NCT05283304

INFORMED CONSENT FORM

Title: NIDA CTN Protocol 0110 Randomized, double-blind, placebo-controlled trial of monthly injectable buprenorphine for methamphetamine use disorder (MURB)

IRB# STU2021-0118

Date: March 1, 2023

Title of Study: NIDA CTN Protocol 0110 Randomized, double-blind, placebo-controlled trial of monthly injectable buprenorphine for methamphetamine use disorder

Consent to be part of a Research Study
To be conducted at
The University of Texas Southwestern Medical Center
University of California- Los Angeles Vine Street Clinic
Oklahoma State University-Center for Health Sciences
CODA Inc.
Alameda Health System- Highland Hospital Bridge Clinic
University of Washington - Harborview Medical Center

Key Information about this Study

The purpose of this study is to test if extended-release injectable buprenorphine (BUP-Inj, Sublocade™) compared to injectable placebo (PBO-Inj) reduces methamphetamine use over a 12-week period in people with moderate to severe methamphetamine use disorder (MUD) who also use opioids. You will be randomly assigned to either take the active medication or a placebo. This medication is given to you as an injection in your stomach and releases medication slowly into your body over the course of a month. This medication is being tested because there is research that suggests this medication may help people stop or reduce their substance use and is approved by the U.S. Food & Drug Administration (FDA) for the treatment of opioid use disorder (OUD). There are no currently available FDA-approved medications to treat methamphetamine use disorder.

As a participant in this study, you will attend approximately 28 visits over about 19 weeks (up to 3 weeks in screening, 12 weeks getting study medication and a follow-up visit 4 weeks after you finish medication), and most visits will last about 1 to 4 hours, but some may be shorter or longer. You will be asked about your substance use and your mental and physical health, and complete questionnaires to tell us about your feelings and symptoms. You will need to provide urine samples, twice weekly, to test for drugs in your system. You will not be penalized for drugs detected in your samples at any time. Your participation in the study may help the study team see if BUP-Inj can help people stop or reduce their methamphetamine use. The study team will work with you to help make sure you get to all your visits. Extended-release injectable buprenorphine (BUP-Inj, Sublocade™) is an investigational medication “Investigational” means that the medication has not yet been approved by the FDA for treating methamphetamine use disorder.

All medications can cause side effects and people have different experiences with the type of side effects, the frequency, and the intensity. There are risks to taking part in this study. The most likely risk is that you may have side effects while on the study medication, such as constipation, nausea, headache, fatigue, or changes in liver enzymes. Side effects from these medications will usually go away after you stop taking them. In some cases, side effects can be long lasting. The study staff will ask you about side effects and can provide some medications that may help you manage them. The study staff will also do blood testing during the study to monitor your physical safety. If you are currently not dependent on opioids, you may become dependent on buprenorphine and other opioids by the end of the study. You may test positive for opioids, including failing drug tests, for up to one year. Withdrawal signs and symptoms may occur when the study medication is discontinued. Other risks to being in the study include loss of confidentiality. The study staff have put things in place to help keep those risks as low as possible.

If you are interested in learning more about this study, please continue to read below.

Information about this form

You may be eligible to take part in this research study. This form gives you important information about the study. This is a multi-site study, meaning it will take place at several locations, so the informed consent form will include two parts. This form is Part 1 and includes information that applies to all study sites, like the purpose of the study and the research procedures to be done.

Part 2 of the consent form will include information specific to the study site where you are being asked to enroll, such as the local contact information for the study team.

Please take time to review this information carefully. You should talk to the study staff about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or a doctor) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Please tell the study staff if you are taking part in another research study.

Voluntary Participation - Taking part in this investigational study is completely voluntary. You do not have to participate if you don't want to. You do not have to participate in this study to get standard medical treatment. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are entitled. Sometimes during a study, the Sponsor may learn new information about the study medication, the risks, or something else. Your study clinician/staff will tell you in a timely manner if there is any new information that might make you change your mind about being in the study.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

General Information - Who is conducting this research?

Study Sponsor and Funding Agency

Madhukar Trivedi, MD, Department of Psychiatry at University of Texas Southwestern (UTSW) Medical Center, is the CTN-0110 study Sponsor. The Sponsor is the person/entity who takes responsibility for and initiates a clinical investigation. The National Institute on Drug Abuse (NIDA), a federal agency that promotes scientific research, is funding this study. NIDA is providing money to each research site so the researchers can conduct the study.

Lead Investigator

The Lead Investigator (LI) is the researcher directing this study; the LI is responsible for protecting the rights, safety, and welfare of participants in the study. The LI for this study is Steven Shoptaw, PhD, Department of Family Medicine at the University of California, Los Angeles (UCLA). His email address is sshoptaw@mednet.ucla.edu and his phone number is (310) 794-6206.

Principal Investigator

The Principal Investigator (PI) is the person directing this study at your local site; the PI is responsible for protecting your rights, safety, and welfare as a participant in this research study. Part 2 of the consent form will have more information regarding your site and site PI.

Why is this study being done?

The purpose of this study is to test if extended-release injectable buprenorphine (BUP-Inj) compared to injectable placebo (PBO-Inj) reduces methamphetamine use over a 12-week period in people with moderate to severe methamphetamine use disorder (MUD) who also use opioids. You will be randomly assigned (like the flip of a coin) to either receive the active medication or a placebo, given as an injection in your stomach that releases medication slowly into your body over the course of a month. This medication is being tested because it may help people stop or reduce their substance use and is approved by the FDA for the treatment of opioid use disorder.

You are asked to participate in this research study because there are no FDA-approved medications currently available for MUD. The researchers are testing if BUP-Inj can help people seeking treatment for MUD. Instead of taking part in this study, you may choose to receive treatment with other medications or treatments available to you. The study clinician will explain to you the benefits and risks of other treatments and will answer any questions you may have.

The researchers hope to learn whether BUP-Inj is better than PBO-Inj in helping to stop or reduce methamphetamine use over 12 weeks of study.

Investigational Use of Drug

This study involves the use of an investigational medication called extended-release injectable Buprenorphine (BUP-Inj), Sublocade™, 300mg dose. “Investigational” means that the medication has not yet been approved by the FDA for treating methamphetamine use disorder. The investigational medication will be given in the form of an injection that goes into your stomach and sits under your skin (abdominal subcutaneous depot injection). The FDA has given us permission to conduct this study. This study is being performed under an Investigational New Drug application.

This study will compare the effects, good and/or bad, of BUP-Inj in people with MUD who co-use opioids, to those of placebo, an injection without active medication. The safety of this medication in humans has been tested in prior research studies; however, some side effects may not yet be known.

The other treatment is buprenorphine combined with naloxone that is placed under the tongue (sublingual). Sublingual buprenorphine plus naloxone (Suboxone™) has also been Food and Drug Administration (FDA)-approved for patients with opioid use disorder.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Who is participating in this research?

You are being asked to be a participant in this study because you met initial prescreening criteria indicating you possibly have MUD with co-use of opioids and are interested in reducing or stopping your methamphetamine use.

How many people are expected to take part in this study?

This study will enroll approximately 246 study participants across 4-8 sites.

What will be done if you decide to be in the research?

While you are taking part in this study, you will be asked to attend around 28 visits with the study staff. This study is divided into 3 phases: Screening, Medication, and Follow-up. The time of your participation in this study will be approximately 19 weeks. In rare cases, it may be necessary for you to return to the hospital/clinic more often for repeating blood tests or to assess side effects, if needed.

Study Procedures Overview:

The table below provides a summary of study procedures and how often you will engage in them. The list of procedures to be done at each individual visit is outlined below the table.

Procedures	Description	Frequency
Urine Samples	To test for substances used (and common infectious diseases as needed)	Every visit
Timeline Followback	To record your self-reported use of substances	Every visit
Self-Report Questionnaires	To record important information about how you are doing in the study	Every visit
Pregnancy Tests	If capable of becoming pregnant, to make sure you are not pregnant before receiving study medication	As needed
Blood Draw (2-4 tablespoons depending on visit)	To check red blood cell and white blood cell counts, liver function, general health, study medication levels, and test for Hepatitis C; some blood will be stored for later testing; and if you agree, some blood will be collected for genetic testing;	Screening, Week 5, 9, 12
HIV Test	For those who have not tested positive for human immunodeficiency virus (HIV), the virus that causes AIDS, blood will be tested for HIV; counseling will be provided before and after you get test results	Screening, Week 12
Vital Signs	Blood pressure, heart rate and temperature	Every visit
Physical Examination	Exam including only height, weight, and listening to your heart and lungs	Screening, Week 12
Clinician Interviews	To check on physical and mental health, sexual risk-taking behaviors, substance use history, depressive symptoms, mood, and feelings	Every Visit
Computerized Cognitive Test	Task that takes about 5-10 minutes on the computer; you will be given specific instructions prior to the task	Screening

Electrocardiogram (ECG)	Sticky patches will be placed on your chest and connected to a machine that shows the electrical activity of your heart	Screening, Week 12
Administer Study Medication	Sublingual buprenorphine over 2-3 days prior to receiving 3 subcutaneous injections of study medication	Week 1, 5, 9
Cognitive Behavioral Therapy (CBT)	Weekly 20-minute CBT session to support your participation and help you learn skills to reduce your substance use	Weekly
Review of Side Effects and Medications	Review your current medications (and any changes throughout the study), and any side effects	Every visit
Injection Site Evaluation	Check on injection site and document any findings for follow-up, if necessary	Week 2, 5, 9, 12

Screening Phase (Up to 3 weeks):

After you sign this consent to participate, you will be asked to complete some exams, tests, and/or procedures to help decide if you can continue in the study. This process is called screening and may take up to three weeks. During screening, you will be asked to come to the clinic at least twice for around 5 hours total for all the needed screening assessments. You will be compensated for your time no matter the results. You may prefer to break up screening assessments into multiple days. However, we need all assessments to be completed within 21 days and will collect urine samples at 2-3 different visits that must occur within a 10-day period, having at least 2 days between each sample collection. Thus, you may need to provide between 2 and 6 urine samples during screening.

Screening Procedures:

The following screening activities will be completed over a maximum of 3 weeks and will help us determine if you qualify to participate in the study. For more information regarding each procedure, please see the table above.

- Clinician Interviews, Timeline Followback, and Self-report Questionnaires about your drug and alcohol use, lifestyle, involvement with criminal justice system, and physical and mental health
- Physical Examination about your medical history, vital signs (heart rate, blood pressure, temperature) and an Electrocardiogram (ECG) to test your heart functioning
- Urine Sample Collections for drug tests, common infectious diseases, and urine pregnancy test for women who can become pregnant
- Blood Samples will be collected for lab testing (including HIV and Hepatitis C) and storage for later testing at the UTSW Repository
- Review of Medications to make sure you are not taking any medications that would make your participation in this study dangerous
- Computerized Cognitive Test to test your ability to win in a gambling experiment
- Administrative Paperwork including Demographics Forms

Medication Phase and Randomization:

The results of the screening exams, tests, and/or procedures will be reviewed to determine whether you will be allowed to continue in the study. If the study staff confirm and document that you are

eligible to continue, you will transition to the Medication Phase, complete some baseline assessments, and be randomized (see process described for group assignment below).

Assignment to Treatment Groups:

There are two treatment groups in the study. You will have a 50/50 chance of being put into each group (like flipping a coin):

- Extended-release injectable buprenorphine (BUP-Inj)
- Injectable placebo (PBO-Inj) which contains no active medication

During this study, neither you nor the study staff will know which treatment group you are in. However, if needed for a medical emergency, the study clinician/staff can quickly find out which treatment group you are in. You will receive the study medication for approximately 12 weeks. Administrative paperwork including reviewing and updating the locator form will be done each week.

On the day you are randomized (Week 1, Day 0), you will start what is called an "Induction" onto the study medication. Prior to receiving your first injection, you will receive a form of study medication that goes under your tongue (sublingual). This Induction will take two to three days, and the study clinicians will help make sure you tolerate the medication appropriately before transitioning you to BUP-Inj or PBO-Inj. Once you have completed the induction on sublingual medication, you will receive your first injection. During these visits, you will be asked to remain at the site for monitoring after you receive your dose. You may feel the effects of the medication or feel tired after receiving the medication. While you wait, you may complete some questionnaires and you might feel some discomfort while answering the questions.

This first visit in the Medication Phase may take approximately 4 hours. The other visit during your first week may take approximately 2 hours.

Week 1, First Visit (~4hrs):

- Interviews such as Timeline Followback to assess your substance use
- Urine sample to test for drugs
- Vital signs to check your health
- Pregnancy test (if you can become pregnant)
- Review of ongoing or new medications
- Self-report questionnaires about your mood, stress, pain, drug cravings, or withdrawal symptoms
- Cognitive Behavioral Therapy to help support your participation in the study

- Start study medication in Induction Phase (sublingual medication for 2-3 days)

Starting Injectable Medication:

Once the study clinician decides that you are tolerating the study medication and the Induction is successful, you will start the injectable medication. During this medication phase you will be expected

to return to clinic once more in Week 1 for your first injection, then twice a week for the rest of the medication phase, for a total of approximately 24 visits over a 12-week period. The study medication should be the only treatment you receive for substance use disorders while in the study.

Depending on which group you are assigned to, researchers will inject BUP-Inj or PBO-Inj under the skin over your stomach (abdomen). You may see or feel a small bump under your skin at the injection site for several weeks. Do not rub against or massage the injection site.

Week 1, Second Visit (~2hrs):

- Pregnancy test before you get an injection of study medication
- Start injectable study medication and make sure you feel ok as you receive the medication
- Self-report questionnaires
- Interviews such as Timeline Followback to assess your substance use
- Urine sample to test for drugs

- Review of side effects and medications

Week 2, 3, 4 Visits (~2hrs total each week):

- Self-report questionnaires
- Interviews such as Timeline Followback to assess your substance use
- Vital signs to check your health
- Urine sample to test for drugs
- Injection site check to make sure everything went ok after getting the injection (Week 2)
- Review of side effects and medications
- Cognitive Behavioral Therapy to help support your participation in the study

Week 5, 9, 12 Visits (~3-4hrs total each week):

- Injectable study medication (projected for first visit of the week during Weeks 5 and 9)
- Pregnancy test before you get injections of study medication and at the end of the medication phase
- Blood draw to check your health (Week 12), how much study medication is in your system, test for HIV and Hepatitis C (Week 12), storage for later testing at the UTSW Repository (Week 12), and, if you agree, for the NIDA genetic sample (Week 5).
- Self-report questionnaires
- Interviews such as Timeline Followback to assess your substance use
- Urine Sample to test for drugs and common infectious diseases (Week 12)
- Injection site check (projected for next visit after injection)
- Review of side effects and medications
- Cognitive Behavioral Therapy to help support your participation in the study
- Vital signs to check your health
- Physical exam and ECG to make sure you are well after taking the medication (Week 12)

Week 6, 7, 8, 10, 11 Visits (~1-2hrs total each week):

- Self-report questionnaires
- Interviews such as Timeline Followback to assess your substance use
- Vital signs to check your health
- Urine Sample to test for drugs
- Review of side effects and medications
- Cognitive Behavioral Therapy to help support your participation in the study

If you become incarcerated at any point during the study, you will no longer be given the study drug. The researchers may still arrange research visits and any needed assessments and procedures the institution will allow to be completed.

Follow-Up Phase (Week 13-16):

During the Follow-Up Phase, you will no longer be taking the study medication. The follow up visit will occur approximately four weeks after the end of the medication phase or if you stop the study early. This visit will take place at the clinic and will involve the following procedures:

Follow-Up Visit Week 16 (~1.5hrs):

- Self-report questionnaires
- Interviews such as Timeline Followback to assess your substance use
- Vital signs to check your health
- Urine sample to test for drugs
- Review of side effects and medications
- Pregnancy test (if you can become pregnant)

OPTIONAL GENETIC TESTING

As part of the study, you have the option to decide whether research can be done with your blood samples that involves genetic testing. The genetic testing would be done from blood stored at the UTSW Repository and at the NIDA Genetics Consortium Repository (a facility where genetic material can be stored safely) to see whether your genetics relates to how you do in treatment and in this research study. If you agree, study staff will collect additional tubes of blood at one of your scheduled blood draws. You will not have another needle stick for the collection of this blood. This genetic testing is only for research. It is not clinical genetic testing, which means the results will not be available to you and won't tell you anything about your health. If you would like such clinical genetic testing, we can refer you to a service that does it.

Your samples will be de-identified, which means that your name or other identifying information will not be connected to it, only a code number. Your DNA may be used not only for this study, but for other research studies in the future.

Below is a list of terms and abbreviations specifically related to genetics studies:

DNA: DNA is the material inside cells that carries genetic information.

Genetics: Genetics is a term for the study of heredity, or how certain traits are passed down from parents to their biological children

Genes: Genes are the fundamental units of heredity and are responsible for how certain traits are passed down from parents to their biological children. Genes are composed of DNA and are found in all cells of the body.

Genetic Material: Genetic material refers to DNA, blood components, and cells that are extracted from your blood and used for genetic research.

Repository: A repository is a facility where genetic material such as DNA, blood components, and cells can be deposited for storage or safekeeping.

Traits: Traits are characteristics that you may inherit from your family members. Traits may be passed down from generation to generation. Examples of traits are height, eye color, and susceptibility to certain diseases.

Your blood contains DNA. DNA makes up the genes that serve as the "instruction book" for the cells in our bodies. By studying genes, researchers can learn more about diseases such as cancer. There are many different types of genetic tests. The testing on your blood samples might include genetic testing called whole genome sequencing (WGS). WGS looks at all the known genes in your cells. This type of testing can provide useful information to researchers. It can also present risks if the test results became known to others, for example you could have problems with family members or insurance companies. There is also a risk that these test results could be combined with other genetic information to identify you.

Will my samples be stored for future use?
Samples stored at UTSW Repository will be stored until the end of the study. Samples stored at the NIDA Genetics Consortium Repository will be stored for an unlimited amount of time, Genetic material (DNA, blood components and cells) will remain frozen at the central repositories and will be tested in future genetics studies. From the frozen cells, researchers may create a living tissue sample called a “cell line.” This cell line provides an unlimited supply of genetic material for future studies; therefore, you will not have to provide any additional blood samples. Future research on your sample may include WGS. The researchers will keep your samples until they are all gone, become unusable, or until the researchers or Sponsor decide to discard the samples. If your samples remain stored beyond your lifetime, your samples will be used as described in this document.

Will the results of research tests be reported to me?
Knowledge of how genes and other factors affect health and disease is gathered by studying groups of people. This study and other genetics studies are not meant to test your individual medical status. Therefore, neither you nor your medical provider will be given the results of the research on your genetic material. However, the researchers will share what they learn with other health professionals and scientists through research publications. If you have questions about whether any genetic tests would be useful to you, please ask your medical provider or health professional.

Will my genetic information be kept confidential?
To protect your privacy, your blood samples will have only a code number that is different from your study code number to identify it. Researchers at this site and the study’s Data and Statistical Center

(DSC) and Clinical Coordinating Center (CCC) will have the code numbers that connect your genetic information to your identifying information. The DSC and CCC are run by Emmes. The genetics researchers will not have access to the link between your identifying information and your code number. At no time will your name or address or any other identifying information be released for research purposes. We are doing everything possible to prevent anyone outside the study from learning your private genetic information.

End of Optional Genetic Testing Section

Retention of Blood Samples for Future Research

Some or all your blood samples may also be kept and used for up to 15 years. This will allow for scientific research to be done in the future as new discoveries are made. The Sponsor will ensure that your samples are kept secure. You can withdraw your consent for your samples to be used for future research. In this case your samples will be destroyed only after they are no longer needed for the main study. You will need to tell the study staff that you are withdrawing your consent for your samples to be used for future research. This will not affect your access to the care, medicine, and equipment you would otherwise be getting. This can be done at any time and for any reason.

To protect your privacy, your blood samples will be labeled with the study number and your participant number. No personal identifiers are used (such as name, initials, social security number). The scientists doing the research will not know your identity.

Your blood samples may also be shared with research partners for scientific research purposes. Your blood samples will not be sold, loaned, or given to any other independent groups for their own use. Research partners working with the Sponsor are not allowed to share blood samples with anyone who is not authorized by the Sponsor. The Sponsor will manage what is done with your blood samples.

You will not be paid for any use of your blood samples, results, or inventions made from research on them. You are providing your blood samples, for use by the Sponsor. The Sponsor (and research partners, where applicable), will own the use of results, treatments, or inventions that can be made from this research.

What do I have to do while in the study?

While you are in the study you **must**:

- Give correct information about your health history, substance use, and health conditions
- Tell the study clinician/staff about any changes to your medicines or drugs you may take
- Tell the study clinician/staff about any health problems you have during the study
- Come to all study visit appointments
- Complete all required study questionnaires
- Comply with study medication administration per the study schedule
- Not take part in any other medical research studies
- Not take any other medications or remedies unless the study clinician/staff has approved them beforehand, including prescription and over-the-counter drugs such as vitamins and herbs

Could your participation end early?

There are several reasons why study staff may need to end your participation in the study, including:

- The researcher believes that it is not in your best interest to stay in the study
- You become ineligible to participate
- Your health condition changes, and you need treatment not allowed while you are in the study
- You do not follow instructions from the study staff
- The study is stopped

Can I change my mind about participating?

Yes, you can agree to be in the study now and change your mind at any time and for any reason. You can withdraw from the study without any penalty or loss of benefits from your regular care with your doctors. You can talk to the study clinician and study staff first before making this decision.

Please be aware that if you become incarcerated while participating in this study, your decision to participate in this study will not affect your sentence, parole, or probation. Your participation cannot be used by any prisoner authorities, in any manner, to affect your conditions at the institution where you are held. If you stop participating, your sentence, parole, or probation will not be affected.

What happens if I stop the study early?

If you stop the study early, the study clinician/staff will ask that you come for a final follow-up visit to have final evaluations. This is to make sure that you are in good health. This information will be added to your study record.

If you stop the study early and withdraw your consent at any time, you agree not to limit the use of your study information collected through your last visit. The Sponsor will not collect any new information from you for any parts of the study from which you have withdrawn. Your collected blood samples will continue to be analyzed as described in this form unless you specifically ask for your blood samples to be destroyed. This is to protect the quality of the study.

Can I take the study medication after the study is over?

After the study is over, the Sponsor will not continue to provide you with the study medication. Your study clinician and study staff will discuss your future medical care options with you.

What other treatments are there outside of this study?

Instead of taking part in this study, you may choose other alternative treatments.

There are no FDA-approved medications for methamphetamine use disorder, but other non-drug treatments are available, such as behavioral therapy.

There are medications that are available to treat opioid use disorder.

The study clinician will discuss with you and inform you of alternative treatment options.

What about my current medications?

You must tell the study clinician/staff about all prescription and over-the-counter medications you take, including vitamins and herbs. Some medications are not allowed during the study. The study clinician will tell you if this applies to you. No medications will be stopped solely for the purpose of making you able to enroll in this study. You should not stop taking any of your current medications unless your doctor tells you to do so.

You must also tell the study clinician all treatments (including psychotherapy) you are using for your methamphetamine use. You should also disclose any medical conditions you suffer from such as high blood pressure, diabetes, high cholesterol, heart disease etc. Also, if anything changes with your medical history you should inform the study staff.

Clinically Relevant Results:

It is possible that tests done as part of this study will give information about you that was previously unknown, such as disease status or risk. You will be told about any clinically relevant test results. Clinically relevant means that you may be at risk for a serious illness known at the time of testing to be treatable and it can be confirmed. In that case, we will attempt to notify you using the contact information you have provided. There may also be test results that we have to tell you and other agencies about as required by law. You may decide now that you do not want to be notified about these test results; you can change your mind about this decision at any time by talking to the study staff.

Please initial below as to whether or not you would like to be notified of these clinically relevant test results.

_____(initial here) **Yes**, please notify me of any clinically relevant test results found from this research.

_____(initial here) **No**, please **do not** notify me of any clinically relevant test results found from this research, except as required by state or local laws or site policies.

What are the risks of participation in the research?

Risks from the Investigational Medication

All medications can cause side effects; the extent to which this occurs differs. There are risks to taking part in this study. You may have side effects while on the study medications. Side effects from this treatment will usually go away soon after you stop taking the medication; however, in some cases, side effects can be long lasting.

Everyone taking part in the study will be watched carefully for any side effects and receive blood testing to make sure that the medication does not cause any damage. However, the clinicians don't know all the side effects that may happen. You should talk to your study clinician about any side effects or other problems that you have while taking part in the study.

Side effects can range from mild to serious. Serious side effects are those that may require hospitalization, are life threatening or fatal (could cause death). The frequency that people feel a certain side effect can range from many (likely), few (less likely) or only one or two (rarely).

Injection site reactions have been the most common side effects associated with BUP-Inj. Other risks and side effects related to BUP-Inj include those that are:

Likely, some may be serious
In 100 people, approximately 21 – 25 people may have:

- Gastrointestinal distress, like nausea, vomiting, or constipation
- Fatigue
- Injection site reactions, including pain, discomfort, erythema, or itching

Less Likely, some may be serious
In 100 people, approximately 4 – 20 people may have:

- Changes in liver enzymes
- Headache, sedation, tiredness or dizziness

Rare and serious
In 100 people, approximately 1 or less may have:

- Severe injection site itching and irritation
- Adrenal insufficiency (dizziness, low blood pressure)
- Severe allergic reaction (anaphylaxis)
- Liver injury (jaundice, where the skin or white part of your eyes turns yellow; dark urine; light stool color; decreased appetite; stomach/abdomen pain; confusion; or nausea

BUP-Inj may block the effects of opioid pain medications. If you need medications for pain relief while on this study, it is important that you tell your doctor that you are in a study and may be on BUP-Inj. BUP-Inj will not affect response to non-opioid pain medications such as aspirin or acetaminophen.

If you receive BUP-Inj, you will be physically dependent on BUP at the end of this study. If you have side effects, we can stop giving you injections but it will take a while to wear off. You may test positive for BUP for a year or more.

The medication used in the Induction, Suboxone™ (sublingual BUP, sublingual buprenorphine), contains the same medication in the BUP-Inj, so the risk and side effects are very similar. Suboxone™ also contains Naloxone which can also cause some of the same side effects, such as gastrointestinal distress, nausea, and vomiting. Dental problems, including tooth decay, cavities, oral infections, and loss of teeth, can occur with the use of transmucosal buprenorphine (e.g., buprenorphine tablets and films that dissolve in the mouth, such as sublingual buprenorphine) and can be serious. These dental problems have been reported even in patients with no history of dental issues. Please discuss any dental concerns with your study team.

It is important that you take the sublingual Suboxone™ exactly as instructed by the study clinician and make sure that you keep it in a safe place where you are the only person who can access it. Many of these side effects can be managed with other medications that can be provided by study staff.

There is a risk of withdrawal from sublingual BUP or BUP-Inj if you stop the medication at any point. There is also a risk of withdrawal if you are dependent on full agonist opioids, because BUP is only a partial agonist. If you feel any agitation, muscle aches, insomnia, nausea, or abdominal cramping, those symptoms will be treated with appropriate medications. Please contact study staff if you feel any discomfort.

There are also some dangerous risks for interactions of sublingual BUP or BUP-Inj with some medications that you may take. **Life-threatening respiratory depression (breathing difficulty), death, or serious harm can happen due to overdose or toxicity if you take anxiety medicines or benzodiazepines, sleeping pills, tranquilizers, muscle relaxants, sedatives, antidepressants, or antihistamines, or drink alcohol during treatment with Sublocade™ (BUP-Inj) or Suboxone™ (sublingual BUP).** It is very important to not use these substances while in the study and to tell the study staff and study clinicians all the medications and drugs that you take for any reason.

BUP can be abused in a manner like other opioids so there are risks for becoming dependent on BUP; however, the risks for untreated methamphetamine use or opioid misuse are believed to be far more serious. You will be carefully monitored to make sure that your dependence on opioids does not become more of a problem. If you become more dependent on opioids, you will be referred to clinical care. For more information about risks and side effects, ask one of the study staff.

Both BUP-Inj and PBO-Inj injections will be performed using safe and sterile techniques but may cause pain, tenderness, hardening, damage of body tissues, swelling, redness, bruising, itching, or infection at the injection site. The injection site will be monitored after each of the injections. You should report any injection site reactions, such as pain, redness, or swelling, immediately to study staff. The medication will be injected into the fat layer underneath the skin. If the medication is injected by mistake into a muscle or into the middle layer of the skin, there may be a more serious injection site reaction. If this happens, you will receive the appropriate treatment and care. We will treat any pain you feel with a non-opioid analgesic whenever possible. If treatment of your pain requires opioid therapy, we will monitor you closely.

Throughout this study, you will be carefully monitored for side effects. Please contact your study clinician as soon as you feel any side effects at home. There may be risks with the use of this new medication that are not yet known. Sometimes during a study, the Sponsor may learn new facts about the study medication. It is possible that this information might make you change your mind about being in the study. If new information is discovered, study staff will tell you about it right away.

Genetic Informational Risks

This research study includes optional genetic testing. Human blood contains genes that determine many of a person's physical characteristics, such as the color of eyes and hair. In some cases, genetic testing of blood can be used to indicate a risk for the development of certain diseases. Genetic information is unique to each individual and there is a risk that these test results could be combined with other genetic information to identify you. It could also potentially be used to

discover possible changes in a person's future health status or life expectancy, or that of his/her children and family members.

Releasing this information to you could cause psychological distress, anxiety, or family problems. Releasing this information to others, like including it in your medical record, could lead to discrimination, or make it hard to get or keep disability, long-term care, or life insurance. These risks would occur if your information were mistakenly released. The measures being taken to protect your privacy are discussed below and make this possibility unlikely.

Even though the results of genetic testing may not be linked to you, it is possible that people of your ethnic background may be found to be at more risk for certain diseases based on future genetic research and this information might harm you in the future as a member of the group. Also, there may be unknown risks of genetic testing in the future.

As technology advances, there may be new ways to access and trace information back to you (or your close biological relatives) that we cannot predict. The Sponsor will use reasonable measures within its control to safeguard your information. Even though no one would be able to know just from looking at your genetic data that the information belongs to you, there is a potential risk to you and to your family. This is because your genetic information is unique to you. Therefore, there is a chance that someone could trace the information back to you or your close biological relatives. This could happen if you (or your biological relatives) had DNA testing done another time that could be matched against your results from this study. The risk of this happening is small but could grow in the future.

Risk of Psychological Stress

Some of the questions we will ask you may make you feel uncomfortable. You may refuse to answer any of the questions, take a break, or stop your participation in this study at any time.

You may feel anxious or sad after receiving the results from your HIV test. A counselor will be available if you want to talk about how you are feeling.

Risk of blood draw

There are minor risks and discomforts associated with blood draw. The risks of a blood draw include pain, bruising, fainting, and in rare cases, infection.

Risk of loss of confidentiality

Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Are there Risks related to withdrawing from the study?

If you decide to withdraw from this treatment early, please discuss with the local site study clinician. The study clinician may ask you to complete treatment withdrawal procedures at a final treatment visit. Because BUP-Inj stays in your system for over a month after you receive your injection, there may be a risk to you if you do not understand how the medication can affect you after receiving it.

However, you may choose to not complete the final withdrawal procedures. You will need to formally communicate your wishes to withdraw to your Site Principal Investigator.

Reproductive Risks

Concerns for sexually active men and women:

You should not become pregnant while taking part in this study because we do not know how the study drugs/procedures could affect a fetus, if a woman becomes pregnant during the study. It is important that you talk to your study clinician about avoiding pregnancy during this study. If you think you might have become pregnant while you are in this study, you must tell one of the study clinicians right away so that you can stop receiving study medication, and to discuss management of the pregnancy and the possibility of stopping the study. There is some evidence that both female and male fertility may be reduced by taking opioid medications like the study medication.

Birth control and pregnancy during the study

If you are a woman able to get pregnant:

- Taking part in the study might harm your unborn child or breastfed baby
- You cannot take part in this study if you are pregnant or breastfeeding a child
- Women must agree to use highly effective methods of birth control throughout the study and for 4 months after the last injection

Examples of highly effective methods of birth control that can be used while in this study include:

- Oral contraceptives (like “the pill”) in combination with barrier method
- Contraceptive injections or patches in combination with barrier method
- Intrauterine devices in combination with barrier method
- Male partner sterilization
- Abstinence (avoiding sexual intercourse)

The type of birth control you use must be discussed with the study clinician before you begin the study. The study clinician must approve the method you use before you can enter the study.

If you get pregnant during the study, you must tell the study clinician immediately. You will have to stop taking the study medication. Your child might experience Neonatal Opioid Withdrawal Syndrome (NOWS), which can be treated. The study clinician will advise you about your medical care and will ask you to allow him/her to collect information about your pregnancy and the health of your baby. The study clinician may share this information with the Sponsor and the Institutional Review Board/Ethics Committee that monitors the trial.

Risks to babies who are being breastfed:

Women who are breastfeeding cannot take part in this study because we know that some of the study medication can enter the breast milk and can affect the nursing child.

Are there risks if you also participate in research or other investigational research studies?

Being in more than one investigational research study at the same time, may increase the risk to you. It may also affect the results of the studies. You should not take part in more than one investigational study without approval from the study staff.

For more information about risks and side effects, ask one of the study clinicians or study staff.

How could you or others benefit from your taking part in this study?

Taking part in this study may help you stop or reduce your drug use and/or improve the symptoms associated with substance use disorders. If you receive BUP-Inj, you may be protected from having effects from an overdose (from opioids or fentanyl) while in the study. However, there is no guarantee or promise that you will receive any benefit from this study. During the study, your condition may stay the same or get worse. Your participation may help future patients have other treatments for stopping or reducing methamphetamine use.

What other options are there to participation in this study?

Instead of taking part in this study, you may choose other alternative treatments. The study clinician will discuss and inform you of available alternative treatment options.

Will there be any payments for participation?

Please see your Part 2 of the consent form for details regarding compensation and your method of payment.

How will your records be kept confidential?

Information we learn about you in this study will be handled in a confidential manner, within the limits of the law. If we publish the results of the study in a scientific journal or book, we will not identify you. The Institutional Review Board and other groups that have the responsibility of monitoring research may want to see study records which identify you as a participant in this study.

Certificate of Confidentiality:

To help us further protect your information, this research is covered under a Certificate of Confidentiality from the U.S. Department of Health and Human Services (HHS). This Certificate adds protections for research information that identifies you and will help study staff protect your privacy.

With this Certificate of Confidentiality, the study staff cannot be forced to disclose information that may identify you in any judicial, administrative, legislative, or other proceeding, whether at the federal, state, or local level. There are situations, however, where we will voluntarily disclose information consistent with state or other laws, such as:

- to HHS for audit or program evaluation purposes;
- information regarding test results for certain communicable diseases to the State's Department of Health Services, including, but not limited to HIV and Hepatitis;

- if you pose imminent physical harm to yourself or others;
- if you pose immediate mental or emotional injury to yourself;
- if the study staff learn that a child has been, or may be, abused or neglected; or
- if the study staff learn that an elderly or disabled person has been, or is being, abused, neglected or exploited.

The Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about your involvement in this research study. In addition, the study staff may not use the Certificate to withhold information about your participation in this research study if you have provided written consent to anyone allowing the study staff to release such information (including your employer or an insurance company). This means that you or your family must also actively protect your privacy.

A Certificate of Confidentiality does not represent an endorsement of this research project by the Department of Health & Human Services or any other Federal government agency.

How will my information and/or samples be used?

With appropriate permissions, your blood samples and collected information may also be shared with other researchers here, around the world, and with companies.

By agreeing to participate in this study, your information or blood samples could be used for future research studies or sent to other investigators for future research studies without additional consent from you. The information that identifies you will first be removed from your information or blood samples. If you do not want your information or blood samples to be used for future research studies without your consent, you should not participate in this study.

De-identified data (which cannot be used to identify you) from this study will be available to researchers on another website, https://datashare.nida.nih.gov/ after the study is complete and the data analyzed. The primary outcome(s) publication for the full study will also be included along with study underlying primary data in the data share repository, and it will also be deposited in PubMed Central http://www.pubmedcentral.nih.gov/. These websites will not include information that can identify you. You can view these websites at any time.

Will you be contacted for future studies?

You may be contacted for future studies if the researchers think you may qualify, but you are under no obligation to participate in a new study. Participation in any additional study is entirely voluntary and refusing to volunteer for an additional study will not affect your participation in the primary study.

Who can you contact if you have questions, concerns, comments or complaints?

Please see Part 2 of the consent form for contact information for your study site. If you have questions now, feel free to ask your study team. If you have additional questions, concerns, comments or complaints later or you wish to report a problem which may be related to this study please contact the individuals listed in Part 2 of the consent form.

Title of Study: NIDA CTN Protocol 0110 Randomized, double-blind, placebo-controlled trial of monthly injectable buprenorphine for methamphetamine use disorder

The University of Texas Southwestern Medical Center Human Research Protection Program (HRPP) oversees research on human subjects. HRPP and Institutional Review Board (IRB) representatives will answer any questions about your rights as a research subject, and take any concerns, comments, or complaints you may wish to offer. You can contact the HRPP by calling the office at 214-648-3060 or e-mail at HRPP@UTSouthwestern.edu located at 5323 Harry Hines Boulevard, Dallas, Texas, 75390-8843.

Concise Summary

This is a research study to find out if a drug called Sublocade™ is safe and effective for treatment of MUD for people who also use opioids.

Sublocade™ is given via an injection in your stomach at the clinic. You will have tests, exams, and procedures while in the study. Each clinic visit will last 1-4 hours but some may be shorter or longer. Study medication will be given during Weeks 1, 5, and 9. After each injection, you will be evaluated, and you may continue to receive study medication if you have had no bad side effects.

There are risks to this study medication that are described in this document.

If you are interested in learning more about this study, please continue reading Part 2.