Cover Page

Principal Investigator: **Sandra D. Comer, PhD.**

IRB #**: 7173**

NCT#: **02692157**

Study: **NT-814: EVALUATION OF ITS ABILITY TO ALTER THE ABUSE LIABILITY OF OXYCODONE IN AN EXPLORATORY CLINICAL STUDY**

Study Protocol Date: **February 18, 2016**

New York State Psychiatric Institute

Institutional Review Board

February 18, 2016

To: Dr. Sandra Comer

From: Dr. Edward Nunes, Co-Chairman
Dr. Laurence Greenhill, Co-Chairman

Subject: **APPROVAL NOTICE**

Your protocol #7173 entitled: **NT-814: EVALUATION OF ITS ABILITY TO ALTER THE ABUSE LIABILITY OF OXYCODONE IN AN EXPLORATORY CLINICAL STUDY** (version date 02-18-16) and consent form have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **February 18, 2016 to February 7, 2017** (Reviewed by the Full Board on 02-08-16).

Consent requirements:

☐ Not applicable

X 45CFR46.116(d) waiver or alteration of consent for the telephone interview

X Signature by the person(s) obtaining consent is required to document the consent process.

☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: **X** No ☐ Yes

Field Monitoring Requirements: ☐ Routine **X** Special: ***Reports on each Holter reading, on a reading-by-reading basis, for the first 5 participants.***

✓ Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.
✓ A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.
✓ Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.
✓ All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.

Enc: CFs (2), recruitment material, HIPAA form

CC: RFMH Business Office (DA037842)
CU Grants & Contracts
CUMC-IRB

EN/LG/Scr

Signed copy on file at IRB

Protocol Title:
NT-814: Evaluation of Its Ability to Alter the Abuse Liability of Oxycodone in an Exploratory Clinical Study

Version Date:
02/18/2016

Protocol Number:
7173

Clinic:
Opioid Research Laboratory

First Approval:
02/18/2016

Expiration Date:
02/07/2017

Principal Investigator:
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Co-Investigator(s):
Jeanne Manubay, MD
Jermaine Jones, PHD
Shanthi Mogali, MD
Verena Metz, PHD

Research Chief:
Herbert Kleber, MD

Cover Sheet

Choose from the following that is applicable to your study
I am submitting a new protocol

Division & Personnel

Division

What Division/Department does the PI belong to?
Substance Abuse
Within the division/department, what Center or group are you affiliated with, if any?
Opioid Research Laboratory

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York

State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

Tanya (Tatiana) Ramey, MD PhD
Medical Officer, Division of Pharmacotherapies and Medical
Consequences of Drug Abuse
National Institute on Drug Abuse

Dr Ajay Duggal, (MB ChB, MRCP, Dip Pharm Med)
CMO NeRRe Therapeutics

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Collection of Biological Specimens
✓ Medication Trial
✓ Biological Challenge Procedure
✓ Administration of Substance of Abuse
✓ Use of Investigational Drug or Device

Population

Indicate which of the following populations will be included in this research

✓ Medically and Psychiatrically Healthy Subjects
✓ Substance Users

Research Support/Funding

Will an existing internal account be used to support the project?
Yes
Describe internal account
RFMH
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
No

Who is the PI of the grant/contract?
Levin, Frances, MD
Select one of the following
The grant/contract is currently funded
Source of Funding
Federal
Institute/Agency
NIDA
Grant Name
Shared Pharmacotherapeutic Strategies for Cannabinoid and Opioid Use Disorders
Grant Number
DA037842
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
To
Name institution(s)
Columbia University

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
Yes

Lay Summary of Proposed Research

Lay Summary of Proposed Research
Healthy adult men, aged 21 to 59 years, who abuse opioids and are physically dependent on them will be recruited to participate in a study to examine the ability of NT-814, a neurokinin (NK) antagonist at the 1 and 3 receptor subtypes, to alter the abuse liability of oxycodone. After participants complete the screening process, they will be scheduled for admission onto the General Clinical Research Unit on 5-South where they will reside during a 13-week study. During Week 1, participants will be detoxified from opioids. During Week 2 after the detoxification period, participants will be randomized to receive one of four maintenance doses of NT-814 (0, 50, 100, or 200 mg). During Weeks 3-4, active (Week 3) and then placebo (Week 4) oxycodone will be available. During Weeks 3-4 on Mon morning, participants will be given $10 and a sample dose of intranasal (IN) oxycodone (0 or 10 mg). The sample dose/$ will be available during subsequent choice sessions on Mon-Thu. On Fri, participants will be given $10 and 10 mg IN oxycodone

during a sample session (the oxycodone dose on Fri morning is always active). Following the sample session on Fri, participants will complete a cue exposure session during which they will be presented with neutral cues followed by drug cues. This procedure will allow the investigators to determine whether the study medication affects reactivity to drug-related cues. After the cue exposure session on Fri, participants will be given the opportunity to self-administer drug and/or money under a progressive ratio procedure. To summarize, Weeks 2, 5, 8 and 11 will be stabilization weeks (on the 0, 50, 100, and 200 mg doses of NT-814 administered in random order) and Weeks 3-4, 6-7, 9-10 and 12-13 will be test weeks under each of the NT-814 maintenance doses. At the conclusion of the study, participants will be given an exit interview during which the study will be described. Those who are interested in treatment for their drug use at the end of the study will be offered referrals to studies at our Substance Treatment and Research Service or other treatment providers.

Background, Significance and Rationale

Background, Significance and Rationale
Results from the 2011 National Survey on Drug Use and Health revealed that the number of new initiates to non-medical use of opioid analgesics exceeded that of cocaine, methamphetamine, and benzodiazepines, and was second only to marijuana (Substance Abuse and Mental Health Services Administration (SAMHSA, 2012)). Furthermore, anecdotal reports suggest that many individuals have shifted their abuse of prescription opioids to abuse of heroin. Although causality could not be determined, the numbers of heroin-use initiates, heroin users, and heroin-dependent individuals have increased over the past 10 years (Muhuri et al., 2013). Fortunately, different medication approaches are available and have been used successfully for treating opioid use disorders (OUD), including methadone, buprenorphine (Johnson et al., 1992, 2000; Ling and Wesson, 2003), and naltrexone (Comer et al., 2006; DeFulio et al., 2012; Everly et al., 2011; Krupitsky et al., 2011, 2012, 2013). However, despite the clear clinical utility of these medications, approximately 40-50% or more of the patients who initiate treatment with them relapse and/or drop out of treatment within 6 months (DeFulio et al., 2012; Krupitsky et al., 2012; Soyka et al., 2008). Thus, there is substantial need for improving the effectiveness of these medications, given the high relapse rates. Preclinical studies have shown that NK-1 receptor antagonists attenuate the acute positive reinforcing effects of heroin in rats (Barbier et al., 2013) and the rewarding effects of morphine in mice (Robinson et al., 2012). Although early clinical studies showed that aprepitant, an NK-1 antagonist, may increase the abuse potential of opioids (Jones et al., 2013; Walsh et al., 2013), the studies were conducted under acute dosing conditions so it is unknown whether chronic treatment with an NK-1 antagonist may be more beneficial in reducing the abuse liability of opioids. The purpose of the present study is to evaluate whether maintenance on NT-814, a potent, insurmountable antagonist at human NK-1 and NK-3 receptors, will be useful for treating OUD using our laboratory model.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
Specific Aim 1: Assess the ability of NT-814 to alter oxycodone self-administration (average percentage of drug choices and progressive-ratio breakpoint values) and positive subjective responses (e.g., visual analog scale ratings of "I feel high," "I like the choice," "I feel a good drug effect"). Hypothesis 1: NT-814 will be

superior to placebo in reducing oxycodone's reinforcing and positive subjective effects. **Specific Aim 2:** Assess the ability of NT-814 to affect opioid craving (ratings of "I want opioids") and physiological responses (galvanic skin response, skin temperature, and heart rate) to drug cues. Hypothesis 2: NT-814 will be superior to placebo in reducing drug craving, as well as physiological and subjective reactivity to drug cues.

Description of Subject Population

Sample #1

Specify subject population
Healthy individuals with moderate-severe OUD who are not seeking treatment
Number of completers required to accomplish study aims
12
Projected number of subjects who will be enrolled to obtain required number of completers
35
Age range of subject population
21-59 years

Gender, Racial and Ethnic Breakdown
Sex: All of the enrolled participants will be male. Race and ethnicity: We anticipate that of the enrolled participants, approximately 40% will be African-American, 30% will be Caucasian, and 30% will be Latino, with a negligible percentage of Asian, Multi-racial, or Other racial groups.
Description of subject population
The participants in this study will be male, healthy (according to medical and psychiatric examinations), and not seeking treatment for their opioid use. All participants will meet DSM-V criteria for moderate-severe opioid use disorder.

Recruitment Procedures

Describe settings where recruitment will occur
All in-person screening and assessments (drug interview, SCID, psychiatric evaluation, medical examination, and naloxone challenge) will occur within the facilities of the Substance Use Research Center (SURC), located on the 3rd floor of the NYPSI.
How and by whom will subjects be approached and/or recruited?
1) Initial telephone interviews will be carried out by research assistants and nurses; 2) drug interview and general assessment related to study issues will be conducted by a psychologist; and 3) psychiatric interviews and intranasal dose administrations will be conducted by a physician. Telephone screens will be recorded either electronically or on paper forms.
How will the study be advertised/publicized?
Recruitment is primarily through word-of-mouth and advertisements in local newspapers such as the Village Voice and AM New York, as well as electronic media (e.g., Facebook, Google, websites that drug users

frequent such as Bluelight and Erowid).
Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
No

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement

6107: Prescription Opioid Effects in Drug and Non-drug Abusers (PI: Sandra Comer, Ph.D.); 6021: Effects of Ibudilast (AV411), a Glial Cell Activation Inhibitor, on Oxycodone Self-administration Among Opioid Abusers (PI: Sandra Comer, Ph.D.); 6723: Risks and Benefits of Overdose Education and Naloxone Prescribing to Heroin Users (PI: Sandra Comer, Ph.D.); 6883R: Reinforcing Effects of Intravenous Buprenorphine versus Buprenorphine/Naloxone in Opioid Abusers (PI: Sandra Comer, Ph.D.)

We will adhere to our Division's policy of requiring a 3-month interval to elapse between the end of one opioid laboratory study and the beginning of another.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Opioid Abusers
Create or insert table to describe the inclusion criteria and methods to ascertain them

1- 21-59 year-old men. Ascertained by: Self-reported age and/or verification with legal identification.

2- Diagnostic criteria for Opioid Use Disorder moderate-severe (304.00) as per DSM V. Ascertained by: Clinical interviews (telephone interview with a research assistant, in-person interviews with psychologists, nurses, physicians, SCID), naloxone challenge test/visual evidence of opioid withdrawal.

3- No current or past diagnosis of schizophrenia, schizoaffective disorder, or other psychotic disorder; bipolar I or bipolar II disorder, or other major mood, psychotic, or anxiety disorder. Ascertained by: Clinical interview with physician or nurse, including a SCID.

4- Physically healthy. Ascertained by: Clinical interview with physician, laboratory tests (urinalysis, blood chemistry, 12-lead ECG), physical examination, self-reported medical history.

5- Able to perform study procedures. Ascertained by: Practice session.

6- Normal body weight. Ascertained by: Weighing participant in the laboratory on a digital scale; participant must have a Body Mass Index < 30 and > 17.5, as well as a total body weight > 50 kg (110 lbs).

7- Current or history of intranasal opioid use. Ascertained by: Clinical interviews (telephone, psychologist, physician).

8- Current use of opioids in amounts and/or frequencies that meet or exceed those used in the proposed study (e.g., 3-4 tablets of a prescription opioid medication per day or 1-2 bags of heroin per day). Ascertained by: Clinical interviews (telephone, psychologist, physician).

9- Must use adequate forms of contraception (e.g. condoms in combination with spermicide). Ascertained by: Clinical interviews (telephone, interviews).

10- Has not participated in another opioid laboratory study within the past 3 months. Ascertained by: Clinical interview, review of laboratory records.

11- Total testosterone in the laboratory normal range (250-1100 ng/dl). Ascertained by: Laboratory testing on blood sample collected between 7am and 10am.

Create or insert table to describe the exclusion criteria and methods to ascertain them

1- Meeting DSM-V criteria for substance use disorder (moderate to severe) on drugs other than opioids, nicotine or caffeine (must be less than 500 mg caffeine daily). Ascertained by: Clinical interview with physician, urine screen, observation.

2- Participants requesting treatment. Ascertained by: Self-report during interview.

3- Treatment with any investigational drug within the last 30 days. Ascertained by: Clinical interview.

4- Participants on parole or probation. Ascertained by: Self-report during interview, criminal background check upon admission.

5- Current or recent history of significant violent or suicidal behavior and/or suicidal/homicidal risk. Ascertained by: Clinical interview (based on current state and history), Columbia Suicide Severity Rating Scale.

6- Cannot read or understand the self-report assessment forms unaided, or cannot comply with the requirements of the study. Ascertained by: Clinical interview, practice session.

7- Elevated liver function tests (i.e., AST and ALT > 2 times the upper limit of normal) or impaired renal function (creatinine within normal limits). If AST and ALT increase to > 3 times the upper limit of normal after beginning study medication, the participant will be withdrawn from the study. Ascertained by: Laboratory tests.

8- Physical disorders that might make participation hazardous such as AIDS, cancer, hypertension (blood pressure > 140/90), uncontrolled diabetes, pulmonary hypertension, arrhythmias, heart disease or any significant cardiac history (structural heart disease, syncope, myocardial infarction, etc.). Please note that participants will be asked about previous visits to a cardiologist, chest pain, or strong palpitations; if these exist, they will be referred to a cardiologist and excluded unless cleared for participation by a cardiologist. Ascertained by: Clinical interview, ECG (baseline ECG must be normal).

9- 12-lead ECG-based repeated demonstration of QTcF > 450 msec at screening. Ascertained by: ECG.

10- Current major Axis I psychopathology other than opioid use disorder (e.g., mood disorder with functional impairment or suicide risk, schizophrenia), that might interfere with ability to participate in the study. Ascertained by: Clinical interviews.

11- Sensitivity, allergy or contraindication to opioids, NK antagonists or similar compounds. Ascertained by: Clinical interviews.

12- Current use of drugs that inhibit CYP3A4 (including but not limited to atazanavir, amiodarone, cimetidine, clarithromycin, diltiazem, erythromycin, fluvoxamine, indinavir, itraconazole, ketoconazole, mibefradil, nefazodone, nelfinavir, ritonavir, troleandomycin, and/or verapamil), induce CYP3A4 (including but not limited to rifampin, rifapentine, rifabutin, phenytoin, phenobarbital, carbamazepine, oxcarbazepine, and/or St. John's Wort), and known P-gp inhibitors (including but not limited to amiodarone, atorvastatin, azithromycin, boceprevir, bromocriptine, captopril, carvedilol, clarithromycin, cobicistat, conivaptan, cyclosporine, diltiazem, doxazosin, dronedarone, felodipine, fluvastatin, indinavir, itraconazole, ketoconazole, linagliptin, lopinavir and ritonavir, lovastatin, meperidine, methadone, nelfinavir, nicardipine, pentazocine, progesterone, quercetin, quinidine, ranolazine, reserpine, ritonavir, saquinavir, simeprevir, simvastatin, suvorexant, tacrolimus, tamoxifen, telaprevir, ticagrelor, verapamil). Use of warfarin and/or non-steroidal anti-inflammatory drugs. Ascertained by: Clinical interviews.

13- Unwillingness to refrain from eating grapefruit, grapefruit juice, Seville oranges,and pomelos. Ascertained by: Clinical interviews.

14- Planning to conceive within 6 months of study participation. Ascertained by: Clinical interviews.

15- HIV positive.

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
Yes

Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
No
Describe procedures used to obtain consent during the screening process

Verbal consent to complete the telephone interview will be obtained initially by a research assistant (for which a waiver of documentation of consent is requested). If the participant roughly meets study criteria, he or she will be scheduled for an in-person screening. Once they arrive at NYSPI, participants will sign a screening consent form that will be explained to them by a research nurse, study investigator or physician.

Please note that we will adhere to our Division's policy of requiring a 3-month period to elapse between the end of one opioid laboratory study and the beginning of another.

Describe Study Consent Procedures
A physician will review the participant's screening chart, comparing it to the study's inclusion/exclusion criteria. If all of the criteria are met, the physician will sign the consent form with the participant.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form
✓ Information Sheet

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following
We are requesting a waiver of consent for our telephone screen.
Explain why your research can not be practicably carried out without the waiver or alteration
Participants first respond to study advertisements via telephone.
Describe whether and how subjects will be provided with additional pertinent information after participation
If participants meet the initial inclusion/exclusion criteria based on the telephone interview, they will be invited to the laboratory for in-person screening visits where the study procedures will be explained again in detail by multiple staff members.

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Manubay, Jeanne, MD

Mogali, Shanthi, MD
Tindall, Claudia
Urban, Nina, MD
Vorel, Stanislav, MD
Type in the name(s) not found in the above list
Janet Murray, RN

Study Procedures

Describe the procedures required for this study

Screening: 1) Initial telephone interviews will be carried out by research assistants and nurses; 2) clinical interviews and general assessments related to the study will be conducted by a psychologist; 3) medical examinations and psychiatric interviews will be conducted by a physician; 4) naloxone challenge procedures (described below) will be conducted by a research nurse. Naloxone hydrochloride for injection, obtainable from Hospira (Lake Forest, IL), may be administered to participants in an intramuscular dose of 0.2-3.0 mg prior to admission to confirm opioid dependence (naloxone challenge). Nurses (or physicians) will administer a starting dose between 0.2-0.8 mg i.m., depending on the urine toxicology and the participant's self-reported last use of opioids. Nurses (or physicians) will wait 0-15 minutes to determine if there are observable withdrawal symptoms. If there are none, they will inject an additional 0.4-0.8 mg naloxone, and again wait for 10-15 minutes to determine if there are observable withdrawal symptoms. This process will continue until a score of > 10 on the Wang Test or a total dose of 3.0 mg has been reached. Once withdrawal symptoms are observed, the participant will be give morphine (up to 50 mg orally or 10-30 mg i.m.) to reverse the withdrawal. This procedure typically takes approximately 45 minutes to complete. Alternatively, participants may show observable opioid withdrawal symptoms prior to admission to confirm dependence. Participants (up to N=35 enrolled with N=12 completers) who pass the physiological and psychological screening will be accepted for participation in the study.

Participants (up to N=35 enrolled with 12 completers) who pass the physiological and psychological screening will be accepted for participation in the study. All participants will be admitted to the GCRU on 5-South and detoxified from opioids (please see representative study design in Table 1). During Week 1, participants will be detoxified from opioids and treated for emergent withdrawal symptoms with supplemental medications (e.g., buprenorphine, milk of magnesia, bismuth subsalicylate, prochlorperazine, loperamide**,** clonidine, clonazepam, compazine, ketorolac tromethamine, ondansetron, ibuprofen or acetaminophen, trazodone, and/or zolpidem) until withdrawal symptoms have dissipated, based on physician judgement and using Subjective Opioid Withdrawal Scale (SOWS) scores as a guide. Because numerous participants in previous studies have reported insomnia during similar procedures, oral doses of trazodone or zolpidem will be available on request at bedtime to alleviate the insomnia that may occur. We will offer a standing dose of trazodone only (100 mg), and a prn dose of 5 mg Ambien if participants continue to have problems with insomnia. If a participant has a history of non-response to trazodone, he or she will be offered 10 mg Ambien each night at bedtime. When withdrawal symptoms have dissipated, based on self-report and observer ratings, supplemental medications, with the exception of trazodone or zolpidem, will no longer be available and experimental sessions will begin. During Week 2, participants will begin the stabilization period on oral NT-814 (0, 50, 100, or 200 mg daily). Doses will be administered once

daily at 8pm. NT-814 powder will be over-encapsulated into size 00 gelcaps (50 mg per capsule); placebo capsules will contain lactose powder. Four capsules will be administered at each dosing opportunity in order to maintain the dosing blind. For the placebo daily dose, four lactose-filled capsules will be administered. For the 50 mg daily dose, one 50 mg NT-814 capsule and three lactose-filled capsules will be administered. For the 100 mg daily dose, two 50 mg NT-814 capsules and two lactose-filled capsules will be administered. And for the 200 mg daily dose, four 50 mg NT-814 capsules will be administered.

Participants will continue to be maintained on the first dose of NT-814 during Weeks 3 and 4. On Mon of Week 3, participants will receive experimenter-administered oxycodone (10 mg) and $10 (Tables 1 and 2). They will be told that they have the choice to receive that dose intranasally or money each hr for the next 4 hr and also on Tue-Thu (every hr for 5 hr beginning at 10 am; Choice Session). A simple verbal choice procedure will be used whereby participants will indicate verbally to research staff whether they would like to receive drug or money. Subjective effects will be assessed before, and 5, 15, 30, 45, and 60 min after administration of each choice (drug or money). A dose of 10 mg oxycodone was selected because it produces a moderate level of effect when given intranasally to non-dependent opioid abusers (Middleton et al., 2012), so it should be safe and well tolerated. On Fri, another experimenter-administered dose of oxycodone (10 mg IN) and $10 will be given to the participants. The Fri morning dose will always be active. Drug and neutral cue exposures and oxycodone self-administration will be completed later in the day on Fri. Week 4 will be identical to Week 3 with the exception that IN lactose powder is available on Mon-Thu instead of 10 mg IN oxycodone. Different NT-814 maintenance doses will be tested during Weeks 2-4, 5-7, 8-10, and 11-13 (see Table 1). Please note that slight modifications may be made to the schedule to accommodate holidays, staff illnesses or vacation days, etc.

Participants who are interested in treatment for their drug use at the end of the study will be offered referrals to STARS or other treatment providers. Referrals will be offered by Opioid Laboratory staff (RN, MD, PhD, research assistant) multiple times prior to discharge, as well as by 5-South staff. Arrangements will be made by SURC and/or 5-South staff for those who express an interest in treatment. Participants will return weekly for their study payments for several weeks after study completion. At each of these weekly visits, we will assess participants' interest in treatment and drug use patterns (via self-report and urine drug toxicology). Within 1 week after discharge, we will assess adverse events using the SAFTEE, general health (complete blood count, blood chemistry, urinalysis, blood pressure, heart rate, body weight, ECG), and suicide (Columbia Suicide Severity Rating Scale).

You can upload charts or diagrams if any
Table 1 NT-814 research design.pdf
Table 2.pdf
Table 3 NT-814_Events rev 11Feb16.pdf

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Participants will be withdrawn from the study if they 1) do not comply with unit policies or study procedures, 2) are deemed medically at risk for further study participation (e.g., inability to tolerate the

detoxification at the beginning of the study, complaints of undesirable sexual side effects from the study medication, oxygen saturation < 90% during a laboratory session that does not increase after administration of supplemental oxygen), or 3) express a strong desire to receive treatment for their drug use. All participants who are withdrawn from the study will be offered referral to treatment facilities and STARS. Those participants who are discontinued from study participation because of sensitivity to the respiratory effects of the opioids administered during the study will receive a special de-briefing by the study physician prior to discharge. All participants will be warned of the risks, namely overdose and death, associated with continued opioid use.

Furthermore, as per the FDA's requirement, the safety monitoring, criteria for discontinuing NT-814, and study pausing criteria are the following:

Safety Monitoring Protocol

Oxygen saturation and vital signs will be continuously monitored during experimental sessions

Continuous cardiac monitoring for 24 hours **at baseline (post-detox, pre-NT-814) and** after each dose change (via Holter monitoring) will be performed, in addition to pre-dose EKG and 24 hours post-dose EKG**; participants will also keep a diary of physical symptoms experienced during each of the 24-hr periods of Holter monitoring [Note: the baseline Holter reading by the cardiologist may uncover an arrhythmia that was not apparent during the EKG rhythm strip or by the physical examination or history at baseline. If this is the case, the participant may be discontinued from the study, as per the cardiologist's judgment.]**

Total testosterone testing will occur at baseline, study midpoint and then again at the 1-week follow-up visit

Liver function tests will be performed (at weeks 2, 4, 6, 8, 10, 12, and 1 week follow up)

Blood biochemistry profile (including renal function) will be performed one week after each dose change

Monitoring for signs of dehydration or poor p.o. intake will be performed, including

- Urine specific gravity at each dose change during the active treatment phase
- Body weight daily during the active treatment phase
- Liquid input/output monitoring for 24 hours after each dose change
- Orthostatic vital signs (blood pressure) daily during the active treatment phase
- Monitoring for clinical signs of dehydration daily during the active treatment phase

Criteria for Discontinuing NT-814

Complaints of undesirable sexual side effects from the study medication

Oxygen saturation < 90% during a laboratory session that does not increase after administration of supplemental oxygen or verbal prompts to take a deep breath

AST and ALT increase to > 3 times the upper limit of normal

Moderate-to-severe cardiovascular AEs or SAEs such as ventricular tachycardia or atrial fibrillation

Clinically significant changes in renal function or blood biochemistry profile change from baseline

Moderate-to-severe AEs or SAEs of dehydration (e.g. thirst, changes in frequency of urination, and moderate-to-severe AEs or SAEs of orthostatic hypotension, lightheadedness, syncope, anorexia, vomiting, or apathy)

Weight loss more than 10% from the baseline

Study Pausing Criteria

If two (2) participants are discontinued due to adverse events or serious adverse events related to the study drug, the entire study will be halted and the dosing schedule will be reevaluated

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens

During the screening process and within 1 week following discharge, blood will be drawn for laboratory testing. In addition, a blood sample will be collected during screening and at discharge to monitor testosterone levels. Blood samples also will be collected to measure NT-814 levels approximately 14 days after initiation of each dose level: 16 samples total will be collected for this purpose per person (4 doses (0, 50, 100, and 200 mg NT-814) x 4 sampling points (just prior to dose administration, and 1, 2, and 12 hr after dosing). A total of approximately 160 cc blood will be drawn throughout the study.

Urinalysis will be performed at each screening visit, weekly while participants are inpatient, and during each follow-up visit.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

See Table 3 for events throughout the study.

Screening Instruments
Telephone Interview: 10 min

General Health Questionnaire: 5 min
Medical History Questionnaire: 10 min
Drug History Questionnaire: 10 min
Short Michigan Alcohol Screening Test: 5 min
Beck Depression Inventory: 15 min
Clinical Drug/History Interview: 30 min
Demographic Information (e.g., age, race, ethnicity, gender, marital status, family income, occupation, etc.): 45 min
Self-reported Trauma Assessments (e.g., Life Events Checklist, Modified Sexual Experiences Survey, Trauma Symptom Inventory, Distress Tolerance Scale): 30 min
Physical and Psychiatric Examination including a Mental Status Evaluation: 1 hr
Laboratory Hospital Tests: 2-3 hr
Columbia-Suicide Severity Rating Scale (C-SSRS): 5 min
Structured Clinical Interview for DSM-5: 1-2 hr

Subjective and Performance Tasks and Sleep Assessments
Digit-Symbol Substitution Task: 3 min
Divided Attention Task: 10 min
Subjective Effects Measures*: 5 min
Actiwatch (Philips Respironics): ~10 hr

*Four questionnaires will be used to assess subjective effects during laboratory sessions (see Comer et al., 1999 for details). The first questionnaire is a 26-item visual analog scale designed to assess subjective and physiological effects. The first 18 lines are labeled with adjectives describing mood states ("I feel...alert, anxious, a bad drug effect, depressed, energetic, a good drug effect, gooseflesh, high, irritable, mellow, muscle pain, nauseated, restless, sedated, sleepy, social, stimulated, talkative") and 4 additional lines are labeled with questions about the dose just received ("The dose was potent," "The dose was of high quality," "I liked the dose," "For this dose I would pay..."). Participants also indicate, by making a mark along a 100 mm line, how much they want each of the following drugs: heroin, cocaine, alcohol, and tobacco. Participants rate each item on the visual analog scale from "Not at all" (0 mm) to "Extremely" (100 mm), except for the "For this dose, I would pay" question, which ranges between $0 (0 mm) and $20 (100 mm). The second questionnaire is a 12-item opioid symptom checklist consisting of true/false questions designed to measure opioid effects ("I feel normal," "My skin is itchy," "I feel relaxed," "I feel like I am coasting," "I feel like I am nodding," "I feel high," "I feel sleepy," "I feel drunken," "I feel nervous," "I have a lot of drive," "I feel like I am 'on a soapbox' (need to talk)," "My stomach is turning," and "I am feeling a pleasant sick"). The visual analog scale and opioid symptom checklist together constitute the subjective-effects battery. The third questionnaire is the 16-item Subjective Opiate Withdrawal Scales. Participants rate each item on a scale from 0 to 4, with 0 being "Not at all" and 4 being "Extremely" ("I feel anxious," "I feel like yawning," "I'm perspiring," "My eyes are tearing," "My nose is running," "I have gooseflesh," "I am shaking," "I have hot flashes," "I have cold flashes," "My bones and muscles ache," "I feel restless," "I feel nauseous," "I feel like vomiting," "My muscles twitch," "I have cramps in my stomach," "I feel like shooting up now"). The fourth questionnaire is a 6-item Drug Effects Questionnaire. Specific items on the Drug Effects Questionnaire are: "How strong a drug effect are you feeling right now?" "Do you feel any good effects from the drug?" "Do you feel any bad effects from the drug?" "Which one of the drugs listed below is the drug most like?" "Rate the degree to which you would be willing to take today's drug again."

"Do you like the way the drug makes you feel right now?" Participants describe drug effects by selecting among a series of possible answers ranging from 0 ("No (good, bad, etc.) effects at all") to 4 ("Very strong effects"). Ratings of drug type are: "Placebo (No drug), Stimulant, Sedative or Tranquilizer." Ratings of drug liking range between -4 ("Dislike very much") and 4 ("Like very much"). In addition to the above items, an Opioid Craving Questionnaire (OCQ) will be administered each evening throughout the study. Each question on the OCQ will be rated on a 7-point scale with "Strongly Disagree" at one end and "Strongly Agree" at the other end. Total scores can range between 0 and 70. A 7-item sleep questionnaire (Haney et al., 2004) asking about the quantity and quality of the previous night's sleep will also be administered each morning. In addition, an objective sleep measure (sleep efficiency: percentage of time spent asleep) will be collected each night via an Actiwatch.

In addition to the above, the following questionnaire will be completed weekly throughout the study:
Cognitive and Physical Functioning Questionnaire (CPFQ): 2 min

Impulsivity Assessments (to be completed after admission to 5-South)
Barrett Impulsiveness Scale: 5 min
Impulsivity Questionnaire: 5 min
Sensation-Seeking Scale: 5 min
UPPS Impulsive Behavior Scale: 5 min
Immediate Memory Task/Delayed Memory Task: 20 min
GoStop Task: 15 min

Please attach copies, unless standard instruments are used
Wang revised.pdf

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
1

Drug #1

Name of the drug
NT-814
Manufacturer and other information

NeRRe Therapeutics was founded in December 2012 to develop a portfolio of clinical and pre-clinical neurokinin (NK) antagonists, including NT-814. An IND for oxycodone is not needed (see enclosed worksheet).

Approval Status
IND application is pending
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Comer, Sandra, PHD

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
No
Treatment to be provided at the end of the study
During the last week of the study and/or prior to discharge, participants will receive counseling about different treatment options. For those participants requesting outpatient treatment, appropriate arrangements will be made during the last week, including placement in an outpatient treatment study at our Substance Treatment and Research Service (STARS), if they are eligible.

Clinical Treatment Alternatives

Clinical treatment alternatives
This is not a treatment study. However, counseling about different treatment options and referrals for treatment are available to participants at any time before, during or after their participation in this study. Participants will also be informed that they do not have to participate in this study in order to get a referral to help stop taking drugs. Referrals will be offered to interested participants by Opioid Laboratory staff (RN, MD, PhD, research assistant) and/or 5-South staff prior to discharge. Arrangements will be made by SURC and/or 5-South staff for those who express an interest in treatment.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

Study Medication (NT-814): To date, 90 healthy volunteers have been exposed to NT-814 in four Phase I clinical studies. In these clinical studies, NT-814 has been reasonably tolerated. The most common adverse events related to treatment with NT-814 are nausea, headache and somnolence. Gastrointestinal adverse events such as diarrhea and abdominal discomfort may be dose related. There were single cases of short periods of ventricular tachycardia and one case of atrial fibrillation following a vaso-vagal syncope reported in studies conducted. Cardiovascular parameters will continue to be evaluated in this clinical study. Three subjects on NT-814 and one on placebo had transient increases in liver function tests that returned to normal while on treatment. One of these occurrences (200 mg dose) was recorded as an adverse event while the others were not considered to be clinically significant by the investigator. Testosterone levels in males at the highest doses tested of NT-814 tended to reduce on treatment, but their levels returned to baseline values

approximately 7-14 days later at the follow-up visits after subjects had completed the treatment. Side effects of low testosterone include changes in mood, energy, muscle mass and libido (sex drive).

Opioid Administration During Laboratory Sessions: The major risks associated with study participation are those related to opioid administration. Potentially, the most serious adverse effects are respiratory depression, apnea, seizures and death. Other frequently reported adverse experiences associated with opioid agonist administration are itchiness, dry mouth, constipation, headache, sweating, anxiety, nausea, vomiting, dizziness, sedation, unconsciousness, irregular heart beats, changes in blood pressure, difficulty urinating, weakness, or tremors. More rarely, arrhythmias and bradycardia have been reported.

Detoxification: The major risks of detoxification are sweating, anxiety, nausea, vomiting, diarrhea, stomach upset, changes in blood pressure, weakness, restlessness, feelings of changes in temperature, sneezing, runny nose, watery eyes, gooseflesh, and insomnia.

Increased Sensitivity to Opioids: Participants who were dependent on opioids upon admission may be less tolerant to the effects of opioids at discharge.

Naloxone Challenge: During the screening process, participants may receive an intramuscular injection of naloxone in order to confirm opioid dependence. Sweating, restlessness, stomach pain, diarrhea, headache, anxiety, nausea, vomiting, dizziness, runny nose, yawning, muscle aches, or tremors may occur as a result of the naloxone injection.

Stabilization Periods: Participants may experience withdrawal symptoms during the stabilization periods.

Intravenous Catheter: Slight discomfort and/or bruising may occur at the site where the needle is inserted. In addition, infection and sterile abscess are potential, though rare, complications when IV catheters are placed.

Inpatient Facility: Participants may become bored or restless when they live on the inpatient unit.

Describe procedures for minimizing risks

Study Medication: Participants will be informed about the possible side effects of NT-814 and told to notify a nurse or physician if they begin to experience any of them. If present, medical staff will note which symptoms are present, their severity, and make a decision whether to continue the participant in the study. In order to monitor potential cardiovascular events, the following procedure will be followed: a) triplicate ECG's will be performed during screening; b) a baseline (post-detox, pre-NT-814) ECG will be performed, as well as ECG's during each dose change (at 30, 60, 90, and 120 min after dose administration, as well as at 24 hr) and 24-hr Holter monitoring **at baseline (post-detox, pre-NT-814)** and after each dose change; and c) in the event of a cardiovascular AE, Dr. Biviano will be contacted or an arrest call will be made, if warranted. **Participants will be escorted by research staff to and from 173 Fort Washington Ave, 4th floor, Room 4-637 at CUMC for placement of the Holter monitors at baseline and after each dose change. We will receive the Holter report within 24-48 hrs, and our study physicians (Drs. Manubay and/or Mogali) will review the results. Any significant abnormalities will be discussed with Dr. Biviano. NT-814 will be discontinued if a moderate-to-severe cardiovascular AE or SAE, such as ventricular tachycardia or atrial fibrillation, occurs. The study will be halted if 2 participants are**

discontinued due to AEs or SAEs related to the study drug. Participants with any significant cardiac abnormality (structural heart disease, syncope, myocardial infarction, etc.) will be excluded. In addition, the ECG must be normal at baseline. With regard to the potential effects of NT-814 on testosterone levels, only men with laboratory normal testosterone levels (250-1100 ng/dl for men) at screening will be accepted into the study. Total testosterone testing will occur at baseline (post-detox, pre-NT-814), study midpoint and then again at the 1-week follow-up visit. NT-814 dosing will be discontinued only if the participant complains of new and distressing sexual dysfunction (if testosterone levels are still low 1 week after the study, the participant will be rechecked 1 month later and appropriate follow-up care will be arranged.) In addition, signs of dehydration or poor liquid intake will be assessed by urine specific gravity at each dose change during the active treatment phase, daily body weight measurements, liquid input/output monitoring for 24 hr after each dose change, orthostatic vital signs (blood pressure) measurements daily during the active treatment phase, and daily monitoring for clinical signs of dehydration during the active treatment phase.

Opioid Administration: Medications will be administered by medical staff trained in the use of opioids, and in the management of respiratory effects of opioids. Emergency doses of an opioid antagonist (naloxone), resuscitative and intubation equipment, and oxygen will be readily available. During experimental sessions, oxygen saturation and vital signs will be continuously monitored, and the participant will be observed for early signs of hypotension, apnea, upper airway obstruction and oxygen desaturation. Criteria for Withholding Drug: Vital signs prior to oxycodone administration must be within acceptable ranges (%SpO2 > 92) for drug administration to occur. Careful attention will be paid to oxygen saturation since respiratory depression is a clear sign that no further doses should be administered. We will ask participants to take a deep breath if their oxygen saturation falls below 90%. In the unlikely event that prompted breaths do not bring the oxygen saturation above 90% within 3 min, we will provide supplemental oxygen through a nasal cannula. We will administer naloxone if the above measures are unsuccessful in restoring normal oxygen saturation. We have safely tested a bolus dose of 50 mg intravenous oxycodone in a previous study, so we do not anticipate problems with the cumulative intranasal dose of 50 mg/day proposed here (Comer et al., 2008).

Detoxification: A number of supplemental medications such as buprenorphine, clonidine, and clonazepam will be available to participants during the detoxification in order to alleviate the withdrawal symptoms that they are likely to experience.

Increased Sensitivity to Opioids: Participants will be counseled about the risks of decreased tolerance to opioids prior to discharge, and made aware that they may be more sensitive to the effects of opioids upon completion of the study. They will be told that this increased sensitivity to opiates could result in overdose and death, and that extreme caution must be exercised after they leave the hospital, if they choose to use any opioid again.

Naloxone Challenge: We will monitor participants' reactions to naloxone for up to 50 min. At the end of this period, we may prescribe oral morphine or an intramuscular injection of morphine to alleviate those symptoms.

Stabilization Periods: If participants experience withdrawal symptoms, we will prescribe drugs such as clonidine, clonazepam, ketorolac tromethamine, ondansetron, and ibuprofen or acetaminophen to alleviate

those symptoms. Trazodone or zolpidem will be available on some evenings at bedtime throughout the study to alleviate the insomnia that participants may experience.

Inpatient Facility: We describe the isolation, boredome and inactivity at length prior to signing the consent form. Of course, participants are free to leave the study at any time and care is taken to be sure that this is understood.

Additional Procedures to Minimize Risk: a) Participants are fully informed of the potential side effects of the drugs and the risks of the procedures. Participants are monitored by trained medical staff during experimental sessions. Emergency medical equipment is available in our laboratory and, as well, we are located in a hospital where a full medical emergency back-up team is constantly available. In addition, we have developed guidelines for opioid administration such that oxygen saturation dictates whether supplemental oxygen will be administered. Naloxone is available during all laboratory sessions in the event of serious respiratory depression. b) An extensive battery of screening tests, including psychometric evaluations, interview assessments, and a medical examination in order to provide as much information as possible upon which to base participant selection. c) The maintenance of continuous visual observation and communication with participants throughout experimental sessions in order to provide adequate information about methods and procedures, as well as to immediately detect any adverse participant reactions. d) Strict adherence to the agreement with participants to permit withdrawal from participation in the research at any time in order to minimize any adverse participant reactions. e) The location of the laboratory within the Psychiatric Institute complex. All participants are informed of the various side effects that they might experience, and since all have had extensive drug histories, these should be familiar to them. Participants are monitored 24 hr/day. Emergency medical equipment is available in our laboratory and, as well. In the event of an emergency, 911 will be called. We anticipate, however, that careful participant selection, dose selection, and participant monitoring will eliminate the need for such emergency care.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
We deal with issues of confidentiality by using coded records, store signed consent forms in a locked safe, and try to the best of our ability to maintain confidentiality. Electronic data are stored on computers that are password protected. We will obtain a Certificate of Confidentiality for this study. We also point out to prospective participants that we cannot assure that their drug histories and other personal records might not become known. Those who are hospitalized have hospital charts and we cannot guarantee the confidentiality of these charts.
Will the study be conducted under a certificate of confidentiality?
Yes, we will apply for the Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects
This study was not designed to benefit subjects directly.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
Participants will be paid $25/day with a $25/day bonus for completion of the study. Use of a per diem bonus is necessary to keep participants from leaving the study during the last several days when the money remaining to be earned would otherwise be proportionately small. In addition to the per diem payment, participants have the opportunity to earn money during the experimental sessions ($10 per sample session plus up to $10 per self-administration session). Participants will also be paid for completing the screening process ($15/visit), one training session prior to admission ($25), a naloxone challenge test ($25), and a follow-up evaluation 3 months after the completion of the experiment ($25). Payments will be in cash, separated into several installments ($300 per week) at the end of the study in order to prevent large one-time payments. Total payments will be between approximately $4800 and $6400. On some occasions, it may be necessary to repeat sessions (e.g., due to catheter failure).

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