

**NATIONAL INSTITUTE ON DRUG ABUSE/
DEPARTMENT OF VETERANS AFFAIRS
Study # 1008B
A Multicenter Safety Trial of Buprenorphine/Naloxone
for the Treatment of Opiate Dependence**

Study Chairman's Office

Co-Principal Investigators: Peter Bridge, M.D. (National Institute on Drug Abuse)^a
Paul J. Fudala, Ph.D. (Department of Veterans Affairs)
Building 15 - DVA Medical Center
University and Woodland Avenues
Philadelphia, PA 19104
Phone: (215) 823-6377; FAX: (215) 823-5919
Study Coordinator: Susan Herbert, M.A.^a
Project Director: Nora Chiang, Ph.D.^a

Study Sponsor

^aNational Institute on Drug Abuse Medications Development Division
Room 11A-55, 5600 Fishers Lane, Rockville, MD 20857
Phone: (301) 443-3318; FAX: (301) 443-2599

Data Coordinating Center for Data Management

Department of Veterans Affairs Cooperative Studies Program Coordinating Center
DVA Medical Center/151E, Perry Point, MD 21902
Chief: Joseph F. Collins, Sc.D.
Study Biostatistician: William Williford, Ph.D.
Phone: (410) 642-2411 ext 5288; FAX: (410) 642-1129

Data Coordinating Center for Statistical/Analytical Support

Department of Veterans Affairs Cooperative Studies Program Coordinating Center
DVA Medical Center/151K, 3801 Miranda Avenue
Palo Alto, CA 94304
Chief: Philip Lavori, Ph.D.
Phone: (415) 617-2719 ext 2524; FAX (415) 671-2605

Pharmacy Coordinating Center

Cooperative Studies Program Clinical Research Pharmacy Coordinating Center
Department of Veterans Affairs
2401 Centre Avenue SE
Albuquerque, NM 87106-4180
Chief: Mike R. Sather, M.S., R.Ph.
Study Pharmacist: Dennis W. Raisch, Ph.D., R.Ph.
(505) 248-3203; FAX (505) 248-3205

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ABSTRACT

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.

The present study is a multicenter, open-label trial (4 sites, 35 patients per site) designed to assess the safety of a buprenorphine/naloxone sublingual tablet formulation as an office-based therapy for opiate-dependence treatment. Patient recruitment will continue for approximately 17 weeks to accrue the requisite number of patients. There is no provision for continued treatment with the buprenorphine/naloxone combination product following the completion of the study.

Thus, individuals completing the trial must (by the end of the study) have their study medication gradually or abruptly discontinued (depending on dosage and clinical response) or be transferred to another treatment modality (e.g., methadone or LAAM pharmacotherapy). Data from this study will be used in support of a New Drug Application for the buprenorphine/naloxone product.

STUDY OBJECTIVE

This 52-week study is designed to assess the safety of a buprenorphine/naloxone sublingual tablet formulation as an office-based therapy for opiate-dependence treatment. The developmental objective for this combination product is an expansion of therapeutic options for the treatment of opiate dependence. The study design will consider this objective by targeting for participation those individuals not presently enrolled in an opiate-substitution treatment program for reasons of choice, eligibility, or availability of services, and by using a treatment environment distinct from current practices to provide opiate-substitution pharmacotherapy. Data from this study will be used to support a New Drug Application (NDA) for the buprenorphine/naloxone combination product as a treatment for opiate dependence. Thus, data will be collected using Food and Drug Administration (FDA) guidelines for good clinical practices.

STUDY SPONSOR

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

BACKGROUND

Introduction

Goals for the effective pharmacological treatment of opiate dependence include reducing illicit drug use as well as the spread of disease and infection (e.g., HIV/AIDS, hepatitis, tuberculosis) secondary to drug use. Substance abuse, including opiate abuse, is one of the most significant public health problems facing society today. According to statistics gathered by the Centers for Disease Control and Prevention (1993), approximately one-third of all reported AIDS cases in the United States are associated with parenteral drug abuse. Further, substance abuse has been reported to be the second leading risk factor for acquiring HIV in adults, with maternal substance abuse being the primary risk factor for neonates (National Commission on AIDS, 1991).

Buprenorphine for the Treatment of Opiate Dependence

Buprenorphine is a mu-opiate partial agonist (Martin et al., 1976) that produces morphine-like subjective effects and cross-tolerance to the effects of other opiates (Bickel et al., 1988). 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 (Budd, 1981). A parenteral dosage form (*BUPRENEX*) has been approved by the FDA for the relief of moderate to severe pain. Buprenorphine has been undergoing clinical study as an opiate-dependence treatment agent for over a decade (for review, see Fudala and Johnson, 1995) and its use in this regard is currently investigational in the United States. It has recently been approved for the treatment of opiate dependence in France, with market availability expected in early 1996.

The pharmacological profile of buprenorphine suggests its usefulness as an opiate-dependence treatment agent. Buprenorphine blocks the euphoria produced by opiates (Jasinski et al, 1978) and decreases heroin self-administration in opiate abusers (Mello and Mendelson, 1980; Mello et

al., 1982). Its duration of action is approximately 29.5 hours (Jasinski et al., 1978), with plasma buprenorphine levels following a multi-exponential decline after parenteral administration of the drug (Bullingham et al., 1980, 1982). The slow elimination of buprenorphine following rapid tissue distribution, and its slow dissociation from opiate receptors (Lewis et al., 1983) also contribute to its potential utility. Buprenorphine produces only mild physical dependence with limited withdrawal signs and symptoms allowing individuals to undergo a detoxification regimen with relative lack of discomfort (Jasinski et al., 1978; Mello et al., 1982). To date, clinical studies of buprenorphine have involved over 2000 human subjects. Of these individuals, over 1400 (about 30% of them female) received sublingual buprenorphine. Treatment durations ranged from one month to one year in maintenance studies and from three days to nine weeks in detoxification studies not involving abrupt withdrawal.

Three clinical studies, summarized below, have been identified by the FDA as pivotal with respect to the proposed approval of buprenorphine for opiate-dependence treatment. The results of these studies were presented at an FDA Drug Abuse Advisory Committee (DAAC) meeting in April, 1995, as part of a planned NDA submission for buprenorphine anticipated for June, 1996. The DAAC concluded that the drug substance buprenorphine is approvable and only limited, additional data are required on the tablet formulation (compared to the liquid formulation used in prior, pivotal studies) for its final approval. Johnson et al. (1992) reported that sublingual buprenorphine, at a dosage of 8 mg/day, was as effective as methadone 60 mg/day and superior to methadone 20 mg/day in maintaining patients in treatment and reducing illicit opiate use. Results from a 12-site (n=736) multicenter study (LAATRC/VA/NIDA Study #999A) comparing a range of buprenorphine doses (1, 4, 8, and 16 mg/day) indicated that sublingual buprenorphine at doses of 4 mg/day or above was a safe and effective opiate-dependence treatment (Ling et al., manuscript in preparation). Johnson and colleagues (1995), in a double-blind, parallel-group comparison (n=150) of sublingual buprenorphine (0, 2 and 8 mg/day), demonstrated the efficacy of buprenorphine over placebo during the initial phase of treatment.

Clinical experience to date indicates that buprenorphine has little toxicity at doses ranging from 1

to 32 mg/day. One-hundred ninety individuals have been maintained on buprenorphine for one year or more, about 63% of whom received sublingual doses of 8 mg/day or higher (Segal and Schuster, 1995). The most commonly reported side effects have been headache, constipation, insomnia, asthenia, somnolence, nausea, dizziness, and sweating.

Rationale for the Use Of a Buprenorphine/Naloxone Combination Product

Clinical trials evaluating buprenorphine for the treatment of opiate dependence have generally used sublingual solutions of the medication in aqueous ethanol. Manufacturing and marketing plans often change during the course of product development, and the manufacturing plan for buprenorphine includes a change in the final formulation for clinical use. Presently, a sublingual tablet is the anticipated formulation. Compared to buprenorphine solutions used previously, this tablet formulation yields buprenorphine plasma concentrations about 50% lower (Mendelson et al., 1995). Two types of tablets are expected. The first is a "mono" (buprenorphine-only) product intended for office/clinic use. The second is a combination preparation which is a 4:1 dose ratio formulation of buprenorphine to naloxone intended for both office and take-home use. The combination product is being developed in response to concerns regarding the potential diversion of buprenorphine since it is expected that this product will have limited potential for abuse. Recently completed studies (Jones et al.; Fudala et al.; manuscripts in preparation) have indicated that the intravenous administration of buprenorphine and naloxone in a 4:1 ratio to opiate-dependent individuals was associated with characteristic opiate-withdrawal signs and symptoms. FDA policy regarding combination drugs (Code of Federal Regulations, 1992a) allows for the addition of one or more medications to an effective pharmacotherapeutic agent in order to minimize the latter's abuse potential. Examples of products where naloxone has been incorporated into opiate analgesic formulations in order to reduce their abuse potential included pentazocine 50 mg/naloxone 0.5 mg (marketed in the United States as *TALWIN NX*), buprenorphine 0.2 mg/naloxone 0.2 mg (marketed in New Zealand as *TEMGESIC NX*) and tilidine 40 mg/naloxone 4 mg (marketed in Europe as *VALORON-N*).

A pilot evaluation of the feasibility of using the proposed new combination-tablet formulation

has recently been completed (see *Initial Clinical Experience with a Buprenorphine/Naloxone Combination Sublingual Tablet - Summary Report*). Results from this 25-subject investigation indicated that the formulation was generally safe and well-tolerated by study subjects. No unexpected adverse events were observed, and subject-reported effects were of the type anticipated for individuals initiating opiate-dependence treatment.

Pharmacology of Naloxone

Naloxone is a short-acting opiate antagonist with a half-life of one hour (Nagi et al., 1976). It does not produce opiate agonist effects or physical dependence (Jasinski et al., 1967; Jaffe and Martin, 1990). Naloxone given intravenously in doses as low as 0.7 mg effectively antagonized the effects of 20 mg of intravenously administered heroin (Fink et al., 1968). Naloxone can precipitate a moderate to severe withdrawal syndrome in opiate-dependent (Jasinski et al., 1967; Jaffe and Martin, 1990) and methadone-maintained individuals (O'Brien et al., 1978). The severity and duration of the withdrawal effects are related to the dose of naloxone, level of physical dependence, and the opiate agonist being administered. Nonetheless, intravenously administered naloxone at doses of up to 4 mg/kg have been reported to be well tolerated by opiate non-dependent individuals (Cohen et al., 1983) and by former addicts in oral doses ranging from 200 to 2000 mg per day for up to six months (Kurland et al., 1973, 1974, 1976; Hanlon et al., 1977). The oral to parenteral potency of naloxone has been reported to be 1:125 to 1:250 (Nutt and Jasinski, 1973).

Pharmacology of Buprenorphine and Naloxone

A combination of buprenorphine and naloxone is expected to be undesirable for parenteral abuse by opiate-dependent individuals. However, it is expected to be safe and efficacious when given sublingually for opiate-dependence treatment.

The parenteral effects of a combination of buprenorphine and naloxone at dose ratios ranging

from 8:1 to 1:2 have been investigated in both opiate dependent and non-dependent individuals (Preston et al., 1988; Weinhold et al., 1992; Jones et al., 1992, 1994; Jones and Mendelson, 1995). The data showed a dose-dependent attenuation of buprenorphine agonist effects and a dose-dependent opiate antagonist effect with higher ratios of naloxone in the combination being associated with greater opiate antagonist effects. At a dose ratio of 4:1 (2 mg buprenorphine/0.5 mg naloxone), significant opiate antagonist effects and "bad drug effects" were reported by opiate-dependent subjects maintained on 60 mg of morphine given parenterally. However, results from another study indicated that naloxone, given sublingually to buprenorphine-maintained individuals, did not attenuate the effects of buprenorphine at doses and dose ratios of both relevant to their use in opiate-dependence treatment (Jones, 1993). Surveys conducted in New Zealand have indicated that a combination tablet product (buprenorphine 0.2 mg/naloxone 0.2 mg) marketed for analgesia was the least preferred of a number of opiates used/abused parenterally (Robinson et al., 1993). Also, neither the analgesic effectiveness of buprenorphine nor its pharmacokinetic profile were reported to be attenuated by naloxone (IND 45,220; 1994).

METHODS

General Methods and Procedures

This is a multicenter, open-label trial that will be conducted at four sites. It is anticipated that patient recruitment will continue for approximately 17 weeks to accrue 140 individuals total (35 patients per site). The objectives are to monitor and assess the safety of the buprenorphine/naloxone combination product, and to satisfy a regulatory request by staff of the FDA that data be obtained from a sample of 300 patients who have been exposed to this product for at least eight weeks. It is anticipated that 524 individuals will need to be enrolled in order to achieve that size sample. Eight sites, contributing a total of 384 individuals to the 524-patient total, will participate in an efficacy/safety study, described separately as CSP protocol #1008A ("A multicenter efficacy/safety trial of buprenorphine/naloxone for the treatment of opiate dependence"). If interim analyses conducted on data from protocol #1008A indicate that the

efficacy assessment component of that trial may be abbreviated (thus decreasing the total number of individuals enrolled), a total of 240 individuals (60 per site) may be enrolled into the current protocol.

Women of childbearing potential must agree to use a medically acceptable form of contraception while participating in the study. Patients who become pregnant while participating in the study will be transferred to a methadone treatment program.

Blood samples, used to provide data for population pharmacokinetic assessments requested by the FDA, will be collected and analyzed for buprenorphine and naloxone. A maximum of three blood samples will be obtained from each patient; the total amount of blood required is 30cc per individual (10cc per sample). These samples will be obtained just prior to dosing and at relevant time points (approximately two and six hours after dosing) on one or multiple day(s). Since times of study medication administration prior to the obtaining of these samples are an important consideration in assessing pharmacokinetic parameters, and because patient self-reports of administration times for take-home doses are expected to be less precise than data obtained from in-clinic dosing records, blood samples will optimally be obtained on Wednesdays through Fridays, and during phase 1 or the first two weeks of phase 2 to minimize potential confounds related to take-home dosing.

Since the providing of the above blood samples is voluntary, a pharmacokineticist will work interactively with the site investigators to assure that an appropriate number of samples are obtained at each of the requisite timepoints. The associated procedures (e.g., sample handling, storage) are described in the study operations manual. The obtaining of these samples may require that patients return to the clinic, or remain at the clinic longer than they typically would. Thus, individuals will be reimbursed \$15 for their time and inconvenience for each occasion on which a blood sample for pharmacokinetic assessments is attempted to be obtained.

Inclusion Criteria

1. DSM-IV (Diagnostic and Statistical Manual of the American Psychiatric Association) diagnosis of current opiate dependence.
2. Individuals seeking opiate-substitution pharmacotherapy for opiate dependence.
3. Males and non-pregnant, non-nursing females, 18 to 59 years of age (inclusive).
4. Individuals able to give informed consent and willing to comply with all study procedures (e.g., providing of urine samples under observation, completing questionnaires).

Exclusion Criteria

1. Any acute or chronic medical condition that would make participation in the study medically hazardous (e.g., acute hepatitis, unstable cardiovascular, hepatic, or renal disease, unstable diabetes, symptomatic AIDS; not HIV-seropositivity alone).
2. Aspartate or alanine aminotransferase (AST, ALT) levels greater than three times the upper limit of normal.
3. Individuals currently taking systemic anti-retroviral or anti-fungal therapy.
4. Current dependence (by DSM-IV criteria) on any psychoactive substance other than opiates, caffeine, or nicotine.
5. Current, primary, Axis I psychiatric diagnosis other than opiate, caffeine, or nicotine dependence.
6. Females of childbearing potential who do not agree to use a medically acceptable method of birth control. Acceptable methods include a) oral contraceptive, b) barrier (diaphragm or condom) plus spermicide, (*amended 072696, condoms without spermicide allowed*) c) levonorgestrel implant, d) intrauterine progesterone contraceptive system, e) medroxyprogesterone acetate contraceptive injection, or f) complete abstinence.
7. Enrollment in an opiate-substitution (i.e., methadone, levo-alpha-acetylmethadol) treatment program within 45 days of enrolling in the present study.
8. Individuals having taken (licitly or illicitly) LAAM, methadone, or naltrexone within 14 days of enrolling in the present study.
9. Individuals having taken buprenorphine, other than as an analgesic, within 365 days of enrolling in the present study.
10. Participation in an investigational drug or device study within 45 days of enrolling in the present study.
11. Anyone, who in the opinion of site principal investigator, would not be expected to complete the first phase of the study protocol (e.g., due to pending incarceration or probable relocation from the clinic area).

Recruitment and Enrollment

Study patients will be recruited from the population of opiate-dependent individuals who are eligible based on the inclusion and exclusion criteria described above. As part of the screening process, the Addiction Severity Index (McLellan et al., 1985) will be administered to appropriately characterize the study population. Attempts will be made to have females comprise at least one third of the total number of patients enrolled. Each site will develop a strategy to ensure that sufficient females are entered into the protocol, and that the targeted recruitment rate (two patients per week) can be attained. This strategy may include the recruitment of patients from individuals presenting at the site for treatment; the use of newspaper and other local advertising; and the assistance of local treatment providers, particularly those with whom site personnel may have developed professional liaisons in the past, and/or where the demand for treatment is greater than its availability.

Individuals will be considered enrolled into the study at the time they are assigned an enrollment number. Informed consent will be obtained prior to enrollment at each study site by one of the local investigators; another member of the site staff will witness subjects' signatures on the informed consent document. Potential subjects will be given time to consider the study procedures and consult with others (e.g., family members), if desired, prior to signing the consent form. Potential benefits (e.g., therapeutic intervention for opiate dependence, routine medical evaluations) and risks (e.g., medication side effects, those related to the drawing of blood) associated with study participation are described fully in the consent form. The responsibilities of the investigators for patients following their termination from the study (e.g., secondary to study completion, pregnancy) are described subsequently in *Medication-Dosing and Patient-Management Procedures*.

Enrollment codes will be developed and maintained at the data coordinating center (Department of Veterans Affairs Cooperative Studies Program Coordinating Center, Perry Point, Maryland; CSPCC). The CSPCC will prepare a non-sequential list of patient enrollment numbers for each participating center. This list will be submitted to the pharmacy coordinating center (Department

of Veterans Affairs Cooperative Studies Program Pharmacy Coordinating Center, Albuquerque, NM; PCC).

Investigators will telephone the CSPCC between 7:30 AM and 4:00 PM Eastern time to enroll patients. CSPCC staff will review eligibility criteria with the investigator and assign a nonsequential patient enrollment number; patients will be dosed as soon as possible after receiving their number. Nonsequential numbers will be assigned to ensure that investigators cannot start a patient on medication without first contacting the CSPCC.

Study Medications

Buprenorphine and buprenorphine/naloxone tablets for sublingual administration will be obtained from Reckitt and Colman, (Hull, England). All study medications will be distributed through the PCC as described in *Drug Treatment and Handling Procedures*.

Medication-Dosing and Patient-Management Procedures

Patients will not receive financial compensation for their participation in this study. The first dose of study medication (buprenorphine 8 mg) will be given on Mondays through Wednesdays only. The second study medication dose (8 or 12 mg, depending on the clinician determined, targeted dosage level) will also be given as the buprenorphine mono-component product. All succeeding dosages, except those used for re-induction, will be given as the buprenorphine/naloxone combination product.

Take-home supplies of medication will be prescribed, based on the judgement of study clinicians and the response of the individual patient. For the first two weeks of the study, these supplies will be limited to weekends and clinic holidays. After the first two weeks, supplies of up to a 10-day duration may be prescribed. Weekly clinic visits will still be required, and an individual must be stabilized for at least seven days at a particular dosage before a take-home supply of more than three days can be dispensed.

Daily dosages may be increased (to a maximum of 24 mg/6 mg) or decreased, based on clinical judgment, in 4 mg/1 mg increments throughout the duration of the study. It will be recommended to clinicians that dosage increases occur no more frequently than every third day so that an individual's response to a particular dosage may be adequately assessed. Additionally, actual dosage changes must occur on days that patients attend the clinic (i.e., planned dosage adjustments may not be made with take-home doses).

Investigators will be instructed to follow their usual clinic procedures with respect to the provision of treatment services for study patients. These services will include those normally associated with total patient management (e.g., counseling). Patients may be administratively or medically discharged from the study as site investigators determine appropriate, consistent with the general policies and procedures of the site. Women who become pregnant while taking the study medication will be transferred to methadone and enrolled in a methadone treatment facility. Individuals desiring to discontinue their study participation, or those being administratively or medically discharged, 1) may have their study medication gradually or abruptly discontinued (depending on dosage and clinical response), 2) may continue to receive only psychosocial treatment services, or 3) may be transferred to another treatment modality (e.g., methadone or LAAM pharmacotherapy) depending on the judgment of the study clinicians and the availability of other services. About one month following individuals' last clinic visit (whether or not the entire study is completed), participants will be reimbursed \$10 to return to the clinic and answer questions about their drug use and general health.

Following the dispensing of take-home medication doses, patients will be required to return empty medication packaging and any extra doses (e.g., doses remaining secondary to patients returning prior to their next scheduled visit) at their subsequent clinic visit. Additionally, at least once monthly on a random basis (or more often if requested by site investigators), patients receiving more than a three-day supply of take-home medication will be asked (with approximately 24-hours notice) to return to the clinic with their remaining take-home medication

doses for an assessment of compliance with the dosing regimen. While this assessment will provide only a cursory measure of compliance, it is expected to identify those individuals who are grossly noncompliant or potentially diverting their study medication.

Patients who miss one, or two consecutive medication doses, will continue on their assigned dosage; i.e., no re-induction procedure will be utilized. Patients who miss three or more consecutive doses will be re-induced onto buprenorphine 8 mg with suggested daily 4 mg increases until the desired dosage level has been attained. Following the first two re-induction doses, treatment will continue with the buprenorphine/naloxone combination product.

There is no provision for continued treatment with the buprenorphine/naloxone combination product following the completion of the second phase of the study. Thus, individuals completing the trial must (by the end of the study) have their study medication gradually or abruptly discontinued (depending on dosage and clinical response) or be transferred to another treatment modality (e.g., methadone or LAAM pharmacotherapy) depending on the judgment of the study clinicians and the availability of other services.

Measures and Measurement Instruments (See also Figure 1 for a schedule of data collection.)

Selection of Primary Outcome Measures

The identification and documentation of adverse medical events and general medical safety is an essential prerequisite for the evaluation of the therapeutic value of any drug treatment. A complete evaluation includes a distinction between known, established, and anticipated medication effects and unexpected or serendipitous effects. The battery of assessments comprising the primary outcome measures were selected to provide a comprehensive appraisal of the safety profile of the buprenorphine/naloxone combination product, as well as to provide guidance to clinicians regarding indications for discontinuation (e.g., pregnancy) of the medication.

The influence of the combination product on HIV-associated risk behaviors when it is used in the context of the present therapeutic paradigm will be evaluated. As noted below, risk behaviors will be assessed using the Risk Assessment Battery (RAB), a self-administered questionnaire that assesses both needle sharing and unprotected sexual behavior. The RAB has been selected as the instrument for assessing HIV risk behaviors in clinical trials sponsored or funded through the NIDA Medication Development Division. The use of this instrument will permit the systematic assessment of HIV risk behaviors generally in a manner critically necessary but not previously undertaken. It will also provide a greater understanding of the relationship between substance abuse patterns, HIV risk behaviors, and the use of investigational pharmacotherapeutic agents for drug-dependence treatment.

Primary Outcome Measures and Assessments

1. Adverse medical events (assessed weekly).
2. Medical evaluation results, including those from physical examinations, pregnancy tests, and clinical chemistry and hematology panels (assessed monthly).
3. Assessment of HIV-associated risk behaviors using the RAB (assessed monthly). The RAB is a self-administered questionnaire designed to offer a rapid (less than 15-minute), private, and minimally intrusive method of assessing both needle sharing and unprotected sex (Navaline et al., 1994). Questions are worded simply and followed by response categories that are checked off by the respondent.

Secondary Outcome Measures and Assessments

1. Patient retention. The date of the last clinic visit will be considered a patient's last day in the study for individuals discharged or voluntarily terminated from the study for any reason.
2. Urine samples negative for opiates, amphetamines, barbiturates, benzodiazepines, cocaine, and methadone. Random samples will be collected under observation *amended 070896, using Franklin Collectors*) twice monthly and sent to a central laboratory (Northwest Toxicology, Inc., Salt Lake City, UT) for analysis. Results will be provided to the individual

sites while the study is ongoing. Additionally, the sites may analyze samples locally to facilitate the expedient dissemination of the results.

3. Amount of psychosocial treatment services provided using the Treatment Services Review (TSR). The TSR is a 10-minute structured interview designed to provide information on the type, amount, and efficacy of services provided (McLellan et al., 1992).
4. Population pharmacokinetic assessments of buprenorphine and naloxone. These assessments will be made from a maximum of three, 10cc blood samples per patient obtained on separate occasions during the study.

Patient Safety Monitoring

The responsibility for independent monitoring of this study, once ongoing, will be assumed by the Data Monitoring Board. This board will meet periodically to review accumulating data and consider recommendations regarding whether the study should continue. Additionally, the study sponsor will monitor safety data on an ongoing basis and review relevant findings with the FDA. Site physicians will be responsible for the day-to-day clinical monitoring of patients. If clinically relevant signs or symptoms of study medication toxicity become evident, the daily medication dose will not be administered. If it becomes necessary to withhold three consecutive daily doses for a patient, the patient will be administratively discharged from the protocol and provided with alternative treatment, or referred to other treatment services as previously described (see medication dosing procedures).

Serious adverse events will be reported promptly to the NIDA study coordinator. As defined by the FDA, a serious adverse event is one which 1) poses a serious threat to the patient's health, including any event which is life-threatening or fatal, permanently disabling, or requires inpatient hospitalization or prolongation of hospitalization; 2) represents a significant hazard, contraindication, side effect or precaution; or 3) is unexpected or previously unreported, including any event which is not identified in nature, severity, or frequency in the product labeling or study protocol (Code of Federal Regulations, 1992b). Additionally, an increase in

AST or ALT to greater than eight times the upper limit of normal will be considered a serious adverse event for the purposes of this study. Individuals presenting with this enzyme profile who desire to continue receiving study medications must have appropriate clinical and/or laboratory follow-up assessments performed at least weekly, as well as a review of their status by a hepatic disease specialist.

Investigators will notify the Study Coordinator by telephone on the next working day after the event becomes known, and their local institutional review board within the time frame it requires. A serious adverse event case report form must be completed within 5 days (or within 72 hours if the event is fatal or life-threatening) and sent to the Study Coordinator with as much documentation as possible. Additional follow-up information will be submitted as required. The Study Coordinator will assume responsibility for reporting events to the FDA.

In the event of the death of a study patient, the site principal investigator will request, collect, and ship the appropriate blood, urine, and tissue samples to the Center for Human Toxicology, University of Utah for analysis. Additional details regarding specimen collection and handling are included in the study operations manual.

Psychosocial Treatment Services

Investigators will be instructed to follow their usual clinic procedures with respect to the provision of treatment services for study patients. At least one, 1-hour session per week of individualized counseling will be available. During these sessions, emergency counseling and referral services will be provided (Childress et al., 1991). All patients will be encouraged to seek psychosocial treatment services in addition to those provided at the study sites. As no single therapy has been shown to be effective for all individuals receiving opiate-dependence treatment, a number of potential therapeutic modalities will be suggested and encouraged. These may include those incorporating 12-step facilitation approaches, as well as motivational enhancement, cognitive-behavioral, and supportive-expressive therapies (Woody et al., 1983; Onken, 1991;

Nowinski, 1994).

Data Management

Data management activities will be coordinated through the CSPCC. Statistical/analytical support will be provided through the coordinating center at Palo Alto, California. Data will be collected at the study sites on NCR (non-carbon reproducing) forms which will be supplied by the CSPCC. Completed forms will be submitted on a regular basis to the CSPCC (first copy to the CSPCC, second copy to NIDA, third copy retained at each site).

When data are received at the CSPCC, they will be key entered and verified, and edited prior to being entered into the main study database. Incomplete or inaccurate data will be returned to the sites for correction using a series of edit reports that will be specifically tailored for the study. Sites will resolve data inconsistencies and errors prior to returning data to the CSPCC. All corrections and changes to the data will be reviewed prior to being entered into the main study database. NIDA and the participating sites will receive reports at least monthly regarding the quality and quantity of data submitted to the CSPCC.

Participating investigators will agree to routine data audits by the PCC's good clinical practices monitoring staff. Staff members will routinely visit each site to assure that data submitted on the appropriate forms are in agreement with source documents at the sites. They will also verify that study medications have been properly stored and accounted for, patient informed consent for study participation has been obtained and documented, all essential documents required by Good Clinical Practice regulations are on file, and that sites are conducting the study according to the research protocol. Any inconsistencies will be resolved and any changes to the data forms will be made using established CSPCC procedures.

The CSPCC will also prepare summary reports of the data so that progress of the study can be monitored. Various reports will be prepared for NIDA, the Data Monitoring Board, and others,

as appropriate. These reports, as well as the final analyses, will be prepared in cooperation with the coordinating center in Palo Alto.

Statistical Considerations and Analyses

The objective of this study is to assess the safety of the buprenorphine/naloxone combination product in patients who have taken the medication for at least eight weeks. A total of 524 individuals will be required to obtain a 300-patient sample. These individuals will be enrolled through the present protocol (140 patients total), as well as through CSP study #1008A conducted at an additional eight sites. In addition to the analytical methodology described in the *Biostatistical Review and Data Processing* section, mean (\pm standard deviations) for continuous measures and frequency tables for categorical variables will be prepared to characterize the safety of the combination product.

- Primary Outcome Measures and Assessments

1. Adverse medical events.
2. Medical evaluation results, including those from physical examinations, pregnancy tests, and clinical chemistry and hematology panels.
3. Assessments of HIV-associated risk behaviors using the RAB.

- Secondary Outcome Measures and Assessments

1. Patient retention. The date of the last clinic visit will be considered a patient's last day in the study. The reason for termination will be determined and recorded.
2. Urine samples negative for opiates, amphetamines, barbiturates, benzodiazepines, cocaine, and methadone. Random samples will be collected under observation twice monthly.
3. Amount of psychosocial treatment services provided using the TSR.

4. Population pharmacokinetic assessments of buprenorphine and naloxone.

- Sample Size

Sample size estimates for this phase of the study were based upon a request made by the FDA that data be presented from a sample of 300 patients who had taken the combination product for at least eight weeks. Retention data from Study #999A were also considered. Using probability theory, it was determined that a sample of 300 individuals is required to detect with 95% confidence at least one individual exhibiting an adverse medical event with a 1% incidence of occurrence. This sample size estimate was confirmed with 100,000 simulated samples of 300 each (Simon, 1993). Based on an approximate eight-week retention rate of 60% in Study #999A, an enrollment of 500 individuals (with 384 of those individuals being enrolled into CSP Study #1008A) would be required to achieve the necessary sample of 300. A total enrollment of 524 is targeted to provide a buffer of 5% on this estimate.

Protocol and Consent Form Approval

The study protocol and accompanying consent form have been reviewed and approved by an human subjects subcommittee convened by the Department of Veterans Affairs Cooperative Studies Program and will also be approved by an human subjects subcommittee at each participating site.

Publications and Presentations

The publication of any findings or results from this study will follow existing CSPCC guidelines. Presentation or publication of study results or findings must have the 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.

PARTICIPATING SITES

The following investigators and associated Department of Veterans Affairs Medical Centers have tentatively agreed to participate in this study or CSP study #1008A contingent upon their approval by the Department of Veterans Affairs Cooperative Studies Program:

Marcos Fe-Bornstein, M.D. (New Orleans, LA)

Richard Douyon, M.D. (Miami, FL)

Joe Liberto, M.D. (Baltimore, MD)

Erick Santos, M.D. (San Juan, PR)

Based on a review of past performance with respect to the conduct of similar trials (e.g., LAATRC/VA/NIDA Study #999A) and/or a recent review of the current resources at the above medical centers, there is expected to be sufficient patient availability for the successful conduct of the study. All of these medical centers have speciality clinics that serve substance-abusing or -dependent patients.

REFERENCES

Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE. A clinical trial of buprenorphine: comparison with methadone in the detoxification of heroin addicts. *Clin Pharmacol Ther* 1988;43:72-78.

Budd K. High dose buprenorphine for postoperative analgesia. *Anaesthesia* 1981;36:900-903.

Bullingham RES, McQuay HJ, Moore RA, Bennett MRD. Buprenorphine kinetics. *Clin Pharmacol Ther* 1980;28:667-672.

Bullingham RES, McQuay HJ, Porter EJB, Allen MC, Moore RA. Sublingual buprenorphine used postoperatively: Ten hour plasma drug concentration analysis. *Br J Clin Pharmacol* 1982;13:665-673.

Centers for Disease Control and Prevention. HIV/AIDS surveillance report. Atlanta: CDCP, 1993;5(3).

Childress AR, McClellan AT, Woody GE, O'Brien CP. Are there minimum conditions necessary for methadone maintenance to reduce intravenous drug use and AIDS risk behaviors? In: Pickens RW, Leukefeld CG, Schuster CR (eds). *Improving drug abuse treatment*. Washington D.C.: U.S. Government Printing Office, 1991:167-177.

Code of Federal Regulations. Washington, D.C.: U.S. Government Printing Office, 1992a:21§300.50.

Code of Federal Regulations. Washington, D.C.: U.S. Government Printing Office, 1992b:21§300.32.

Cohen MR, Cohen RM, Pickar D, Weingartner H, Murphy DL. High dose naloxone infusion in normals: dose-dependent behavioral, hormonal and physiological responses. *Arch Gen Psychiatry* 1983;40:613-619.

Fink M, Zaks A, Sharoff R, Mora A, Bruner A, Levit S, Freedman AM. Naloxone in heroin

dependence. *Clin Pharmacol Ther* 1968;9:568-577.

Fudala PJ, Johnson RE. Clinical efficacy studies of buprenorphine for treatment of opioid dependence. In: Cowan A, Lewis JW (eds). *Buprenorphine: Combating drug abuse with a unique opioid*. New York: Wiley-Liss, 1995:213-239.

Hanlon T, McCabe L, Savage C, Kurland AA. Narcotic antagonist treatment of addict parolees - the failure of an effective approach. *Comp Psychiatry* 1977;18:211-219.

IND 45,220: Vol 9, Reckitt and Colman Pharmaceuticals; 1994.

Jaffe JH, Martin WR. Opioid analgesics and antagonists. In: Gilman AG, Rall TW, Nies AS, Taylor P. (eds). *The pharmacological basis of therapeutics*. New York: Pergamon Press 1990:485-521.

Jasinski DR, Martin WR, Haertzen CA. The human pharmacology and abuse potential of n-allylnoroxymorphone (naloxone). *J Pharmacol Exp Ther* 1967;157:420-426.

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

Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE. A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. *Drug Alcohol Depend* 1995;40:17-25.

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

Jones R. Subchronic buprenorphine study: Sublingual buprenorphine/naloxone interaction. NIDA contract report summary 271-90-7307; 1993.

Jones R, Mendelson J. Effects of buprenorphine and naloxone combination in opiate-dependent volunteers. Abstract presented at the annual meeting of the College on Problems of Drug Dependence; Scottsdale, AZ; June 15, 1995.

Jones R, Mendelson J, Upton R. Intravenous buprenorphine and naloxone (high dose) interactions in opiate-dependent volunteers. NIDA contract report summary 271-90-7307; June, 1994.

Jones R, Mendelson J, Upton R. Low dose buprenorphine and naloxone interactions in opiate-dependent volunteers. NIDA contract report summary 271-90-7307; August, 1994.

Jones R, Upton R. Buprenorphine and naloxone interactions in methadone maintenance patients. NIDA contract report summary 271-90-7307; 1992.

Kurland AA, Krantz JC Jr., Henderson JM, Kerman F. Naloxone and the narcotic abuser: A low dose maintenance program. *Int J Addict* 1973;8:127-141.

Kurland AA, Hanlon T, McCabe OL. Naloxone and the narcotic abuser: A controlled study of partial blockade. *Int J Addict* 1974;9:663-672.

Kurland AA, McCabe L, Hanlon T. Contingent naloxone treatment of the narcotic addicts: A pilot study. *Int J Addict* 1976;11:131-142.

Lewis JW, Rance JJ, Sanger DJ. The pharmacology and abuse potential of buprenorphine: A new antagonist analgesic. *Adv Subst Abuse* 1983;3:103-154.

Martin WR, Eades CG, Thompson JA, Huppler, RE, Gilbert, PE. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J Pharmacol Exp Ther* 1976;197:517-532.

McLellan AT, Alterman AI, Cacciola J, Metzger D, O'Brien CP. A new measure of substance abuse treatment. Initial studies of the Treatment Services Review. *J Nerv Ment Dis* 1992;180:101-110.

McLellan AT, Luborsky L, Cacciola J, Griffith J, Evans F, Barr HL, O'Brien CP. New data from the Addiction Severity Index: Reliability and validity in three centers. *J Nerv Ment Dis* 1985;173:412-423.

Mendelson J, Upton R, Jones RT. Buprenorphine pharmacokinetics: Bioavailability of an 8mg sublingual tablet formulation. Abstract presented at the annual meeting of the College on Problems of Drug Dependence; Scottsdale, AZ; June 15, 1995.

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

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

Nagi SH, Berkowitz BA, Yang JC, Hempstead J, Spector S. Pharmacokinetics of naloxone in rats and in man. *Anesthesiology* 1976;44:398-401.

National Commission on AIDS. A report: The twin epidemics of substance abuse and HIV. NCA, 1991(July).

Navaline HA, Snider EC, Petro CJ, Tobin D, Metzger D, Alterman AI, Woody GE. An

automated version of the Risk Assessment Battery (RAB): Enhancing the assessment of risk behaviors. *AIDS Res Human Retroviruses* 1994;10(Suppl 2):S281-S283.

Nowinski J, Baker S, Carroll K. Twelve step facilitation therapy manual. A clinical research guide for therapists treating individuals with alcohol abuse and dependence. NIH Publication No. 94-3722. Rockville: National Institute on Alcohol Abuse and Alcoholism, 1994.

Nutt JG, Jasinski DR. Methadone-naloxone mixture for use in methadone maintenance programs. *Clin Pharmacol Ther* 1973;15:156-166.

O'Brien CP, Greenstein R, Ternes J, Woody GE. Clinical pharmacology of narcotic antagonists. *Ann NY Acad Sci* 1978;311:232-239.

Onken LS. Using psychotherapy effectively in drug abuse treatment. In: Pickens RW, Leukefeld CG, Schuster CR (eds). *Improving drug abuse treatment*. Washington D.C.: U.S. Government Printing Office, 1991:267-278.

Preston KL, Bigelow GE, Liebson IA. Buprenorphine and naloxone alone and in combination in opioid-dependent humans. *Psychopharmacology* 1988;94:484-90.

Robinson GM, Dukes PD, Robinson BJ, Cooke RR, Mahoney GN. The misuse of buprenorphine and a buprenorphine-naloxone combination in Wellington, New Zealand. *Drug Alcohol Depend* 1993;33:81-86.

Segal DL, Schuster CR. Buprenorphine: What interests the National Institute on Drug Abuse? In: Cowan A, Lewis JW (eds). *Buprenorphine: Combating drug abuse with a unique opioid*. New York: Wiley-Liss, 1995:309-320.

Simon JL. *Resampling: The new statistics*. Arlington VA: Resampling Stats, Inc., 1993.

Weinhold LL, Preston KL, Farre M, Liebson IA, Bigelow GE. Buprenorphine alone and in combination with naloxone in non-dependent humans. *Drug Alcohol Depend* 1992;30:263-274.

Woody GE, Luborsky L, McLellan AT, O'Brien CP, Beck AT, Blaine JT, Herman I, Hole A. Psychotherapy for opiate addicts - does it help? *Arch Gen Psychiatry* 1983;40:639-645.