

**NATIONAL INSTITUTE ON DRUG ABUSE/
DEPARTMENT OF VETERANS AFFAIRS
Study# 1018
A Multicenter Safety Trial of Buprenorphine/Naloxone
for the Treatment of Opiate Dependence**

May 1, 2000 - VERSION 3*

Study Chairman's Office

Co-Principal Investigators:

Paul Casadonte, M.D.
VAMC, New York (630)
Psychiatry Service (116A)
Room 17021 West
423 East 23rd Street
New York, NY 10010
Phone: (212) 263-7260
FAX: (212) 951-3356

Paul J. Fudala, Ph.D.
Dept. of Psychiatry, Ward 7 East
VA Medical Center (642)
University and Woodland Avenues
Philadelphia, PA 19104
Phone: (215) 823-6377
FAX: (215) 823-5919

Walter Ling, M.D.
VAMC, Long Beach (600)
10350 Santa Monica Blvd., Suite 340
Los Angeles, CA 90025
Phone: (310) 785-6665
FAX: (310) 785-9165

Study Director: Robert Walsh, R.A.C.^a
NDA Project Director: Nora Chiang, Ph.D.^a

Study Sponsor

^aNational Institute on Drug Abuse
Medications Development Division
6001 Executive Boulevard, Room 4123, MCS 9551
Bethesda, MD 20892-9551
Phone: (301) 443-9825; FAX: (301) 443-2599

Data Coordinating Center for Data Management

Cooperative Studies Program Coordinating Center (151E)
VA Medical Center (512A5), Perry Point, MD 21902
Director: Joseph F. Collins, Sc.D.
Study Biostatistician: William Williford, Ph.D.
Phone: (410) 642-2411 ext 5302; FAX: (410) 642-1129

Pharmacy Coordinating Center

VA Cooperative Studies Program
Clinical Research Pharmacy Coordinating Center (151-I)
2401 Centre Avenue, SE
Albuquerque, NM 87106
Director: Mike R. Sather, M.S., R.Ph.
Study Pharmacist: Dennis W. Raisch, Ph.D., R.Ph.
(505) 248-3203, FAX (505) 248-3205

*Revised date and version reflects changes for correction or clarification only. No substantial changes were made to the March 1, 1999 protocol. Please refer to the Face Sheet for revisions.

EXECUTIVE SUMMARY

Although many compounds have been evaluated for the treatment of opiate-dependence, only three medications have been approved by the Food and Drug Administration for this indication: methadone, levo-alpha-acetylmethadol (LAAM), and naltrexone. Methadone and LAAM are mu (morphine-like) opiate agonists which are administered orally both to substitute for illicit opiates and to suppress the opiate-abstinence syndrome. Because of pharmacokinetic differences between the two medications, methadone must be administered daily while LAAM is administered three times weekly or on alternate days. Naltrexone is an effective opiate antagonist that has shown therapeutic utility in only limited patient populations.

Buprenorphine is a mu opiate partial agonist that is currently under active investigation as a treatment for opiate dependence. Results from numerous studies have supported its therapeutic utility. Buprenorphine produces morphine-like subjective effects and cross-tolerance to other opiates similar to that produced by methadone and LAAM. As a partial agonist, the effects of buprenorphine in non-tolerant individuals are dose-dependent within a limited range, above which increasing dosages do not produce corresponding increases in effect. Thus, for certain pharmacological effects (e.g., respiratory depression, sedation), buprenorphine may exhibit an enhanced safety profile compared to full opiate agonists. A combination product containing both buprenorphine and the opiate antagonist naloxone is expected to be undesirable for parenteral abuse by opiate-dependent individuals. However, the product, when administered sublingually, is expected to be a safe and efficacious pharmacotherapy for opiate dependence.

Currently, there are clinical and legislative initiatives to extend the availability of buprenorphine and the buprenorphine/naloxone combination tablet to physicians in office-based practice. The general consensus is that the initial effort should involve physicians experienced in the treatment of opiate dependence. The fact that buprenorphine is already in a formulation available as a schedule V analgesic should allow for its administration in and dispensing from a physician=s office. The research data showing its high level of safety, patient acceptance and clinical efficacy, and its availability as a formulation that can be given for take-home dosing with low intravenous abuse liability, argue compellingly for exploring alternative implementation strategies in settings other than the traditional narcotic treatment programs.

The present study is designed to determine the safety of a buprenorphine/naloxone sublingual tablet formulation as an office-based therapy for opiate-dependence treatment. Data from this study will be used to expand labeling and will be considered in developing guidelines for the administration of buprenorphine/naloxone in office-based settings.

STUDY SPONSOR

The National Institute on Drug Abuse (NIDA) is the study sponsor. This protocol will be conducted under IND # 35,877.

OFFICE-BASED BUPRENORPHINE TREATMENT FOR OPIATE ADDICTION

BACKGROUND AND RATIONALE

Recent epidemiological evidence shows an increase in the prevalence of heroin use (141,000 new users in 1995) and a trend for increased use since 1992 (National Household Survey on Drug Abuse, 1996). Heroin-related emergency room visits comprised 14 percent of all drug-related episodes in 1995 and rose 64 percent between 1988 and 1994 (Drug Abuse Warning Network, 1996). The age of first use continues to decline and children as young as 12 years reportedly have used heroin (National Household Survey on Drug Abuse, 1996). The increase in use and the downward trend for age of first use may be related to the newer, more potent forms of heroin which can be sniffed or smoked (NIDA, 1997). Reflecting these national trends, patients enrolled in a recent pilot study with the buprenorphine/naloxone combination tablet were, demographically, 10 years younger on average and had nearly a decade less history of heroin use compared to patients entering methadone treatment (Ling, personal communication). Many of the patients had mild to moderate heroin dependence, had rejected methadone treatment, and were desirous of becoming drug free. Many were middle-class and held steady jobs.

Detoxification is often a daunting task for these patients. The cost of inpatient detoxification has become prohibitive for most and is rarely covered by health insurance. Outpatient methadone detoxification is not only highly restrictive in setting but carries an unacceptably high rate of failure. Outpatient clonidine detoxification is difficult due to serious side effects from the medication,

incomplete suppression of opiate withdrawal, and a high rate of treatment failure. The recent widespread, commercial use of the as yet unproven ultra-rapid opiate detoxification (UROD) suggests that there is a serious, unmet demand for alternative opiate detoxification strategies that can be made available to clinicians treating opiate dependence in settings other than the traditional methadone clinic. Such strategies could attract these younger addicts who are seeking treatment in increasing numbers as well as the increasing number of patients who fail detoxification and require extended opiate maintenance treatment in settings apart from the current narcotic treatment programs.

Buprenorphine, a mu opiate partial agonist, appears to hold great promise for meeting this need. Its partial agonist property confers on it a high clinical safety profile, and its tight binding to, and slow disassociation from, opiate receptors confer on it a long duration of action, allowing for every-other-day or even three-times weekly dosing in stabilized patients. Early investigators suggested the utility of buprenorphine to substitute for morphine, suppress withdrawal, and decrease heroin self-administration (Jasinski, 1978; Mello and Mendelson, 1980; Mello et al., 1982). Since then, extensive clinical research in the U.S., including several large-scale, controlled clinical trials (Johnson et al., 1992, Ling et al., 1998, Schottenfeld et al., 1994) involving approximately 1000 patients, has demonstrated buprenorphine=s safety and efficacy in the treatment of opiate dependence in traditional research/clinic settings. A recently completed study using the buprenorphine/naloxone combination tablet suggests that this formulation can be given for take-

home dosing without significant risk to patients or the public (Fudala et al., in press). The partial agonist nature of buprenorphine should facilitate eventual discontinuation of the medication when maintenance treatment is no longer necessary (Jasinski et al., 1978).

In France, more than 50,000 patients have been treated with buprenorphine, prescribed by private physicians in an office setting and provided by local pharmacies. This experience indicates that treatment can be effectively and safely rendered in this manner without undue patient or public health risk. Although a small number of fatalities have been reported, all appear to have been associated with combined abuse of benzodiazepines. While this suggests the need for caution, the potential risks, viewed in the context of the associated risks of untreated opiate addiction, seem quite small. Additionally, recent work comparing the liquid preparation used in earlier clinical studies to the tablet formulation shows that the bioavailability of the latter approaches 70 % or more of that achieved by the former (Ling et al., unpublished data). It also appears that the 4:1 buprenorphine/naloxone combination formulation can significantly deter intravenous abuse and may be safely dispensed to patients for take-home dosing (Mendelson et al., 1996, Fudala et al., 1998).

Currently, there are clinical and legislative initiatives to extend the availability of buprenorphine and the buprenorphine/naloxone combination tablet to physicians in office-based practice. The general consensus is that the initial effort should involve physicians experienced in the treatment of opiate dependence. The fact that buprenorphine is already in a formulation available as a schedule V

analgesic should allow for its facile prescribing from a physician=s office. The research data showing its high level of safety, patient acceptance and clinical efficacy, and its availability as a formulation that can be given for take-home dosing with low intravenous abuse liability, argue compellingly for exploring alternative implementation strategies in settings other than the traditional narcotic treatment programs. This protocol is designed to address the needs of opiate dependence treatment in the next decade. Specifically, this protocol will examine a range of issues related to treatment settings, length of treatment episodes, and concomitant psychosocial treatment strategies for relapse prevention and for sustaining a lifestyle free from illicit opiate use. The protocol will document physician training and prescribing practices, the extent and nature of ancillary personnel support needed, and any medical and economic issues that emerge during treatment.

As an immediate goal, this protocol will be implemented in multiple settings, e.g., (1) university-based or affiliated clinics; (2) community mental health clinics; (3) private physicians= offices within which buprenorphine will be prescribed, supplemented with relapse prevention therapy delivered by an appropriately trained medical assistant. A collaborative arrangement of this protocol allows physicians practicing in one of the above settings to participate in this study provided they agree to adhere to the requirements of the protocol. Such collaborative efforts must have prior approval from an appropriate Institutional Review Board (IRB) and, where applicable, from local research review groups (e.g., the California Research Advisory Board [RAB]) or other governing body.

SPECIFIC AIMS

The specific aims of this study are:

To determine if the 4:1 buprenorphine/naloxone combination tablet can be effectively used to treat patients with opiate dependence in various treatment settings. Induction will be accomplished with the 4:1 buprenorphine/naloxone combination tablet and flexible dosing data will be obtained.

To determine and document the safety, efficacy and feasibility of extending buprenorphine treatment to a younger population (ages 15-21).

To document physicians= patterns of preferred prescribing practices, including induction, dose adjustment, maintenance, and take-home dosing.

To document the ease or difficulty physicians encounter in delivering buprenorphine treatment in the various treatment settings, the accommodations they find necessary to make, and the advantages/disadvantages of these treatment strategies from the physicians= perspectives.

To document the acceptance, compliance, preferences, and necessary adjustments from the patients= perspectives.

To document treatment education issues regarding consideration of physician accreditation to use buprenorphine/naloxone following anticipated FDA approval.

STUDY DESIGN

This study will be conducted open-label with no random assignment or stratification. Patients may be accepted for detoxification or longer-term treatment (6 to 12 months of buprenorphine therapy). Patients under the age of 21 will initially be admitted for detoxification; longer treatment of these patients will be based on physician judgment of the necessity of continued treatment.

Patients will be inducted directly onto buprenorphine/naloxone 4:1 combination tablets. Patients treated in private practice settings will be asked to sign a treatment contract which will delineate the terms and conditions of treatment.

Patients:

A total of 600 persons seeking treatment for opiate dependence will be recruited at participating sites (up to 10 sites per state, 6 states participating). Patients will be recruited by any of numerous strategies including utilization of central recruiting telephone number systems, word of mouth, self-

referral, local fliers, newspapers, and radio advertisements. Patients must meet all of the inclusion criteria and none of the exclusion criteria listed below:

Inclusion Criteria - Patients must:

- (1) Be 15 years or older. Patients must fulfill DSM-IV criteria for opiate dependence.

- (2) Be seeking treatment with the desire to discontinue opiate use as an initial goal but willing to consider and accept longer treatment if necessary.

- (3) Be in good physical health or, in case of a medical condition needing ongoing treatment, be in the care of a physician who is willing to take responsibility for such treatment and is willing to work with the site physician. Site physicians able to manage these patients for their general medical condition, may be assigned this role. These same conditions apply in cases of patients with a psychiatric disorder needing ongoing treatment.

- (4) Be agreeable to and capable of signing an informed consent form that has been approved by an Institutional Review Board. *Patients under 18 years of age (legal age of majority) must have concurrent consent from a responsible parent or guardian, as applicable.*

Exclusion Criteria - Patients must not:

(1) Have any acute medical condition that would make participation, in the opinion of the site physician, medically hazardous, (e.g., acute hepatitis, unstable cardiovascular, liver or renal disease).

Patients with liver enzyme values (AST or ALT) greater than 8 times the normal range may be admitted following a consultation with a hepatologist.

(2) Have known sensitivity to buprenorphine or naloxone.

(3) Be acutely psychotic, severely depressed in need of inpatient treatment, or an immediate suicide risk.

(4) Be dependent on alcohol, benzodiazepines or other drugs of abuse (except tobacco) to the point of requiring immediate medical attention.

(5) Have participated in an investigational drug study within the past 30 days.

(6) Have discontinued participation in an opiate-substitution (i.e., methadone, LAAM) treatment program within 30 days of enrolling in this study.

(7) Have currently taken (licitly or illicitly) LAAM, methadone or naltrexone for more than 30 days before enrolling in this study.

(8) Be a nursing or pregnant female.

(9) Be a female of childbearing potential who does not agree to use a medically acceptable method of birth control. Acceptable methods include a) oral contraceptive, b) barrier (diaphragm or condom) with or without spermicide, c) levonorgestrel implant, d) intra-uterine progesterone contraceptive system, e) medroxyprogesterone acetate contraceptive injection, or f) complete abstinence.

Females who become pregnant during the course of the study will be referred to a methadone program.

(10) Have any pending legal action that could prohibit continued participation.

(11) Be expecting to leave the clinic's geographic area prior to study completion.

PROCEDURES:

Patient Assignment and Length of Study: Eligible patients will be given an explanation of the study. Study participation will be 9 to 12 weeks for patients who successfully achieve detoxification and up to 12 months for patients requiring longer buprenorphine treatment.

This will be an open-label study with no random assignment or stratification. Each principal investigator (PI) may recruit up to 5-10 site physicians working in a variety of care delivery settings. Physician eligibility will be determined by the PIs and the sponsor (National Institute on Drug Abuse). Each site physician may admit up to 10-20 patients per site (90-110 patients per state). All patients will sign an informed consent approved by national and local Institutional Review Boards. Patients under 18 years of age must also obtain concurrent consent from a parent or guardian, as applicable. Prior to starting the study and after signing the informed consent, patients will receive the following:

A general medical and psychiatric evaluation, including a history of drug use and assessment of HIV risk, any medical or psychiatric illness requiring ongoing treatment, and any concomitant medications received either over the counter or under the prescription of a physician. Off-site HIV testing and HIV counseling will be encouraged.

A physical examination (to be repeated at the end of the study to the extent possible) to include vital signs, ECG for all patients over 40 and for patients under 40 with a history of cardiovascular disease, routine laboratory chemistry panel, urinalysis, and urine screen for drugs of abuse. Urinalyses will be performed weekly throughout the first 9 weeks of the study and periodically thereafter (for an anticipated maximum of 21 urine tests per 12 month treatment*) to test for drugs of

abuse. Females will also undergo pregnancy testing at baseline and monthly during their study participation.

Treatment Schedule: The following treatment schedule will apply according to the specific treatment setting assignment:

Week 1: On the first day of treatment, patients will see the site physician and receive a 2, 4 or 8 mg dose (expressed as amount of buprenorphine) of the buprenorphine/naloxone combination tablet to be taken sublingually. Patients may receive an additional buprenorphine/naloxone dose of up to a maximum of 8 mg at the site physician's discretion. Patients should be prescribed enough medication to continue dosing until the next office visit. Patients will make contact with the site physician on the following day and be seen by the physician at least one more time during the first study week for follow-up evaluation to include drug use, signs and symptoms of opiate withdrawal or over medication, and any adverse medication effects. At this time, dosage may be adjusted, by 8 mg/day increments, up to a daily maximum of 24 mg buprenorphine (24 mg will be the maximum dose used throughout the study.)

Weeks 2-6: Patients will see the site physician once weekly for evaluation of treatment progress and medication effects and side effects. A urine sample will be obtained at each visit to screen for drugs of abuse. Additional visits may be scheduled as medically indicated. During this treatment period, a decision will be made as to whether the patient can be detoxified or should continue in buprenorphine/naloxone treatment.

After Week 6: Patients expected to be successfully detoxified will have their buprenorphine/naloxone dose tapered according to the physician's discretion from weeks 7 to 9. If the taper is unsuccessful, patients may remain on buprenorphine/naloxone. Patients needing further buprenorphine treatment will be continued on medication with doses adjustable to 24 mg/day maximum. These patients will be seen by the site physician weekly for the next 3-6 weeks for review of their treatment progress and to explore other treatment options, including further continuation of buprenorphine treatment.

Detoxification vs Maintenance: The decision to detoxify will be based on patient performance. As a minimum criterion for buprenorphine tapering, at least half of the urine samples obtained between weeks 3 and 6 must have been negative for opiates including the last sample obtained in week 6. If it is decided that detoxification should be attempted, the buprenorphine dose will be tapered over the next 3 weeks until, by week 9, a zero mg dose is achieved. The rate of taper will be individually determined. If detoxification appears impossible due to inability to achieve minimum criteria,

buprenorphine treatment will be continued for up to 52 total weeks. During this extended treatment period other treatment options will be explored or subsequent detoxification may be attempted.

Missed visits: Patients should be encouraged to keep their scheduled appointments. After two missed visits, patients should be considered for reinduction and dose scale up. Alternatively, patients may be re-evaluated for other types of therapy if compliance is poor.

Urine Screening for Drugs of Abuse: Urine samples will be obtained weekly for the first 9 weeks of treatment and assayed for the presence of opiates, benzoylecgonine, benzodiazepines, and amphetamines. Thereafter, an additional 12 urines* may be obtained if the patient stays in for the full year of treatment. Clinical decisions on extending the length of prescriptions for buprenorphine can be made, in part, on the urine results.

Psychosocial Treatment: In addition to the site physician=s visits, patients can receive psychosocial treatment from any of the following sources: an on-site medical assistant (trained to administer relapse prevention counseling), a drug counselor (on-site or off-site), or Narcotics Anonymous. For patients who will undergo detoxification, the psychosocial treatment will be extended to week nine and, thereafter, patients will be encouraged to enroll in aftercare self-help groups. Patients who require further treatment with buprenorphine will continue to participate in relapse-prevention programs at reduced frequency of visits. Patients receiving long-term buprenorphine/naloxone

treatment may receive up to 26 counseling sessions in the first year. In addition to the psychosocial treatment provided as part of this protocol, patients will be encouraged to attend other self-help support groups in the community (e.g., AA, NA).

Post-Treatment Follow-Up: Patients will be contacted for a 30-day follow-up assessment of their post-treatment status. This will consist of self-report of whether the patient is currently using opiates

*Additional tests may be performed if a therapeutic need arises.

or other drugs illicitly and/or currently receiving substance abuse treatment (drug or alcohol). The patient will also be asked if they would take the study medication again if it were generally available for opiate dependence treatment. If the patient is deceased, the date and cause of death will be obtained and site staff will verify the information. This information will be captured on Form 12.

Pregnancy: Women of childbearing potential must have pregnancy tests performed monthly using an FDA approved device or method. Women becoming pregnant during the study will be referred to a methadone program.

Study Termination: Patients may be terminated from the study if the site physician determines that it is in the patient's best interest (ex. safety concerns, etc.). A patient may also be removed for continued failure to keep appointments and for diverting or failure to handle medications

responsibly. Women who become pregnant during the course of the study will be referred for methadone treatment. Patients who drop out or are terminated from the study will not be readmitted.

MEDICATION

Medication will be supplied free of charge from Reckitt and Colman through NIDA. Medication will be tamper-proof and labeled with the following warning:

ACaution: New Drug - Limited by Federal (or United States) Law to Investigational Use.©

The 4:1 combination tablet will be supplied in the 2mg/.5mg and 8mg/2mg buprenorphine/ naloxone strengths. Medication will be supplied in blister packs as a one-week supply, and labeled as follows:

ABuprenorphine/naloxone combination tablets (2mg/.5mg and 8mg/2mg).

In case of emergency, please call:

(telephone number to be determined)©

Medication will be stored in a secure, limited-access location under the conditions specified by the label.

Medication Dispensing: The site physician will prescribe buprenorphine/naloxone for pick up at a specified local pharmacy. A two to four-week supply of medication will be the maximum dispensed

or prescribed at any time during the course of the study. Take-home medication will be provided according to the following schedule:

Week 1: Enough medication will be dispensed to last between visits by the site physician.

Weeks 2-6: A one-week supply of medication will be dispensed or prescribed.

Weeks 6-12: A one-week supply of either tapering (weeks 6-9) or fixed dose medication will be dispensed or prescribed.

Beyond Week 12: Take-home doses may be dispensed or prescribed at the discretion of the physician, not to exceed a two-week supply for weeks 13-26 and not to exceed a four-week supply for weeks 27-52. Patients should be considered for a dose tapering regimen or transfer to a methadone program during the last four weeks of the study.

Other Medical Treatment and Concomitant Medications: Patients may receive other treatment and concomitant medication provided they do not interfere with buprenorphine treatment. If such treatment is provided by other than the site physician, both physicians must be made aware of, and concur with the other treatment.

Medication Replacement: There will be no replacement of any prescribed or dispensed medications.

Drug Accountability: The site physician and the pharmacy will maintain an accurate and current accounting of all dispensed and returned medication. Such records will be made available for verification by the study project monitor. Returned medications will be accurately labeled and kept separately until the end of the study. The medication will then be returned to the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) or otherwise properly disposed of. Returned medication will not be re-used.

Medication Compliance: At each visit, patients will be required to bring all unused medications to the site physician=s office for accounting. The amount of buprenorphine returned and any discrepancy in medication counts will be recorded. To verify medication compliance, there will be one random call back during the first 9 study weeks and two during the remainder of the study. The random (or unannounced) medication callbacks will require contacting the patient and asking them to come to the site physician=s office and have all of the medication in their possession counted. The amount of medication they bring should show that they are taking the medication as prescribed.

MEASURES

Clinical Rating Instruments

The measures for this study are the Risk Assessment Battery (RAB), the Addiction Severity Index (ASI), the Opiate Symptom Checklist, the physician=s assessment of overall condition, the DSM-IV checklist for dependence.

DSM-IV Checklist for Substance Dependence - Form 06

The DSM-IV Checklist for Substance Dependence is a clinician-rated questionnaire used to determine the patient=s dependence on opiates, benzodiazepines and other sedatives, alcohol, cocaine, and amphetamines. The checklist will be completed during screening and should take approximately 10-15 minutes to complete.

Risk Assessment Battery (RAB) - Form 07

The RAB is a self-administered questionnaire designed to offer a rapid, private, and minimally intrusive method of assessing a patient=s risk for contracting or spreading of HIV. The instrument provides a brief lifetime overview and a past one-month history of a patient=s high-risk behavior for acquiring or spreading HIV. The RAB will be completed during the screening phase and at the end of the study. The RAB will take approximately 10 minutes to complete.

Addiction Severity Index (ASI) - Form 08

The ASI is a clinician-rated scale measuring 7 areas of functioning typically affected by substance abuse. These 7 areas are: medical condition, employment status, psychological condition, alcohol-related impairment, drug-related impairment, legal status, and interpersonal functioning. The full ASI will be administered initially and thereafter an abbreviated version will be used to obtain a composite score. The ASI will be administered during the screening phase and at the end of the study. The ASI should take approximately 45-60 minutes to administer initially, and approximately 15-20 minutes thereafter.

Opiate Symptom Checklist Symptom Checklist - Form 09

The Opiate Symptom Checklist is a clinician-rated, 12-item instrument used to indicate the presence or absence of symptoms typically seen with opiate withdrawal. This checklist will be rated at each office visit throughout the study, including the follow-up visits. The Opiate Symptom Checklist should take less than 5 minutes to complete.

Clinical Global Impression Scales - Observer - Form 09

The Clinical Global Impression Scale - Observer is a clinician-rated instrument of severity and global impression of change from the clinician=s perspective. The clinician rates the patient=s improvement on a 5-point scale from Amuch worse@ to Amuch improved.@ The severity item will be rated prior to enrollment and the global impression of change will be rated at each office visit throughout the study, including the follow-up visits. It should take less than 5 minutes to complete.

Clinical Global Impression Scales - Self - Form 09

The Clinical Global Impression Scale - Self is a patient-rated instrument of severity and global impression of change from the patient=s own perspective. The clinician will record the patient=s impression of their improvement on a 5-point scale from Amuch worse@ to Amuch improved.@ The severity item will be rated prior to enrollment and the global impression of change will be rated at each office visit throughout the study, including the follow-up visits. It should take less than 5 minutes to complete.

Physician=s Survey - Form 14

The Physician=s Survey is a questionnaire that each site physician will be asked to complete at the end of the study. It will record such information as usual prescribing patterns, adjustments required for

integration into their treatment setting, and ease and effectiveness of administration to a younger population.

Patient=s Survey - Form 15

The Patient=s Survey is a questionnaire that each patient will be asked to complete at the end of the study. It will record such information as the patient=s acceptability of office-based treatment, whether they felt that the office-based paradigm made it easier to be compliant, what their preferences would be and what adjustments, if any, that they found necessary to make.

Efficacy Evaluations

The outcome measures will include opiate use as determined by the urine drug screens, the clinical ratings from the opiate symptom checklist, the clinical global impression scales, and patient retention in the study. The primary focus will be on patient retention in the study and opiate use as determined by the urine drug screens.

Additional secondary outcome measures will include scores on the ASI, RAB, and opiate symptom checklist.

Safety Evaluations

Safety assessments will include a physical examination during the screening phase and upon termination from the study, laboratory tests taken during the screening phase and upon termination from the study, vital signs and urine drug screens obtained weekly, weekly evaluations by the site physician, and opportunities to report adverse events each week. In addition, monthly pregnancy tests will be performed on women of child-bearing potential.

Patients will be interviewed and monitored weekly for adverse experiences throughout the treatment period under the direct close supervision of the investigator or designated staff. All adverse experiences, either observed by the site physician or one of his/her professional colleagues, or reported by the patient spontaneously or in response to a direct question will be noted in the adverse events section of the patients Case Report Form.

The site physician or designated staff will evaluate the intensity, seriousness, and causal relationship to the study medication of all adverse experiences whether or not thought to be drug related. Any adverse experience will be recorded and listed on the CRF. The IRB and the sponsor, NIDA, will be informed by telephone within 24 hours by the investigating institute of any serious adverse experiences. A written report to NIDA will follow within three days. All serious adverse events will be reported whether or not considered drug-related.

Definitions of serious, unexpected or life-threatening experiences are summarized below.

Serious Adverse Experiences: Any adverse experience that is fatal or life-threatening, results in persistent or significant disability or incapacity, requires inpatient hospitalization or prolongation of hospitalization, requires intervention to prevent permanent impairment or damage, or is a congenital anomaly/birth defect.

Unexpected Adverse Experiences: Any experience that is not identified in nature or severity in the current literature (e.g., Investigator=s Brochure, Buprenex labeling).

Life-Threatening Experiences: Patient is, in the view of the site physician, at IMMEDIATE risk of death from the reaction as it actually occurred. This definition does not include reactions that might be fatal if they were to occur in a more severe form.

In addition, any overdose should be reported to NIDA within 24 hours.

A complete list of definitions for the terms used to describe clinical and laboratory adverse experiences is given in Appendix I. The regulatory reporting time frames are also given in this appendix.

In the event of an adverse event felt to reflect drug-related toxicity, appropriate evaluation and management will be undertaken and may include, in addition to medical management, a reduction in

study drug dose, temporary cessation of study drug, or early termination of the trial. Any patient who receives at least one dose of study medication will be included in the evaluation for safety. Patients who do not receive at least one dose of study medication will be listed separately.

Compliance

Compliance to dosing will be measured via pill counts at each visit and by random medication callbacks. One callback will occur during the first 9 weeks of the study; and up to two more will occur during the remainder of the study.

Data Analysis

Power and Sample Size Considerations

Retention rate is one of the primary outcome measures and is a proportion. Many of the descriptions of the patients' use as determined by opiate positive urines may also be a proportion (e.g., percentage of subjects who have 6 consecutive clean urines). The maximum variability for a proportion occurs when the proportion equals one-half, thus any sample size estimate obtained for this proportion would be conservative in that it will require more subjects than actually needed. To compute a 95% confidence interval for the observed proportion, with precision of $\pm 5\%$, a sample size of approximately 400 is needed when the expected proportion is 0.5.

Since the dropout rate is expected to be between 70 and 80%, the total number of patients that need to be enrolled is between 500 and 575. This number has been rounded to 600 to permit each of the primary VA Medical Centers (across 6 states) to enroll about 100 subjects. Each site physician will be allowed to enroll between 10 and 20 subjects so that they gain sufficient experience to permit results to be generalized.

Demography and Baseline Outcome Analyses

The number of patients enrolled in the study will be summarized overall, by site and by treatment setting. For patients who are screened but not enrolled, a distribution of the reasons for discontinuation will be provided.

Demographic, as well as other pretreatment characteristics and baseline parameters, will be summarized overall, by site and by treatment setting.

Efficacy Analyses

Although the study design does not permit an unconfounded assessment of treatment efficacy, treatment improvement, or lack thereof, will be documented.

Patient retention rates will be the primary outcome measure and will be summarized using descriptive statistics, overall, by site and by treatment setting. The NIDA-VACSP Multicenter

Buprenorphine

Study #999A, a 16-week efficacy and safety study using a traditional clinical trial setting, has shown a retention rate of 51%. About 82% of those completers, chose to enter the #999 Extension Study which provided for an additional 36 weeks of maintenance. Of the patients entering the extension study, 57% completed a total of 52 weeks (this would be a 24% retention rate for all patients enrolled). In the NIDA-VACSP Multicenter Buprenorphine Studies #1008A and B, a retention rate of about 30% was seen for 52 weeks for all patients enrolled.

The proposed length of patient accrual for this study is estimated to be 20 weeks. This is based upon the assumption that 5 patients will be able to be recruited in each state per week. A patient's participation in the study can last up to 1 year with follow-up being conducted thirty days after their completion/termination in the study. Accounting for the needs for data edits and clarifications, the total length of the study at each site is estimated to be 2 years.

Emphasis also will be placed on the urine toxicology screen results, the self-reports of drug use and the clinician rating of improvement obtained at the end of treatment. Other self-reports and ratings will be considered secondary. The results (actual values and change from baseline) will be summarized using descriptive statistics overall, by site and by treatment setting. These summaries will be performed for the end of treatment, and for the follow-up separately.

Physical Effects, Prescribing Patterns, and Survey Results

The effects of the medication itself, as well as, the effects of withdrawal from opiates will be measured. The results will be summarized using descriptive statistics overall, by site and by treatment setting.

The Office Visit Checklist (Form 09) contains information on the treatment prescribed (induction, maintenance, dose taper) and on the actual prescription (amount, frequency, duration). The information from this checklist will be summarized using descriptive statistics. At a minimum, the summaries will be prepared overall, by site and by treatment setting. Further summaries by induction, maintenance and/or dose-tapering may be performed.

Patients will be surveyed about prior treatment experiences, their experience in the current trial, and in their resource utilization during the follow-up period. Site physicians will be surveyed about the impact of the study on personnel, costs, and the integration of buprenorphine treatment into their practice. The results of these surveys are exploratory in nature and thus will be summarized in narrative form. Similarities and differences among the treatment settings will be emphasized.

Analyses of Safety

All safety data including adverse experiences, vital signs and laboratory tests will be summarized overall, by site, and by treatment setting. All patients who receive at least one dose of medication will be included in the safety evaluation. Adverse experiences occurring during screening but ending

prior to enrollment will be excluded. If a patient has the same adverse experience more than once, then the most severe evaluation (during the enrollment phase) will be used in the summaries.

Exploratory Analyses

In addition, exploratory analyses will be performed to determine if any demographic or pre-enrollment characteristics are prognostic or influence efficacy outcome measures. In particular, race, gender, and age will be evaluated.

SAFETY DATA MONITORING BOARD

Safety data will be reviewed as described below by a safety data monitoring board which will meet at least once yearly. Since the study is open-label, the board will review the data with respect to safety only. Focus will be on incidence and pattern of adverse events and their relation to the study drug.

HUMAN SUBJECTS

This protocol was reviewed and approved by the Perry Point VACSP human subjects subcommittee/IRB and will be reviewed by local IRBs at the various sites. All patients will sign an informed consent prior to study entry. The risks of participating in this study are detailed in the consent form.

All patients will be issued an ID card stating that they are participating in a federally funded study of buprenorphine/naloxone. This card will include a phone number to call in case of an emergency.

PUBLICATIONS AND PRESENTATIONS

The publication of any findings or results from this study will follow CSPCC guidelines. Presentation or publication of study results or findings must have prior approval of the study's executive committee. The executive committee may establish one or more publication committees, comprised of investigators and/or members of the executive committee, for the purpose of generating manuscripts for publication. Manuscripts will be circulated to study investigators for review and comment prior to their submission for publication.

LITERATURE CITED

Celleno D, Capogna G, Sebastiani M, Costantino P, Muratori F, Cipriani G, Emanuelli M. Epidural analgesia during and after cesarean delivery. Comparison of five opioids. *Reg Anesth* 1991;2:79-83.

Fisher (sic) Gabriele, Kathrin S-M, Petra E, Harald E, Reinhold J, Wolfgang G. Buprenorphine maintenance in pregnant opiate addicts. NIDA Research Monograph #178. Rockville: DHHS/NIH/NIDA, 1997;134.

Fudala PJ, Bridge TP, Herbert S, Leiderman D, Chiang CN for the BUP/NX Collaborative Study Group. A multisite efficacy evaluation of a buprenorphine/naloxone product for opiate dependence treatment. NIDA Research Monograph, Rockville: DHHS/NIH/NIDA, In Press.

Fudala PJ, Yu E, Macfadden W, Boardman C, Chiang CN. Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts. *Drug Alcohol Depend* 1998;50:1-8.

Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine. *Arch Gen Psychiatry* 1978;35:501-516.

Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA* 1992;267:2750-2755.

Johnson RE, Svikis DS, Kissin WB, Alpan G, Bienstock J, Cone EJ, Golden AS, Haug NA, Huggins GR, Jansson L, Lantz ME, Wilkins D, Jasinski DR. Pilot open label safety study of buprenorphine (BUP) during pregnancy. NIDA Research Monograph, Rockville: DHHS/NIH/NIDA, In Press.

Lehmann KA, Stern S, Breuker KH. Geburtshilfliche peridural-anästhesie mit bupivacain und buprenorphin. Eine randomisierte doppelblindstudie im vergleich zur unbehandelten kontrolle. [Obstetrical peridural anesthesia with bupivacaine and buprenorphine. A randomized double-blind study in comparison with untreated controls]. *Anaesthesist* 1992;41:414-422.

Ling W, Charuvastra C, Collins JF, Batki S, Brown LS Jr., Kintaudi P, Wesson DR, McNicholas L, Tusel DJ, Malkernecker U, Renner JA Jr., Santos E, Casadonte P, Fye C, Stine S, Wang RIH, Segal D. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction* 1998;93:475-486.

Marquet P, Chevrel J, Lavignasse P, Merle L, Lachatre G. Buprenorphine withdrawal in a newborn. *Clin Pharmacol Ther* 1997;62:569-571.

Mello NK, Mendelson JH. Buprenorphine suppresses heroin use by heroin addicts. *Science* 1980;207:657-659.

Mello NK, Mendelson JH, Kuenle JC. Buprenorphine effects on human heroin self-administration: An operant analysis. *J Pharmacol. Exp Ther.* 1982;223:30-39.

Mendelson J, Jones RT, Fernandez I, Welm S, Melby AK, Baggott MJ. Buprenorphine and naloxone interactions in opiate-dependent volunteers. *Clin Pharmacol Ther* 1996;60:105-114.

National Institute on Drug Abuse. Epidemiological trends in drug abuse: Vol. 1. Highlights and executive summary of the community epidemiology work group. NIH Pub. #97-4204. Washington, D.C.: U.S. Government Printing Office, 1997.

Reisinger M. Treatment of four pregnant heroin addicts with buprenorphine; history and outcome. NIDA Research Monograph #162, Rockville: DHHS/NIH/NIDA, 1996;261.

Schottenfeld RS, Pakes JR, Oliveto A, Zeidonis D, Kosten TR. Buprenorphine versus methadone maintenance treatment for concurrent opiate dependence and cocaine abuse. *Arch Gen Psychiatry* 1994;54:713-720.

Substance Abuse and Mental Health Administration. Preliminary results from the 1996 National Household Survey on Drug Abuse. Rockville: SAMHSA, 1997.

Substance Abuse and Mental Health Administration. Preliminary estimates of drug related emergency department episodes: Advance report number 17. Rockville: SAMHSA, 1996.

Appendix I

ADVERSE EVENTS

Definitions:

Adverse Event (or Adverse Experience)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Drug Reaction (ADR)

In the *pre-approval clinical experience* with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, *all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.* (The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.)

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is *not* the same as "serious," which is based on patient/event *outcome or action* criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

Results in death,

Is life-threatening, (*NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*)

Requires inpatient hospitalization or prolongation of existing hospitalization,

Appendix I
ADVERSE EVENTS

Results in persistent or significant disability/incapacity, or

Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Expectedness of an Adverse Drug Reaction

An "unexpected" adverse reaction is one, the nature or severity of which is not consistent with information in the relevant source documents (e.g., Investigator's Brochure, Buprenex labeling). Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.

Causality assessment is required for clinical investigation cases. All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs.

Note: The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

REPORTING TIME FRAMES

Fatal or Life-Threatening Unexpected ADRs (Expedited Reporting)

Certain ADRs may be sufficiently alarming so as to require very rapid notification to regulators in countries where the medicinal product or indication, formulation, or population for the medicinal product are still not approved for marketing, because such reports may lead to consideration of suspension of, or other limitations to, a clinical investigation program. Fatal or life-threatening, unexpected ADRs occurring in clinical investigations qualify for very rapid reporting.

Appendix I

ADVERSE EVENTS

The sponsor should be notified (e.g., by telephone, facsimile transmission, or in writing) as soon as possible but no later than 24 hours after first knowledge by the investigator that a case qualifies, followed by as complete a report as possible within 5 additional calendar days. This report should include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products.

All Other Serious, Unexpected ADRs

Serious, unexpected reactions (ADRs) that are not fatal or life-threatening must be communicated to the sponsor as soon as possible but no later than 5 calendar days after first knowledge by the investigator that the case meets the minimum criteria for expedited reporting.

Minimum Criteria for Reporting

Information for final description and evaluation of a case report may not be available within the required time frames for reporting outlined above. Nevertheless, for regulatory purposes, initial reports should be submitted within the prescribed time as long as the following minimum criteria are met: an identifiable patient; a suspect medicinal product; an identifiable reporting source; and an event or outcome that can be identified as serious and unexpected, and for which, in clinical investigation cases, there is a reasonable suspected causal relationship. Follow-up information should be actively sought and submitted as it becomes available.

How to Report

The MedWatch form has been a widely accepted standard for expedited adverse event reporting. All reports must be sent to the sponsor.

Post-Study Events

Serious adverse events that occurred after the patient had completed the clinical study (i.e. during follow-up) should be reported by an investigator to the sponsor. Such cases should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

The following list of items has its foundation in several established precedents from various regulatory authority forms and guidelines. Some items may not be relevant depending on the circumstances. The minimum information required for expedited reporting purposes is: an identifiable patient, the name of a suspect medicinal product, an identifiable reporting source, and an event or outcome that can be identified as serious and unexpected and for which, in clinical investigation cases, there is a reasonable suspected causal relationship. Attempts should be made to obtain follow-up information on as many other listed items pertinent to the case.

1. Patient Details: Initials, Other relevant identifier (clinical investigation number, for example), Gender, Age and/or date of birth, Weight, Height.

Appendix II

KEY DATA ELEMENTS FOR INCLUSION IN EXPEDITED REPORTS OF SERIOUS ADVERSE DRUG REACTIONS

2. Suspected Medicinal Product(s): Brand name as reported, International Non-Proprietary Name (INN), Batch number, Indication(s) for which suspect medicinal product was prescribed or tested, Dosage form and strength, Daily dose and regimen (specify units - e.g., mg, mL, mg/kg), Route of administration, Starting date and time of day, Stopping date and time, or duration of treatment.

3. Other Treatment(s): For concomitant medicinal products (including non-prescription/OTC medicinal products) and non-medicinal product therapies, provide the same information as for the suspected product.

4. Details of Suspected Adverse Drug Reaction(s): Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious should be given. In addition to a description of the reported signs and symptoms, whenever possible, attempts should be made to establish a specific diagnosis for the reaction. Start date (and time) of onset of reaction, Stop date (and time) or duration of reaction, Dechallenge and rechallenge information, Setting (e.g., hospital, out-patient clinic, home, nursing home), Outcome: Information on recovery and any sequelae; what specific tests and/or treatment may have been required and their results; for a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction should be provided. Any autopsy or other post-mortem findings (including a coroner's report) should also be provided when available. Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations.

5. Details on Reporter of Event (Suspected ADR): Name, Address, Telephone number, Profession (speciality).

6. Administrative and Sponsor/Company Details: Source of report: Was it spontaneous, from a clinical investigation (provide details), from the literature (provide copy), other? Date event report was first received by sponsor/manufacture, Country in which event occurred, Type of report filed to authorities: initial or follow-up (first, second, etc.), Name and address of sponsor/manufacture/company, Name, address, telephone number, and FAX number of contact person in reporting company or institution, Identifying regulatory code or number for marketing

Appendix II

**KEY DATA ELEMENTS FOR INCLUSION IN EXPEDITED REPORTS
OF SERIOUS ADVERSE DRUG REACTIONS**

authorization dossier or clinical investigation process for the suspected product (for example IND or CTX number, NDA number), Sponsor/manufacturer's identification number for the case (This number should be the same for the initial and follow-up reports on the same case).