR in the 0.12 to 0.40 Hz frequency band. Heart rate is recorded at a sampling rate of 1 kHz using the ECG module of the Biopac system. The dependent variables are HR, respiratory sinus arrhythmia (RSA), and HR reactivity as previously performed by members of our research group. Respiration (breathing rate) is measured throughout the psychophysiological assessment by attaching an elastic band around the participant's chest.

7.1.2 STANDARD OF CARE STUDY PROCEDURES

No procedures or assessments for this study are considered standard of care.

7.1.3 MEDICAL MANAGEMENT

At each visit, the participant meets with the medication provider (MD, PharmD, RN, or APN)

who is qualified to provide Medical Management[42] (MM). MM includes instructions on the study medication, adjust the dosing, and evaluate side effects. The initial visit focuses on educating the patient on medication regiment and adherence, negative consequences of drinking, and other health issues. Follow-up visits focus on medication adherence, evaluating and managing side effects, and psychoeducation. The MM provider remains masked to the treatment assignment and is not involved in the outcome assessments. The CRC is responsible for the pill count and gives the pill count information to the MM provider for use in counseling the participant on the importance of adherence to the treatment and dosing. Adverse events might be identified during MM and subsequently documented and reported according to instructions in Section 8.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Laboratory studies (complete blood count, comprehensive chemistry which includes liver and kidney function tests) are performed at screening and end of treatment (Week 12) or early termination visit. *Additional labs may need to be drawn at Week 4 and Week 8 depending on ALT and AST values at screening and study enrollment.

- Laboratory tests (except for pregnancy tests and urine drug screens) performed within 90 days of screening are acceptable for study screening purposes.
- All laboratory test results are reviewed by the investigator or qualified designee and acknowledged.
- Any value outside of the normal range is flagged and the investigator determines whether it is clinically significant.
- If a test is questionable, the test(s) may be repeated, or additional testing done to provide clarification.
- Unscheduled laboratory testing may be done at the discretion of the investigator for appropriate medical care.

- **Hematology** – White blood cell count (WBC), Red blood cell count (RBC), hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), platelet count (PLT)
- **Thyroid Function –** Thyroid Stimulating Hormone (TSH) *at screening only to confirm participant eligibility.*
- **Serum Chemistry –** basic metabolic panel (BMP); must include liver (ALT, AST, GGT) and kidney function labs (BUN and Creatinine). However, GGT is collected at baseline, Week 8 and Week 12.

Added procedures with v7:

- If baseline ALT or AST is between 3x to 5x ULN
  - Recheck ALT and AST at Week 4 visit:
    - If ALT or AST >4x ULN, PI may consider discontinuing the study medication if clinically indicated.
  - Recheck ALT and AST at Week 8 visit:

    - If ALT or AST >3x ULN , PI may consider discontinuing the study medication if clinically indicated.
- The PI may consult with the medical monitor as needed.

A history and physical (H&P) and ECG within the prior 90-days is acceptable for the study screening purposes; otherwise, it should be repeated.

Pregnancy Testing: Urine pregnancy dip tests for women of childbearing potential are processed in the research clinic by a member of the study team at screening, Week 4, Week 8, and Week 12 (or end of study/early study termination), as well as any time that pregnancy is suspected.

Urine Drug Screening: Urine samples are collected using a CLIA waived 10 panel drug test. Urine drug screens are conducted in the research clinic by a member of the study team at screening, baseline, and each study visit. The results are retained in the participant's research files. Urine drug screen results are not entered into the participant's medical record. Buprenorphine is not included in the urine drug screen to avoid accidental un-masking of the study team members to the treatment arm. Osmolality, temperature, pH, and adulterants will be assessed at collection time to ensure sample validity.

Alcohol Breathalyzer Test: Breathalyzer tests are conducted at each research visit in the research clinic by a trained clinical research coordinator and used to measure participants' breathalyzed alcohol concentration (BrAC). Samples >0.01 g/dl are considered positive. Results are kept in research records and not entered in medical records.

(Note: this test may not be conducted if restricted by local COVID protocols).

7.2.2 OTHER ASSAYS OR PROCEDURES

Not applicable.

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Phosphatidyl ethanol (PEth) Testing by Dried Blood Spot Collection

Phosphatidyl ethanols (PEth) are a series of abnormal phospholipids located in the cell membrane and formed in the presence of ethanol and phospholipase D. PEth serves as a biomarker of alcohol ingestion in the past 2-3 weeks using liquid chromatography tandem mass spectrometric assessment of human blood (whole or dried spots). PEth is not significantly affected by age, gender, or medical disease.

Dried blood spots offer numerous advantages over venipuncture including reduced costs, invasiveness and discomfort. Five dried blood spots are obtained from a finger puncture onto a lab provided collection card. The collection is performed by the participant under the observation of the study team staff. Sample results are available to the study team via the commercial lab's portal using a study specific username/password combination and the unique non-PHI identifier on the blood spot collection card. NOTE: For this study, only the unique study participant number is used to identify the sample. The chain of custody process as

described in the instruction sheet and video (participant signature, picture identification card, participant name, etc.) is not applicable to this protocol.

Serum Buprenorphine

Buprenorphine and its metabolite norbuprenorphine are assayed using liquid chromatography tandem mass spectrometry by a commercial laboratory. Approximately 2.5 to 10 mL of blood will be collected by a trained phlebotomist into a red-top tube. The sample is allowed to clot and then centrifuged to separate the serum from the cells before transferring the serum into a standard transport tube labeled with a unique study participant code. Sample results are available via the commercial laboratory portal using a study specific username/password combination and the unique participant code/requisition number.

7.2.4 SPECIMEN SHIPMENT

The PEth collection card is placed in the box provided and shipped in a standard cardboard (non-plastic) envelope along with the laboratory requisition form to the commercial lab using tracked carrier such as FedEx or UPS. Biohazard shipping labels are not required for this type of specimen. The dried blood specimens are stable, without refrigeration, thus they do not require overnight shipping, ice packs, or dry ice for shipping.

Buprenorphine sample(s) and lab requisition form are transported to the commercial lab using tracked carrier such as FedEx/UPS or by direct pick-up by a commercial lab courier (available at some sites). Samples should be shipped overnight, at ambient temperature (no dry ice required) using IATA guidelines in a UN 3373 Overpack (Biological Substance Category B) envelope.

So that local sites remained masked from serum BUP levels, lab results will be securely provided to the DCC. Samples and subsequent results will be identified only by the unique participant ID and the visit week.

7.3 STUDY SCHEDULE

7.3.1 SCHEDULE OF ASSESSMENTS

Assessments	Schedule of Assessments: Screening, Baseline, Week (#) or Telephone (T) Visit																	
	Screen	Baseline	Baseline (Day 2)	Week 1	Week 2	T	Week 4	T	Week 6	T	Week 8	Week 8 (Day 2)	T	Week 10	T	Week 12	T	Week 14
Assessments to Qualify for Study and Characterize Population																		
Demographics	X																	
Smoking Status*	X										X					X		
MINI-5	X																	
H&P**	X																	
VS, BMI, BrAC	X	X		X[&]	X[&]		X		X[&]		X			X[&]		X		X
Labs/ECG**	X						X**				X**					X		
Pregnancy	X						X				X					X		
CIWA-Ar	X	X														X		X
COWS	X															X		X
ADS	X																	
OSU-TBI	X																	
BIS	X																	
Psychophysiology Study																		
Fear Conditioning		X[+]									X[+]							
Psychophys. Tests			X[+]		X[+]						X[+]	X[+]						
Alcohol Related Outcomes																		
TLFB	X	X		X	X		X		X		X			X		X		
OCDS		X		X	X		X		X		X			X		X		
Peth		X									X					X		
Serum BUP											X					X		
SIP		X									X					X		
DAQ		X			X						X							
Urine Drug Screen	X	X					X				X					X		
PTSD Related Outcomes																		
LEC-5 Checklist	X																	
PCL-5	X	X		X	X		X		X		X			X		X		
CAPS-5****		X					X				X					X		
Psychological Symptoms and Quality of Life																		
C-SSRS*****	X	X									X							
PHQ-9		X					X				X					X		
VR-12		X									X					X		
CGI-S		X					X				X					X		
CGI-I							X				X					X		
Adverse Events and Concomitant Medications																		
Con-Meds	X	X		X	X		X		X		X			X		X		X
Adverse Events				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug***																		
Dispense Drug		X					X				X[$]							
Pill Counts				X	X		X		X		X			X		X		
Study Drug Knowledge																X		

*Smoking: Will include both tobacco and marijuana at baseline, and marijuana only at Weeks 8 and 12. **H&P, laboratory tests, and ECG within previous 90 days is acceptable at screening visit. (At Week 12: The H&P, thyroid test, and ECG do not need to be repeated.) If baseline level was between 3x-5x ULN, ALT and AST needs to be repeated at week 4 and week 8 visit. At Week 8,GGT needs to be repeated. [&]**Vital signs and breathalyzer on** Week **2, 6, 10 may be omitted due to COVID-19 reduction of in-person visits.** [+]Psychophysiologic assessments are optional so as to not be a barrier to enrollment or randomization.***Day of Randomization is on Baseline. The schedule of follow-up visits is anchored to Baseline. ****CAPS-5 and C-SSRS can be administered prior to day of baseline so long as it is within one week of day of randomization and scores are entered as baseline. *****C-SSRS can be done either at screening or baseline visit, as well as Week 8. [$] Baseline and week 8 drug dispensing will occur on day 1 if not participating in psychophysiology testing and on day 2 if participating in testing

7.3.2 SCREENING

During the process of informed consent and screening, the investigators and CRCs provide thorough pre-enrollment education for all prospective participants and confirm the participant's commitment to and feasibility for follow-up. Screening and baseline visits are separate from day of randomization so that any ambivalence can manifest, and participants can back-out prior to randomization.

Screening takes place over 1 to 14 days and includes the study instruments listed in table above and laboratory tests described in section 7.2. A history and physical (H&P) and ECG within the prior 90-days is acceptable for the study screening purposes; otherwise, it should be repeated. Laboratory tests (except for pregnancy tests and urine drug screens) performed within 90 days of screening are acceptable for study screening purposes. All laboratory test results are reviewed by the investigator or qualified designee and acknowledged. Any value outside of the normal range is flagged and the investigator determines whether it is clinically significant. If a test is questionable, the test(s) may be repeated, or additional testing done to provide clarification. Unscheduled laboratory testing may be done at the discretion of the investigator for appropriate medical care.

At any point in the screening process and based on the inclusion and exclusion criteria listed above, the participant may be deemed eligible and proceed to baseline visit or investigator may exclude a participant and refer him/her for appropriate treatment.

Participants **should not** be taken off psychotropic or disallowed medications for purposes of entering the study. However, he/she can work with their provider to discontinue and washout excluded medication(s) that are not clinically indicated or effective and subsequently be referred to the study. A participant who is otherwise meeting eligibility criteria except for taking an excluded medication can undergo a medically supervised discontinuation and 5-day (or longer if indicated) washout of medication(s), if representative of the clinical plan regardless of study participation, (i.e., psychotropic medications are only be discontinued for washout if the consenting participant is not tolerating or not responding to the medication).

At screening and baseline, the investigators will evaluate the participant for signs and symptoms of acute withdrawal from alcohol. In addition to vital signs and participant verbal history, the Clinical Institute Withdrawal Assessment (CIWA-Ar) will be used to facilitate assessment of withdrawal, and decisions regarding appropriateness for study entry and continuation with respect to physical dependence will be made by the investigators based on the judgment of study physicians. We will use a CIWA-Ar score of $\leq$ 8 for an approximate cutoff level for inclusion into the study. A CIWA-Ar score of 10 – 15 indicates a need for medical treatment, which may include chlordiazepoxide (Librium), benzodiazepines, or anticonvulsants (in addition to thiamine and folate). All our study physicians have extensive experience in assessing and triaging patients who may be experiencing alcohol withdrawal. Participants that show signs or symptoms of alcohol withdrawal and who need detoxification will be referred for detoxification at the local outpatient clinic or an inpatient unit (depending on the level of care needed) and

managed according to local VA Center Memorandum or policies for managing alcohol withdrawal.

If it is in the best interest of the patient, the investigators may begin standard treatment for alcohol withdrawal without delay for a referral or outpatient MD or APN in mental health or primary care (i.e., not research activity). After detoxification, the participant may be eligible for the study at a later time under re-consent and re-screening. In addition, at any time during the course of the study, if relapse into heavy drinking has occurred, the investigators may repeat the CIWA-Ar as needed to evaluate need for exit from the study and medical detoxification. The CIWA-Ar is repeated at the conclusion of the 12-week medication treatment period and at the week-14 follow-up visit to confirm that the patient is medically stable and can be referred to usual care treatment without the need for treatment for withdrawal.

7.3.3 BASELINE AND RANDOMIZATION VISITS

The investigators and CRCs provide ongoing support and education during the study to reinforce the participants' commitment and resolve logistical barriers to keeping the appointments. Participant burden is kept to a minimum (i.e., small number of assessments and low frequency). Adherence and attendance are vital to the success of both treatment and the study. Patient education on study procedures and the treatment approach in the study is the cornerstone to promote adherence. To maximize participant retention, study coordinators are trained to have a substantial focus, especially in the first several meetings with participants, on developing a strong alliance, educating them about the study, understanding the importance of adhering to treatment, what is expected of them as a study participant, and eliciting commitment.

At the baseline visit, the research team evaluates the participant per the study instruments listed in the Schedule of Assessments table in 7.3.1. Participants undergoing the optional two-day psychophysiological assessments, as described above, will complete both days of the psychophysiological testing prior to beginning the study medication.

The research medication provider enters the medication orders (one for XR-NTX and one for SL-BUP) and the local site pharmacy dispenses the study medication according to the randomized assignment to one of two treatments:

- **Treatment A (SL-BUP 2mg + XR-NTX 380mg) or**
- **Treatment B (SL-PLC and XR-PLC)**.

SL-BUP is taken daily and XR-NTX is given every 4 weeks. All medications are dispensed by local site pharmacies with clearly labeled instructions.

The participant receives the first dose of XR-NTX injectable in the research clinic and remains in the clinic under the supervision of the research team for approximately 1 hour after the 1st dose is administered.

The medication provider or trained CRC reviews the medication instructions with the participant (how to administer sublingual, keeping up with medication dosing, and need to return any

unused medication to the research medication provider at the next visit). The participant initiates SL-BUP on the following day.

7.3.4 FOLLOW-UP VISITS

Assessments occur at screening, baseline, and post-randomization Weeks 1, 2, 4, 6, 8, 10, and 12. There is a visit window of +/- 7 days for follow-up visits.

The investigators and CRCs provide ongoing reinforcement of the patients' commitment to long-term follow-up. The study medication providers emphasize the need to properly adhere to prescribed treatments or to call to revise the treatments if side effects occur or therapeutic effects are lost.

Adherence to SL-BUP medication is confirmed by pill count. Concomitant medications are updated at each of these visits.

If participants experience side effects that cannot be managed by adjustments in the timing of the medication (i.e., taking at bedtime, etc.), they may have their medication titration either held or the medication dosing may be decreased (i.e., less frequent).

The CRC makes a telephone (t) contact with the participant between face-to-face visits to remind the participant of the next office visit and to check on adherence to the study medication and if there have been any serious adverse events.

*Psychophysiologic assessments are optional to not be a barrier to enrollment or randomization.

The one-day psychophysiological assessment is repeated at Week 2.

The two-day psychophysiological assessment is repeated at Week 8.

At Week 8, the participant remains on the assigned treatment and dose from Week 8 to Week 12.

While every attempt is made to retain the participant in the study on medication for the full 12 weeks, the participant may discontinue medication at any point and remain in the study for assessments through Week 12.

7.3.5 FINAL STUDY VISITS

At Week 12, the study medication is discontinued, and all Week 12 assessments are completed. At Week 12, the participant is referred back to his/her previous or newly assigned long-term PTSD provider for follow-up and continued treatment. At Week 14, the participant is assessed for discontinuation or withdrawal side effects and resolution or emergence of adverse events. The participant's ongoing clinical treatment plan is confirmed.

7.3.6 EARLY TERMINATION VISIT

If a participant exits prior to Week 8, all procedures for Week 8 are completed. If the participant exits after Week 8 but prior to Week 12, all Week-12 procedures are completed.

7.3.7 COVID-19 SAFETY PRECAUTIONS

COVID-19 Safety Precautions:

1. Adhere to local VA or University policies or mandates, for example:
    a. Screening before entering the facility, which may include a 'no touch' method to check temperature and COVID-19 screening questions.
    b. Participants encouraged or required to wear facial covering/mask while in the buildings, as mandated by the facility.
    c. Anyone who screens positive for COVID-19 (exposure or symptoms) and/or has a fever will be rescheduled (and possibly tested for COVID-19 as deemed clinically appropriate).
2. Study staff:
    a. The research team will monitor scheduling of participants in order to allow for social distancing and cleaning procedures between participant visits.
    b. Research staff members will sanitize high-touch surfaces before and after each in-person visit with disinfectant wipes or sprays.
    c. Staff members will adhere to local policies regarding wearing protective facial masks, frequent handwashing/use of alcohol-based hand sanitizer, and social distancing.
    d. Visits will take place in a large enough space so that study staff and the participant can practice social distancing.
    e. As much as possible, self-assessment forms should be completed via telehealth or phone; and can be given directly to or mailed to the participant in advance of any appointment.
    f. If the patient desires to complete in-person visit forms on site, staff will honor that request, but maintain social distancing.
    g. Participants will receive compensation for visits. As needed, study staff will verify their current address in order to be able to mail compensation to the participant.
3. In-Person visits:
    a. The in-person research visits will be restricted to those that are clinically essential (screening, baseline, Week 4, Week 8, Week 12, and Week 14; due to required labs and/or medication injections).
4. Telehealth/Phone visits:
    a. Week 1, 2, 6, & 10 visits may be conducted over the phone or telehealth to limit the participants contact (study staff and time in the clinic).
5. Week 14 Visit:
    a. Week 14 is highly preferred to be conducted in-person or by telehealth due to need for safety check and treatment planning (not as easy to assess over phone without video component).
    b. At this visit, participant has been off study medications for 2 weeks. Investigators would like to visually assess participants for withdrawal symptoms.
    c. All safety precautions will be followed during these visits to protect participant and study staff members.

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable.

7.5 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Due to the potential drug: drug interactions (e.g., opiates) or confounding therapeutic effects (e.g., naltrexone or acamprosate), participants may not use the medications listed in the table below, unless authorized by PASA medical monitor and approved by the lead PIs.

PROHIBITED MEDICATIONS		
Opioids		
Abstral, Actiq, Duragesic, Fentora, Onsolis (fentanyl)	Exalgo (hydromorphone hydrochloride)	Oxycet, Percocet, Roxicet, Xartemis XR (oxycodone/ acetaminophen)
Anexsia, Co-Gesic, Hycet, Lorcet, Lortab, Liquicet, Maxidone, Norco, Vicodin, Xodol, Zolvit, Zydone (hydrocodone/ acetaminophen)	Hycodan, Hydromet (hydrocodone/ homatropine)	Percodan (oxycodone/ aspirin)
Avinza, Kadian (morphine sulfate)	Hysingla (hyrocodone)	Rezira (hydrocodone/ pseudoephedrine)
Butrans (buprenorphine)	Ibudone, Reprexain, Vicoprofen	Targiniq ER (oxycodone/ naloxone)
Demerol (meperidine)	Morphabond, Oramorph, Roxanol-T, Sublimaze (morphine)	TussiCaps and Tussionex, Vituz (hydrocodone/ chlorpheniramine)
Dilaudid, Zohydro ER (hydromorphone)	Nucynta ER (tapentadol)	Tylenol #3 and #4 (codeine/ acetaminophen)
Dolophine, Methadose (methadone)	Oxaydo, Xtampza ER (oxycodone)	Zutripro (hydrocodone/ chlorpheniramine/ pseudoephedrine)
Embeda (morphine/ naltrexone)	OxyContin, Palladone (oxycodone hydrochloride)	
Medications Used to Treat AUD		
Antabuse (disulfiram)	Revia (naltrexone hydrochloride)	
Campral (acamprosate)	Vivitrol (extended-release naltrexone as a non-study drug)	
Medications Thought to Effect ETOH Consumption		
Gablofen, Lioresal (baclofen, muscle relaxant)	Topamax (topiramate; also listed under mood stabilizer)	
Zofran (ondansatron; prevents nausea and vomiting)		
Stimulants and/or ADHD Treatment		
Adderall (amphetamine, dextroamphetamine)	Dexedrine (dextroamphetamine)	Vyvanse (lisdexamfetamine)

PROHIBITED MEDICATIONS		
Desoxyn (methamphetamine)	Ritalin, Concerta (methylphenidate)	
Antipsychotics (except for quetiapine that may be used for insomnia)		
Benperidol (benperidol)	Mellaril (thioridazine)	Saphris or Sycrest (asenapine)
Clozaril, FazaClo, Versacloz (clozapine)	Moban (molindone)	Serentil (mesoridazine)
Geodon (ziprasidone)	Navane (thiothixene)	Stelazine (trifluoperazine)
Haldol (haloperidol)	Orap (pimozide)	Trilafon (perphenazine)
Invega (paliperidone)	Prolixin (fluphenazine)	Vraylar (cariprazine)
Latuda (lurasidone)	Risperdal (risperidone)	Zyprexa, Zydis (olanzapine)
Loxitane (loxapine)	Ruxulti (brexpiprazole)	
Alzheimer's Medications		
Aricept (donepezil)	Reminyl (galantamine)	
Benzodiazepine/ Other Sedatives		
Ativan (lorazepam)	Luminal (phenobarbital)	Thorazine (chlorpromazine)
Belsomra (suvorexant)	Novo-Clopate, Tranxene (clorazepate)	Tranxene (clorazepate)
Diastat, Valium (diazepam)	Prosom, Eurodin (estazolam)	Valium (diazepam)
Frisium, Onfi, Tapclob, Urbanol (clobazam)	Restoril (temazepam)	Vistaril (hydroxyzine)
Gabitril (tiagabine)	Rozerem (ramelteon)	Xanax (alprazolam)
Klonopin (clonazepam)	Novo-Clopate, Tranxene (clorazepate)	
Librium (chlordiazepoxide)	Serax (oxazepam)	
Mood Stabilizers (except for lamotrigine that may be used in this population)		
Depakote, Depakene (valproic acid/sodium valproate, divalproex)	Keppra (levetiracetam)	Tegretol (carbamazepine)
Eskalith, Lithobid (lithium)	Trileptal (oxcarbazepine)	Topamax (topiramate)

Due to the potential confounding therapeutic effects of psychotherapy,[43] concurrent evidence-based psychotherapy for PTSD (EMDR, Cognitive Processing Therapy, Prolonged Exposure, and cognitive behavioral therapy) are not allowed during the study. Participants who want this type of treatment may enroll in a course of treatment and complete it prior to the study participation.

If a participant develops suicidal, homicidal, or psychotic symptoms or a significant exacerbation of depression or anxiety, that clinically requires non-protocol allowed psychotropic medications,

the individual is withdrawn from the study and treated by a mental health provider in the appropriate setting.

7.6 ALLOWABLE CONCOMITTANT MEDICATIONS AND TREATMENTS

Concomitant psychotropic medication use for the 60 days prior to baseline and during the study is documented at each office visit. Non-psychotropic medications are reviewed by the medication management provider at each visit and the list is retained in source documents (i.e., the local site pharmacy profile from the participant's medical records).

Participants may be maintained on a stable dose of psychotropic medications listed in table below, which has been prescribed for ≥ 2 months and current dose being stable for ≥3 weeks prior to randomization and held constant during the trial.

ALLOWED PSYCHOTROPIC MEDICATIONS		
Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRI)		
Celexa (citalopram)	Luvox (fluvoxamine)	Prozac (fluoxetine)
Lexapro (escitalopram)	Paxil (paroxetine)	Zoloft (sertraline)
Antidepressants: Serotonin–norepinephrine reuptake inhibitors (SNRI)		
Cymbalta (duloxetine)	Fetzima (levomilnacipran)	Pristiq (desvenlafaxine)
Effexor (venlafaxine)	Ixel, Savella, Dalcipran, Toledomin (milnacipran)	
Antidepressants: Serotonin Modulator and Stimulator (SMS)		
Brintellix, Trintellix (vortioxetine)	Desyrel, Oleptro, Trittico (trazodone)	Viibryd (vilazodone)
Antidepressants: Atypical		
Remeron (mirtazapine)	Serzone (nefazodone)	Wellbutrin (bupropion)
Antidepressants: Tricyclic		
Allegron, Aventyl, Noritren, Nortrilen, and Pamelor (nortriptyline)	Elavil (amitriptyline)	Tofranil (imipramine)
Anafranil (clomipramine)	Norpramin (desipramine)	Vivactil (protriptyline)
Aponal, Quitaxon, Sinequan (doxepin)	Pamelor (nortriptyline)	
Asendin (amoxapine)	Surmontil (trimipramine)	
Antidepressants: Monoamine oxidase inhibitors (MAOI)		

ALLOWED PSYCHOTROPIC MEDICATIONS		
Emsam (selegiline)	Marplan (isocarboxazid)	Nardil (phenelzine)
Parnate (tranylcypromine)		
Alpha-1-adrenergic Antagonist		
Minipress (prazosin)		
Non-benzodiazepine Hypnotics		
Ambien (zolpidem)	Imovane (zopiclone)	Lunesta (eszopiclone)
Sonata (zaleplon)		
Non-benzodiazepine Anxiolytic		
BuSpar, Vanspar (buspirone)		
Other		
Neurontin (gabapentin)	Seroquel (quetiapine)	Lamictal (lamotrigine)
Melatonin	Clonidine	If not listed on prohibited medication list, consult with PI or medical monitor for approval.

Participants may attend PTSD support and educational groups and continue with supportive psychotherapy that was initiated prior to study entry.

7.7 ALLOWABLE RESCUE MEDICATIONS

As a provision to support participants who might be in distress during the trial, a medication for severe insomnia and severe agitation is allowed on a case by case basis. From screening to Week 12 and excluding the week prior to CAPS-5 assessments, **diphenhydramine or hydroxyzine** may be used sparingly, defined as up to 50 mg twice per day not to exceed three days per week), for severe insomnia (described as sleeping less than 4 hours per night) or severe agitation (described as persistent and unmanageable), based on the participant's self-report and the Investigator's clinical judgment. **Benzodiazepines are not allowed.**

7.8 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY EXIT

Naltrexone is currently on VA formularies and the participant may have access to this medication from his/her clinic provider. Although SL-BUP is on VA formulary, it is not currently indicated for AUD or PTSD.

8 ASSESSMENTS OF SAFETY AND ADVERSE EVENTS

8.1 SPECIFICATION OF SAFETY PARAMETERS

At each visit participants are asked by the CRC and/or investigator if they are experiencing any discomfort or symptoms that might indicate potential side effects of the study drug. Any reported complaints are documented by the CRC or investigator and, if serious, are reported to the IRB (per local IRB reporting requirements) and the DSMB (in regularly scheduled DSMB reports).

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

An Adverse Event (AE) is any untoward medical occurrence temporally related with the use of a drug in humans, whether or not considered drug related per 21 CFR Part 312.32(a). An adverse event (also referred to as an adverse experience) can be unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route or administration, formulation, or dose, including an overdose. For purposes of this study, a laboratory abnormality (i.e., out of the normal range) that is considered not clinically significant is not considered an AE.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious Adverse Events (SAEs) are defined as any adverse event that in the view of the investigator, results in any of the following outcomes:

- death
- life-threatening
- inpatient hospitalization or prolongation of hospitalization
- persistent or significant disability/incapacity
- congenital anomaly/birth defect

This category includes any other important medical event that an LSI judges to be serious because it may jeopardize the participant or require intervention to prevent one of the above reportable outcomes, or which would suggest a significant hazard, contraindication, side effect, or precaution. Other medically significant events that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasia or convulsions that do not result in hospitalization, or the development of drug dependency of drug abuse).

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The US Department of Health and Human Services Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of whether the event exceeds the nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Only a small subset of adverse events occurring in participants are likely to meet these three criteria for an unanticipated problem. Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human participants' research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place participants or others at increased risk of harm, but no harm occurs.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

Severity of AEs is determined by the LSI or designee using *FDA's Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials,* as a guide. General parameters for each grade are as listed in table below.

General Parameters for Grading an Adverse Event				
Vital Signs*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°F) **	100.4 – 101.1	101.2 – 102.0	102.1 – 104	> 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock

Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea or vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 g/24 hours	4 – 5 stools or 400 – 800 g/24 hours	6 or more watery stools or > 800 g/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of nonnarcotic pain med >24 hrs. or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity; requires medical intervention	ER visit or hospitalization

Serum Laboratory*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4) **
Sodium; Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium; Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium; Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium; Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose; Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose; Hyperglycemia Fasting – mg/random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine; mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium; hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium; hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium; hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous (K); hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK; mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin; Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein; Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--

Alkaline phosphate; increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
ALT, AST; increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin; when accompanied by any increase in LFT; increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin; when LFT normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	--
Pancreatic enzymes; amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Hematology*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/d	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Neutrophils Decrease - cell/mm3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm3	650 – 1500	1501 - 5000	> 5000	Hyper-eosinophilic
Platelets Decreased - cell/mm3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	<100; bleeding; disseminated intravascular coagulation
Urine*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic); red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. ** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a grade-3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.
***ULN" is the upper limit of the normal range.

8.2.2 RELATIONSHIP TO STUDY AGENT

Relationship of AE to study agent is recorded by the LSI or designee and identified as:

Definitely related – the AE can be fully explained by administration of the study drug.

Probably related – the study drug is more likely the cause of the AE than other factors.

Possibly related – there is a reasonable possibility that the study drug is the cause of the AE, including that the study drug and other factor(s) are equally likely as causes of the AE.

Unlikely related – the AE is not a previously known or suspected effect of the test drug, does not follow a sequence of time from drug administration for which the event could be attributed to the administration, and/or cannot be readily explained by the characteristics of the population under study but for which another incontrovertible cause is not immediately identified.

Definitely not related – another factor is clearly (incontrovertibly) the cause of the AE.

8.2.3 EXPECTED AND ANTICIPATED ADVERSE EVENTS

An unexpected AE experience is any AE in which the frequency, specificity or severity is not consistent with the risk information described in the investigator brochure (e.g., product labeling) or as anticipated from the pharmacological properties of the medication class of the study medication(s). This includes events that are new or greater than previously known in terms of nature, severity, or frequency per the pharmacological properties of the study medications.

Anticipated events, related to both AUD and PTSD, are expected to occur in the study population independent of study medication exposure.

8.3 ADVERSE EVENT ASSESSMENT AND FOLLOW-UP

AEs are collected from time of first dose taken after randomization through Week 14 follow-up visit. Study investigators follow all SAEs clinically until resolved or clinically stable. The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. At each study visit, the LSI or trained designee asks the participant about the occurrence of AE/SAEs since the last visit. All AEs are captured on the appropriate CRF.

Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship.

Any medical condition that is present at the time that the participant is screened is considered as a baseline condition and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it is recorded as an AE.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

All AEs and SAEs occurring during the clinical trial are collected, documented, and reported by the Principal Investigator according to the specific procedures detailed below. Study staff also review the previous Adverse Event Case Report Form and inquire whether any of those events are continuing. Each new or unresolved adverse event is recorded on the Adverse Event Case Report Form using a brief verbatim term, a severity ranking, and any additional description, according to the procedures. If an adverse event is reported that requires medical attention, it is reported to the study physician immediately. The LSI reviews each AE to assess their possible relationship to study medications and expectedness.

All AE are entered into the data management system. Timely mandatory reporting is required for AEs that are serious; unexpected; unanticipated, and definitely, probably, or possibly related to study drug. Section 8.4.2 details reporting of serious events. For all other events, sites follow institutional policy for reporting to the IRB. Reporting to the DSMB occurs via study reviews occurring on a prescheduled frequency as detailed in Section 8.6.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

Each AE is classified by the LSI or designee as serious or non-serious. SAEs are reported by the LSI to their local IRB, according to that site's local IRB reporting requirements.

The study PI will notify Alkermes (the manufacturer and supplier of XR-NTX and XR-NTX Placebo) of SAEs, that are possibly, probably, or definitely related to study treatment, as quickly as feasible (with a goal of within 24 hours of identification by site personnel).

Initial reports should include as much information as possible but at a minimum should include the event term, onset date, severity, serious criterion, relationship to study drug, date of resolution or continuing (if known), action taken with study drug because of the reported event, and an event outcome (if known).

Initial reporting is followed up with reporting all missing adverse event characteristics and a description of the event. The description provides relevant screening measures, medical history & physical, treatment compliance, reports of other relevant AEs and any other information the LSI deems appropriate. If the participant experiences additional events deemed serious, then these should be reported separately. However, if the participant experiences non-serious AEs during the same period, these are detailed in the SAE description and are reported separately as part of AE collection in the EDC system.

Determination of whether the event may be unexpected and at least possibly temporally related to study drug is made by the LSI in collaboration with the PASA Consortium medical monitor. Any SAE that are deemed at least possibly related and unexpected or unanticipated is submitted by PASA Consortium Leadership, in conjunction with the study team, via study DSMB reviews occurring on a prescheduled frequency.

The medical and research Monitor for this study is:

Thomas R. Kosten, MD, Medical Monitor and Research Monitor
Vice-Chair of Psychiatry for Research
Houston/Michael E. DeBakey VAMC

The Research Monitor role is a role independent of the research team and is achieved through study oversight as part of the PASA DCC CLT through regular attendance and participation in DSMB meetings, and through ongoing review of SAEs.

The Research Monitor:

- may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research, if needed.
- shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report.
- shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the United States Army Medical Research and Material Command's Human Research Protection Office (HRPO), and other relevant regulatory bodies.

In collaboration with the PASA Consortium Leadership, the medical monitor, and DSMB; the LSI determines whether there is a need to redesign or amend the protocol, and/or to inform current and future participants of a change in description of risk; either in the consent form and protocol, or by other written or verbal communication.

8.4.3 UNANTICIPATED PROBLEM REPORTING

Unanticipated problems that may involve risk to the participant or study staff, but do not necessarily result in an adverse event (i.e., harm) are reported separately from adverse events. An example of an unanticipated problem that may not result in an adverse event (i.e., harm) is misplacement of a participant's research record containing identifiable private information such that the risk of loss of confidentiality is introduced. This event is reportable regardless of whether the confidentiality is breached or not breached.

Any unanticipated problem that involves substantive harm (or genuine risk of substantive harm) to the safety, rights, or welfare of the site's research participants, research staff, or others is reported by the LSI or designee to the IRB and PASA Consortium Management within 48 hours of identification. Otherwise, the site LSI reports the event(s) to the local IRB on an annual basis at the time of continuing review and to the PASA Consortium Management as part of usual data collection for the participant.

8.4.4 REPORTING OF PREGNANCY

All pregnancies are reported by the LSI to the PASA Consortium Management and Alkermes within 48 hours of detection. A pregnancy is not considered an AE.

8.5 STUDY HALTING RULES

Study halting rules are determined by the study team and submitted to the PASA Consortium Management. The DSMB will review the halting rules, as part of their protocol review.

A 'study halting rule' typically specifies the outcome differences detected between groups during an interim analysis that can stop a clinical trial or study. Since the sample size for this study is at a minimum to determine a difference between groups, an interim analysis is not planned. Thus, our halting rules reflect guidelines to be considered for temporarily halting or permanently stopping the study.

New Information - There may be new information available to cause the DSMB to halt or stop the study, such as the following:

- The results of other trials indicate that the benefits far outweigh the risks or vice versa,
- A change in the understanding of the underlying biology of the disorders that indicate this pharmacological approach is ineffective or poses a substantial risk to participants,
- A change in the understanding of the pharmacology or interaction of the study drugs, such that the combination poses a substantial risk to participants, or,
- Outside evidence of unacceptable adverse effects from the study drug(s) and/or their interactions.

Safety Reporting - There may be serious adverse reactions reported in which unmasked information would trigger the DSMB to review the study in advance of regularly scheduled meetings and the DSMB may halt enrollment of new participants, such as the following:

- Three (3) Serious Adverse Events in a single organ system or related pathophysiology that are possibly, probably, or definitely related to the drug(s);
- A single occurrence of an unexpected serious and severe, life-threatening adverse event that is uncommon or previously not reported and determined to be strongly associated with drug exposure (e.g., angioedema, aplastic anemia, Stevens-Johnson Syndrome);
- Occurrences of an adverse event determined to be strongly associated with drug exposure that are not commonly associated with drug exposure and otherwise uncommon in the population exposed to the drug.

After review, the DSMB will recommend whether to permanently halt the study, modify the protocol, or continue the protocol. Based on the type of uncommon or previously not reported

adverse events and relatedness to the drug(s), the DSMB may determine that these types of events from safety reports may lead to a modification of the informed consent rather than study halting.

8.6 SAFETY OVERSIGHT

The PASA Consortium Management has established a DSMB to oversee this study. Members of the DSMB are independent of the study investigators and include representatives with substance abuse, pharmacology and psychology/psychiatry expertise, a biostatistician and an ethicist. None will have financial, scientific, or conflicts of interest which might interfere with their unbiased assessment of the progress of the trial. The DSMB meets at least once every four months as specified in the DSMB charter to review the study, although may be convened between planned meetings to discuss study issues related to adverse events/safety. This protocol should be approved by the DSMB prior to initiation of recruitment. The DSMB monitors study progress and has the ability to recommend that the trial be stopped for safety or futility. No formal interim assessments of efficacy are planned for this protocol and thus, the DSMB makes no recommendations related to stopping the study for efficacy.

During their reviews, the DSMB is responsible for a) reviewing research protocols, informed consent documents, and plans for data safety and monitoring; b) evaluating the progress of the study, including periodic assessments of data quality and timelines, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome; c) considering factors external to the study, when relevant, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial; protecting the safety of the study participants; d) reporting on the safety and scientific progress of the trial; e) ensuring the confidentiality of the data and the results of monitoring; and f) assisting the investigators by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

The DSMB provides recommendations to the DoD Grants Officer Representative (GOR) for further distribution to the GSC, and to the PASA Consortium PI (or designee) for archiving and further distribution to the Study PIs and all sites for IRB submission. Recommendations are also reported to the U.S. Army Office of Research Protections (HRPO) via annual reports for the study. While study halting rules described in Section 8.5 are to be considered by the DSMB in their deliberations about study safety and futility, final stopping recommendation criteria will be established by the DSMB.

8.7 RISKS MINIMIZATION

To mitigate the potential for misuse, dependency, and withdrawal, SL-BUP is combined with XR-NTX, a medication that blocks the mu receptor involved in psychogenic properties of buprenorphine. As stated earlier, XR-NTX can antagonize the effects of opioids via competitive inhibition of opioid receptors, which raises the concern that the combination of SL-BUP and XR-NTX will make SL-BUP less effective. This would be a risk for individuals who are using opiates or SL-BUP on a regular basis prior to starting XR-NTX, (i.e., the addition of XR-NTX may

precipitate opioid withdrawal symptoms). For this reason, this study excludes patients who have recent opioid use or opioid use disorders, and opiates are not allowed to be concurrently taken during the study. XR-NTX is contraindicated in patients receiving opioid analgesics and in patients with current physiologic opioid dependence, acute opiate withdrawal, acute hepatitis or liver failure, and previous hypersensitivity reaction to XR-NTX. Patients with these contraindications are not eligible to participant in this study.

In the current study, XR-NTX is administered as a long-acting injectable, the protective pharmacologic properties are present for the full duration of treatment with SL-BUP, thereby eliminating the risk that the participant will get psychologically or physically addicted to SL-BUP. In addition, we are using low dose SL-BUP (Note: the dose is lower than 16mg dose used in CURB study). At the end of the study XR-NTX gradually eliminates from the body. Thus, a pharmacologic taper is not needed for either XR-NTX or SL-BUP. Participants should not experience withdrawal symptoms, but to be conservative, they are followed by the investigators for an additional two weeks to monitor the participants for any adverse events related to discontinuation. To be cautious and thorough, the investigators assess for signs and symptoms of opioid withdrawal at the end of the study.

A caution that included in the informed consent states that in a situation when analgesia may be required in a patient who has received full blocking doses of XR-NTX, consideration should be given to regional analgesia, conscious sedation with a benzodiazepine, use of non-opioid analgesics, or general anesthesia. If opioid analgesia is required, the amount of opioid needed may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged. In this case, a rapidly acting opioid analgesic that minimizes the duration of respiratory depression is preferred. XR-NTX can also diminish the benefit from opioid-containing cough, cold, and antidiarrheal preparations, which is listed as a warning in the informed consent. These warning are standard when treating patients with XR-NTX.

SL-BUP is contraindicated in patients who have had prior hypersensitivity to any formulation of buprenorphine. Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol). Buprenorphine, particularly when taken by the IV route, in combination with benzodiazepines or other CNS depressants (including alcohol), has been associated with significant respiratory depression and death. Many, but not all post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines involved misuse by self-injection.

Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other CNS depressant drugs. For these reasons, participants are not allowed to take concomitant benzodiazepines or CNS depressant drugs (i.e., neuroleptics or sedating anticonvulsants) during the study. **In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.** Patients should be warned of the potential danger of self-administration of benzodiazepines or other depressants while under treatment

with SL-BUP. SL-BUP should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression). Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. For this reason, patients with severe liver disease or liver failure are excluded, and liver enzymes are measured at baseline and endpoint. SL-BUP may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during treatment induction and dose adjustment. Patients should be cautioned about driving or operating hazardous machinery until they are reasonably certain that buprenorphine therapy does not adversely affect his or her ability to engage in such activities. SL-BUP is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when SL-BUP sublingual tablet is given concurrently with agents that affect CYP3A4 activity. The concomitant use of SL-BUP sublingual tablet with CYP3A4 inhibitors (e.g., azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors) should be monitored and may require dose-reduction of one or both agents.

The LSI or designee instruct participants (in the consent form and verbally) to immediately report any adverse experiences that may arise and/or any changes in concurrent medications, whether prescription, over-the-counter medications, or herbal supplements.

In the unlikely event that a participant experiences a medical emergency, the local site has access to a medical Center that is fully prepared to respond to any medical event that may arise. Physicians and nurses are fully trained to respond to all types of medical and psychiatric emergencies. A fully equipped crash cart is available near the research clinic.

The risks of complications during pregnancy or congenital problems with this drug combination is not fully known, although much is known about each medication separately. As a conservative measure, we are asking that women use contraception and have not found that this requirement negatively impacts recruitment rates for women. There is no evidence that either medication affects reproductive risks after discontinuation. Similarly, there is no evidence that either medication affects male reproductive risks. Thus, women of child-bearing potential are informed of this unknown risk and are tested at baseline, as needed during follow-up, and at study endpoint.

During the psychophysiological assessments, participants may experience minor discomfort associated with delivery of the air blasts for the fear conditioning task. The air blast is described by participants as “annoying” but not painful. The decibel levels and duration of the auditory stimuli are not enough to cause any damage to the ear. If any part of the psychophysiological procedures or assessments are uncomfortable or distressing, the participant can take breaks or stop the procedures at any time.

To minimize breach or invasion of privacy, records that have personal identifiers (i.e., clinical records or source documents) are stored in a locked cabinet behind a locked door. Only the research team and clinical staff assigned to the care of the participants have access to non-anonymous research records. In addition, the study monitors, trained in Good Clinical Practice

(GCP), will have access to source documents while auditing the local site. Research case report forms do not contain personal identifiers and are labeled with a study i.d. number. Files that link participants' names with screening and randomization numbers are maintained in a secure location either on VA server or in a locked file within a locked office in the research clinic.

No presentation or publication of the study results will refer to participants individually. Manuscripts published regarding this work will be based on the accumulated database.

A federal Certificate of Confidentiality, which protects participants' records against subpoena will be acquired prior to study start. Exceptions to confidentiality for participants are those required by law and include suspicion of child abuse, elder abuse, and threat of imminent action on suicidal or homicidal ideation. Participants are informed of these exceptions in the informed consent process. In addition, representatives from PASA and the IRB will have limited access to the research record (e.g., in the event of a SAE, the IRB may request a review of the chart to assess adequacy of care during the trial).

9 CLINICAL MONITORING

Clinical monitoring is conducted by PASA Consortium representatives. Monitoring occurs after the start of study enrollment; and at interim visits at time intervals that are determined by the PASA Consortium. For additional information on clinical monitoring practices and procedures, including the Clinical Monitoring Plan, please refer to the PASA Manual of Operations.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

Analysis will be guided by the Statistical Analysis Plan (SAP) specified in accordance with the RTI PASA statistical quality plan: PASA Stats Quality Plan. The study-specific SAP will be finalized prior to locking the study data and unmasking the data.

10.2 STATISTICAL HYPOTHESES

To test the therapeutic actions of kappa-opioid receptor antagonism, we propose a proof-of-concept study to evaluate the effects of sublingual buprenorphine (SL-BUP; Subutex) combined with extended-release injectable naltrexone (XR-NTX; Vivitrol) in the treatment of comorbid AUD and PTSD. In addition to the primary clinical outcomes for AUD and PTSD we plan to measure pre- and post-treatment psychophysiological correlates of fear and alcohol craving that include 1) measure of the extinction of fear-potentiated startle and 2) stress reactivity to trauma stimuli and alcohol cues. The overarching hypothesis is that KOR antagonism achieved by the combination SL-BUP and XR-NTX will be effective in the treatment of comorbid AUD and PTSD and that these effects will be associated with psychophysiological changes. There will be two groups: XR-NTX + 2mg SL-BUP group and a PLACEBO group. With respect to sample size, the goal is to obtain at least 90 participants randomized to either of the two retained arms. Recruitment will occur over a 24-month enrollment period. If this goal is met with time left in the

enrollment period, sites will be allowed to randomize additional participants but will not exceed the original planned sample size of 135 randomized participants across all study arms.

The primary efficacy endpoint is a reduction of both AUD and PTSD symptoms, such that lowering both will be coded success and any other outcome will be failure. As a complement to the primary outcome, the AUD and PTSD components of the composite will be evaluated individually.

Secondary outcomes will also be examined both between group and over time (where applicable). These outcomes include:

- Examine differences in baseline psychophysiological measures, severity of AUD and PTSD, and treatment outcomes.
- Examine whether SL-BUP/XR-NTX improve psychophysiology measures at Week 8 (primary endpoint).
- Examine whether the degree of change from baseline to 2-week psychophysiological measures are associated with AUD and PTSD outcomes at Week 8.

*Psychophysiologic assessments are optional to not be a barrier to enrollment or randomization.

10.3 ANALYSIS DATASETS

The safety population will include all randomized participants that receive any study drug defined by treatment they actually received (either of the SL-BUP or XR-NTX treatments or placebo).

Analyses of efficacy outcome measures will be done using an intention to treat (ITT) population defined by the randomization irrespective of whether any study drug/placebo was actually received.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

All statistical computations will be performed by biostatisticians at the PASA Consortium data coordinating center [part of the Research Triangle Institute (RTI)]. For summaries of study data, categorical measures will be summarized in tables listing the frequency and the percentage of participants; continuous data will be summarized by presenting mean, standard deviation, median and range; and ordinal data will be summarized by only presenting median and range. P-values presented will be based on two-sided tests unless otherwise specified and generally adjusted for randomization factors. For continuous outcomes, checks of normality will be performed and if required, transformations or non-parametric tests will be employed. Additional details for potential covariate adjustments in secondary analyses or handling violations of analytic method assumptions will be detailed in the statistical analysis plan.

The analyses will include all available observations (i.e., from the various assessment times) from each participant. The Mixed-Effects Model of Repeated Measures (MMRM) provides valid inference under the assumption of ignorable missingness. No imputation processes will be used to replace missing data. However, every effort will be made to minimize missing data. Because missing observations have the potential to alter the results of analyses, we will examine whether the pattern of missing data is different among the groups. We will also examine the distribution of baseline covariates between those with and without missing outcome data. If there are no systematic differences between those with and without missing data, the data will be considered to be missing at random. If there are significant differences in dropout or missing data patterns between treatment arms, we will conduct sensitivity analyses to determine the impact of missing information on the treatment comparisons.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary dependent variable will be response status at Week 8 for each participant. A positive response is defined as a decrease from baseline of at least 8 points on the CAPS-5 score and a reduction of at least 1 risk level of alcohol use, as defined by WHO, at Week 8. Response data will be analyzed using mixed logistic regression with treatment group, measurement visit as a categorical variable, gender, site, presence/absence of anti-depressants, and other potential confounders as explanatory variables. A treatment group by measurement visit interaction will be included to account for the longitudinal nature of the data with the Week 8 effect being the primary outcome of interest. A two-sided p-value will be reported from the primary analysis for the all pairwise comparisons of SL-BUP/XR-NTX treatment and placebo groups.

As a complement to the primary outcome, the AUD and PTSD components of the composite will be evaluated individually. Difference in heavy alcohol use at Week 8 (defined as *>4 standard drinks/sessions for men and >3 standard drinks/sessions for women*) will be analyzed using a generalized-linear mixed model with treatment group, gender, site, presence/absence of anti-depressants, and other potential confounders as explanatory variables. Difference in reduction of PTSD symptoms at Week 8 (as measured by the CAPS-5) will be analyzed using a generalized-linear mixed model with treatment group, gender, site, presence/absence of anti-depressants, and other potential confounders as explanatory variables. For both outcomes, a treatment group by visit interaction term will be included to account for the longitudinal nature of the data, with Week 8 effect being the primary outcome of interest.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

SL-BUP/XR-NTX treatment will be compared with the PLACEBO (PLC) group for the following secondary outcomes:

- Examine differences in baseline psychophysiological measures, severity of PTSD and AUD, and treatment outcomes.
- Examine whether BUP/NTRX improve psychophysiology measures at 8 Weeks (primary endpoint).

- Examine whether the degree of change from baseline to 2-week psychophysiological measures are associated with AUD and PTSD outcomes at Week 8.

*Psychophysiologic assessments are optional to not be a barrier to enrollment or randomization.

Continuous data will be analyzed using MMRM with treatment group, gender, site, presence/absence of concomitant antidepressants, and other potential confounders as between-participant factors and visit (categorical) as a within-participant repeated measure. The model will also include the two-way interaction between treatment group and visit. When appropriate, significant differences between treatment groups will be further analyzed with post-hoc comparisons. Adjusted marginal means (also called LS means) will be used to report and test for differences in mean change at Week 8 for the placebo and SL-BUP/XR-NTX groups providing 95% confidence intervals and a p-value for the difference between them.

10.4.4 SAFETY ANALYSES

The safety analyses population includes all randomized participants. These analyses will include those participants who have reported an adverse event as well as those who do not report an adverse event. The incidence of treatment emergent adverse events, type of adverse events, and frequency of withdrawals due to an adverse event will be summarized by treatment group. Appropriate statistical comparisons will be made between treatment groups in terms of 1) rates of adverse events, 2) discontinuation due to adverse events, and 3) side effect scales. Rates will be compared using time to event hazard analysis. Frequencies will be analyzed using the chi square or Fisher Exact test. The scales will be examined using non-parametric analyses when appropriate. This study is not powered as an equivalence study so the non-significance of differences between groups does not truly imply equivalence.

10.4.5 ADHERENCE AND RETENTION ANALYSES

To assess medication adherence, blood samples collected at study Week 8 and Week 12 will be tested for buprenorphine and its metabolite, norbuprenorphine, using quantitative assessments. We will also incorporate a self-report medication adherence CRF that will be completed at each study visit. Results of pill counts will be summarized over time by treatment group.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Prior to the formal analysis of outcomes, all data will be examined using summary statistics (e.g., mean, standard deviation, median, etc.) and statistical graphs. Demographic variables (e.g., age, gender, race/ethnicity, etc.) will be compared between treatment groups using t-tests for continuous data and chi-square tests for categorical data. If necessary, non-parametric tests will also be used to compare demographic variables between treatment groups. Significant demographic variables will be included in all subsequent models.

10.4.7 PLANNED SAFETY AND INTERIM ANALYSES

The study will be monitored by the DSMB as detailed in Section 8.6. Baseline; participant disposition; study drug exposure; and primary and secondary outcome data will be summarized for each study review with a focus on participant safety. While there are study halting rules that will trigger a study review by the DSMB, there are no formal study stopping rules based on the safety review that would trigger permanent study termination without the review and recommendation of the DSMB.

No formal interim analyses for efficacy are planned for this study.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

No specific sub-group analyses are planned for this study. Any additions of such analyses will be discussed in the statistical analysis plan.

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

No adjustments for multiple comparisons are planned for the primary efficacy or safety outcomes. For the secondary outcomes, we will group by outcome domain and apply Benjamini-Hochberg (1995) false discovery rate correction to maintain the nominal alpha level of 0.05.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

Study data will be tabulated and summarized as described in 10.4.1. Additional details will be discussed in the statistical analysis plan.

10.4.11 EXPLORATORY ANALYSES

Certain measures included in the study were added at the suggestion of the Government Steering Committee to harmonize with the Simpson-Saxon study (including the PCL-5). The study plans to analyze all AUD and PTSD measures collected throughout the study and most can be analyzed using similar mixed modeling techniques described above for the secondary outcomes. Additionally, study group comparisons for all AUD and PTSD outcomes will be made across time from baseline to Week 12. All exploratory analyses will be described in the statistical analysis plan.

10.5 SAMPLE SIZE

The sample size for a proof-of-concept study should be large enough to be able to detect a drug effect or surrogate signal, but at the same time expose a minimum number of participants to an experimental drug combination in a reasonable timeframe within a restricted budget. Sample size was determined based on sample sizes used in similar double-mask, placebo-controlled studies of AUD and PTSD, and based on the estimated recruitment rate over the allotted enrollment timeline.

With these factors in mind, we plan to enroll approximately 180 participants to allow for screen failures/dropouts prior to randomization.

With respect to sample size, the goal is to obtain at least 90 participants randomized to either of the two retained arms (XRNTX/2mg BUP arm and PLACEBO arm). Recruitment will occur over a 24-month enrollment period. If this goal is met with time left in the enrollment period, sites will be allowed to randomize additional participants but will not exceed the original planned sample size of 135 randomized participants across all 3 originally planned study arms.

To ensure balance within each treatment group we will use stratified randomization on site, presence/absence of concomitant antidepressants, and gender. We plan to use blocking within each stratum of the randomization scheme to balance treatment assignments. We estimate that attrition will be approximately 30%. However, all randomized participants will remain in analysis (intent-to-treat) regardless of how long they participate in the study.

For the primary outcome, we assume 90 randomized participants (allowing for screen failures/dropouts) allotted equally among the two study arms and with the success rates shown in the below table. We calculated power for two by two contingency tables for comparisons with each treatment arm and the Placebo arm using a Fisher's Exact test with the Walters approximation applying a nominal two-sided alpha level of 0.05.

In examining our primary outcome, we provide a table of power calculations with a range of potential placebo and treatment responses for a sample size of 45 in each group. The value in orange (0.560) is from the original protocol where the assumption was for an 11% (5/45) positive response rate in the placebo arm and a 31% (14/45) positive response rate in the active treatment arm. All cells shaded in yellow have a value of 0.7 or greater and all cells shaded in green have a value of 0.8 or greater. A sample size of 45 in each group will be able to detect a clinically meaningful difference between groups. For example, a treatment response of ≥38% (17/45) in the active treatment arm (consistent with ALKS-4561 for depression) and ≤11% (5/45) in placebo arm (conceivable in a dual-diagnosed PTSD-alcohol population) would have power of 0.8 or greater. In addition, a situation with more positive responses in the active treatment arm or fewer positive responses in the placebo arm would increase apparent power.

		Treatment Positives									
		24%	27%	29%	31%	33%	36%	38%	40%	42%	44%
Placebo Positives		11	12	13	14	15	16	17	18	19	20
2%	1	0.860	0.908	0.941	0.964	0.979	0.988	0.993	0.996	0.998	0.999

4%	2	0.714	0.791	0.853	0.900	0.934	0.958	0.975	0.985	0.991	0.995
7%	3	0.556	0.651	0.734	0.804	0.861	0.905	0.937	0.960	0.975	0.985
9%	4	0.409	0.506	0.600	0.687	0.762	0.826	0.877	0.916	0.944	0.964
11%	5	0.286	0.375	0.467	0.560	0.647	0.726	0.795	0.851	0.895	0.929
13%	6	0.192	0.265	0.348	0.437	0.527	0.615	0.696	0.767	0.828	0.877
16%	7	0.125	0.180	0.248	0.326	0.412	0.500	0.587	0.669	0.743	0.807
18%	8	0.081	0.119	0.170	0.235	0.309	0.392	0.478	0.565	0.647	0.723
20%	9	0.057	0.079	0.114	0.163	0.224	0.295	0.375	0.460	0.545	0.628

For secondary hypotheses, we estimate that with equal numbers of participants randomized to each of two treatments groups we will have >80% power to detect a medium effect size (Cohen's f=0.25, two-sided alpha level of 0.05) at Week 8. Under optimal conditions, where the correlation between consecutive observations on the same participant is high, and the variability observed between pairs of time points is fairly constant, fewer participants would be required (see table below). Under a less than ideal, worst-case situation where correlation between measurements is low and the variability observed between pairs of time points changes, the proposed sample size is still large enough to detect a moderate effect size, even after accounting for screen failures and drop-outs.

Estimated Sample Sizes per Group for Detecting a Moderate Effect Size at 80% Power			
Modeling Conditions	AUD Outcome	PTSD Outcome	Higher of PTSD/AUD with Screen Failures and Drop-outs (+15)
High Correlation, Constant Variance	42	30	57
High Correlation, Non-constant Variance	42	63	78
Low Correlation, Constant Variance	81	57	96
Low-Correlation, Non-constant Variance	81	120	135

For the Psychophysiological and Fear Conditioning analyses, a total sample size of 90 (45 per group) will allow for a conservative dataset with over 80% power to detect significant differences between the treatment group and the placebo group at the $\alpha = 0.05$ level. Estimates were based on means and standard deviations from previous study samples.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

To minimize bias, a placebo drug is employed as the comparison group to active study drug and the study is conducted in a double-masked fashion in that both the participants and the Independent Assessors who are assessing study outcomes are masked to treatment assignment. The only individuals at the site with access to treatment assignment information are the research pharmacists.

At baseline, participants who meet eligibility criteria are randomized to treatment A (buprenorphine 2mg SL with naltrexone 380mg IM) or treatment B (SL placebo and IM placebo) in a double-mask fashion for 8 weeks. The treatment allocation ratio for the treatment vs. placebo regimens is 1:1 and is stratified by site, presence of concomitant antidepressants, and gender using a random permuted block scheme with variable block size. The randomization schedule is created by the PASA statistician who coordinates with the local research pharmacies and develops the web-based randomization assignment system. At Week 8, the participants remain on the assigned treatment and dose from Week 8 to Week 12.

10.6.2 EVALUATION OF SUCCESS OF MASKING

Any unmasking of study participants or study staff is reported as a protocol deviation to the PI (Davis), LSI, and PASA Consortium Management. However, the site should not have to report which treatment that the participant is assigned unless such information is needed to ensure the safety of the participant. At the end of the study, the participant is asked to complete a survey as to whether he/she could tell which treatment arm was assigned, and if so, which treatment and why.

10.6.3 BREAKING THE STUDY MASK/PARTICIPANT CODE

The local site pharmacy maintains the masking record, which can be broken only upon request by the treating provider in order to protect the participant from a life-threatening event. In the event of an emergency, the research pharmacists may unmask without advance permission from PASA Consortium Management, but the site must report the unmasking within 24 hours by contacting the PASA Consortium Management. If the mask is ever broken on any individual participant, the pharmacist must record that fact in the pharmacy study records and report to PI, LSI, and PASA Consortium Management.

In instances where the study mask needs to be broken, permission and approval to break the mask should be obtained in advance by a research pharmacist from appropriate PASA Consortium Management point of contact as defined in the pharmacy study medication accountability binder. PASA Consortium Management includes:

- Tracy Nolen, Ph.D., PASA Consortium Leadership
    - Principal Scientist, RTI International

- Nathan Vandergrift, Ph.D., PASA Consortium Leadership
    - Senior Research Statistician, RTI International
- Thomas Kosten, MD, PASA Consortium Leadership
    - Medical Monitor, Professor of Psychiatry, Neuroscience, Pharmacology, Immunology & Pathology Baylor College of Medicine, Michael E DeBakey VAMC (Houston, TX)

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants. All physical research data are stored in either locked files or secure computers, which are always kept in locked rooms at the local sites. All electronic research data are stored on the secure VA server behind the VA firewall. An Accounting of Disclosure (AOD) is maintained by the CRC that lists any disclosure of individually identifiable information outside the VA. The manual spreadsheet includes the date of the disclosure, nature or description of the individually identifiable information disclosed, purpose of each disclosure and the name and address of person or agency to which the disclosure was made. Besides the PI, the study staff, the IRB, and the PASA Consortium; people who ensure quality from the local site where the research is being done, federal and other regulatory agencies have access to all the research data.

Source documentation includes any documents used to record all original data from participants that support and verify information recorded on the Case Report Forms, such as medical records, screening visits, telephone conversations, study procedures, self-report instruments, diagnostic and study-related data, and study visits.

The study monitor, authorized representatives of the PASA Consortium, representatives of the IRB or research oversight administrators may inspect all documents and records required to be maintained by the investigator, including, but not limited to, research records and pharmacy records for the participants in this study. The investigational site must provide direct access to all trial related sites, source data/documents, and reports for monitoring and auditing by the PASA Consortium, and inspection by local and regulatory authorities.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. The QC monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

13 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

13.1 ETHICAL STANDARD

The local site investigator is responsible for ensuring that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 11, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312), and ICH E2, E3, E6, E8 and E9.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

Potential participants are given ample time to consider the informed consent, along with other options for treatment presented by the research assistant, investigators and/or treatment team. They may have as much time as needed (no time limit) to read and consider the risks and benefits of the study participation and they may involve family members, significant others, and primary treatment team in the decision on whether or not to participate in the study. Participants are informed that refusal to participate in research projects will not change their eligibility for VA services, treatment, or disability payments. No guarantees are made for symptom improvement during the research study. Compensation is commensurate with time and inconvenience needed to complete the procedures.

Prior to entering the study, a member of the study team provides the potential participant with detailed information regarding the study's purpose, procedures, potential risks and benefits, alternative treatment, compensation and other required elements. This is done by a study team member in a private setting and documented on a signed and dated informed consent form. The investigators are responsible for answering questions pertaining to the study medication and their side effects. A participant's willingness to take part in the study is subsequently documented in the medical records. If a participant agrees to participate, his/her consent is recorded on the Agreement to Participate in Research Form, VA Form 10-1086. Informed consent requires that the participant understand the details of the study, including its risks and benefits, and agrees without coercion to participation. The signed and dated consent form is distributed to: Participant's study file (original) and participant (copy). A note is entered by the CRC into the participant's medical record to document the process of informed consent.

All participants must have the capacity to provide their own informed consent. Surrogate consent is not allowed. Only those patients with capacity for informed consent are eligible. Persons who lack capacity to give independent informed consent (i.e., severe cognitive disorder

such as dementia, severe traumatic brain injury, or other known cognitive or psychotic disorder that impairs decision making) are not eligible to be enrolled. Persons with a terminal illness, minors, and prisoners cannot be recruited or enrolled in this study.

Protection of participants from harm must be balanced against the potential for benefit to participants themselves, and to other persons with their disorders, that may arise from research participation. Since new treatments must eventually be tested in persons suffering from the condition, a policy totally excluding vulnerable participants from research would preclude the development of improved treatment for persons with AUD or PTSD. This study specifically recruits veterans and service members, as well as non-veterans, with AUD or PTSD, which may be considered as a vulnerable patient population. Vulnerable populations, i.e., prisoners, individuals with mental retardation, minors, persons with dementia or severe cognitive disorders, and persons deemed legally incompetent are not eligible for this study. The decision-making capacity of individuals with AUD or PTSD at this stage of recovery is typically intact, however, veterans are accustomed to taking and following direct orders, which requires a greater need for researcher to prevent coercion, either directly or indirectly. Potential participants are given ample time to read and consider the informed consent with other treatment options explained in the consent form. Family members, significant others, and primary treatment teams may also be involved in the decision-making process if the potential participant wishes. For veterans and service members, they are also informed that declining participation in a study does not change their eligibility to VA services, treatment, disability or other VA benefits. Those individuals who are economically or educationally disadvantaged may be considered vulnerable. The VA population includes individuals in this category; however, the study keeps payments to participants at a minimum to avoid coercion based on economic hardship. In addition, the informed consent is written at a grade school level of education to minimize vulnerability to the educationally disadvantaged.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Among Veterans and service members, concerns about confidentiality, stigma associated with receiving any form of mental-health care and concerns related to present military policies underlie low rates of treatment

Participants' confidentiality is strictly held in trust by the participating investigators, their staff, and the PASA Consortium and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated are held in strict confidence. No information concerning the study, or the data is released to any unauthorized third party without prior written approval of the PASA Consortium.

The study participant's contact information is securely stored at each clinical site for internal use during the study. At the end of the study, all records are kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, are transmitted to and stored at the PASA Consortium Data Coordinating Center (DCC). This does not include the participant's contact or direct identifying information. Rather,

individual participants and their research data are identified by a unique study identification number. The study database will contain dates: date of study entry, dates of assessments, dates of adverse events, date of death (if applicable and unlikely). The study data entry and study management systems used by the clinical site and by the PASA Consortium DCC research staff are secured, and password protected. At the end of the study, all study databases are de-identified and archived at the PASA Consortium DCC. In addition, information about SAEs and any pregnancy will go to Alkermes (providing the study drug naltrexone and its injectable placebo kits).

As part of QA processes a data use agreement is in place between VA and Dr. Weathers who will be reviewing recorded CAPS interviews for both training and maintaining assessor quality.

To address concerns about confidentiality, we will obtain a Certificate of Confidentially (CoC). CoCs allow researchers to refuse to disclose names or other identifying characteristics of research participants in response to legal demands. Certificates are to researchers to help protect the privacy of human participants enrolled in sensitive, health-related research. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

Samples collected under this protocol are not stored and are analyzed immediately for participant health safety purposes and toxicology screens. Samples are destroyed after analysis.

Data stored for the study at the PASA Consortium DCC will be used for future analyses as well as potential regulatory submission.

13.5 FUTURE USE OF STORED SPECIMENS

Per Section 13.4.1, samples collected under this protocol will not be stored for future use of any kind.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT erase, overwrite, or use correction fluid or tape on the original.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Medidata Rave, a 21 CFR Part 11-compliant data capture system provided by the PASA Consortium DCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 STUDY RECORDS RETENTION

All VA research records in accordance with the new Veteran Health Administration's Records Control Schedule 10-1 (RCS) policies for the Office of Research and Development which states that the LSI **may** destroy research records 6 years after the end of the fiscal year in which the IRB and R&D has been closed; however, **before any destruction the LSI will need to obtain PASA Consortium approval**. Electronic data will be deleted from the VA secure network and hardcopy data will be destroyed according to the approved VA Records Management policies and secure practices.

Only data collected as part of the study for analysis, study reporting and/or safety monitoring (e.g., SAE reports) will be transferred to the central DCC of the PASA Consortium. The individual investigators at each site will get a final copy of the data collected at their site at the end of the study. None of these data will have direct identifiers, and the data will be retained centrally with no plans for destruction. In the event of Consortium close-out, any data archived at the Consortium would be transferred to DOD CDMRP as the primary funder of the project.

14.3 PROTOCOL DEVIATIONS

Compliance with the protocol will be monitored throughout the study. Any deviations noted during conduct of the study are to be reported by the LSI, or their designee, to the IRB and PASA Consortium Management. A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. The MOP details the process for reporting protocol deviations.

14.4 PUBLICATION AND DATA SHARING POLICY

The PASA Consortium will ensure results of the study are published and shared. As such, this study will:

- Following the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11), register with ClinicalTrials.gov and submit results. Primary

outcome results from this trial will be submitted to ClinicalTrials.gov within 1 year of completion.

- Publish results. Every attempt will be made to publish results in peer-reviewed journals. All final peer-reviewed journal manuscripts from this study will be submitted to the digital archive PubMed Central upon acceptance for publication.
- Deposit data for data sharing with other researchers. Within the bounds of relevant IRB approvals and guidelines for protection of personally identifiable data, de-identified data from this study will be deposited in an appropriate, publicly available data repository.

15 AMENDMENTS

As the study is being conducted, the PI will promptly inform the PASA Consortium of any changes in recruitment or in the protocol that are relevant to safety, as well as any actions taken by the IRB because of its continuing review of the study. In the event of any major changes in the status of an ongoing protocol, the Principal Investigator will inform the PASA Consortium's program officer immediately. Such changes would include:

- Amendments to the protocol
- Temporary suspension of participant accrual, or of the protocol
- Any change in informed consent or IRB approval status
- Termination of participant accrual, or of the protocol
- Other problems or issues that could affect the human participants in the study

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the GSC has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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