

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

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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 trial (8 sites, 48 patients per site) designed to determine the efficacy and safety of a buprenorphine/naloxone sublingual tablet formulation as an office-based therapy for opiate-dependence treatment. During the first, 4-week phase, patients will be randomly assigned to either 1) placebo, 2) buprenorphine 16 mg, or 3) buprenorphine 16 mg/naloxone 4 mg. Approximately 24 weeks will be required to accrue the requisite number of

patients. Patients completing the first study phase will be given the opportunity to continue in a second, open-label, 48-week phase focusing on the collection of additional safety data.

Alternatively, after completing phase 1, patients will be referred to other treatment services, as desired and appropriate. There is no provision for continued treatment with the buprenorphine/naloxone combination product following the completion of the second phase of the study. 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 determine the efficacy and 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, clinical trial that will be conducted in two phases. The first, 4-week phase will be conducted at eight sites as a randomized, double-blind efficacy assessment in which patients will be randomly assigned to one of three treatment groups: 1) placebo, 2) buprenorphine 16 mg, or 3) buprenorphine 16 mg/naloxone 4 mg. A total of 384 patients (N = 48 per site, 16 per group per site) will be recruited at a rate of about 2 per week at each study site. It is anticipated that patient recruitment will continue for approximately 24 weeks to accrue the required number of individuals.

Patients completing the first study phase will be given the opportunity to continue in the second,

48-week phase (52 weeks of total participation in both phases) so that additional safety data may be collected. Alternatively, after completing phase 1, they will be referred to other treatment services, as desired and appropriate. Phase 2 will be conducted as an open-label safety assessment of the buprenorphine/naloxone combination product only. Patients electing to continue in the second phase will be re-inducted onto buprenorphine (as described in *Medication Dosing Procedures - Phase 2*) in a manner that avoids the breaking of the phase 1 medication blind. At the conclusion of the study, individuals may be gradually tapered from their assigned treatment or referred to other treatment services, as desired and appropriate.

The objectives of phase 2 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 this size sample. Thus, four additional sites will participate only in the second phase of the study, described separately in protocol #1008B ("A multicenter safety trial of buprenorphine/naloxone for the treatment of opiate dependence").

Women of childbearing potential must agree to use a medically acceptable form of contraception while participating in the study. Patients receiving buprenorphine or buprenorphine/naloxone who become pregnant while participating in the study will be transferred to methadone; those receiving placebo will be transferred to methadone or maintained on placebo as medically indicated. These individuals may continue to receive psychosocial intervention, or be administratively discharged with referrals for further treatment as appropriate.

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, (*amendment 072696, condom without spermicide acceptable*)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 randomized to a treatment assignment (first phase) or at the time they receive an enrollment number (second phase). Subjects will sign a separate consent form for each phase of the study. 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*.

Randomization Procedures

Randomization codes for patient treatment assignments during the first phase of the study will be developed and maintained at the data coordinating center (Department of Veterans Affairs Cooperative Studies Program Coordinating Center, Perry Point, Maryland; CSPCC).

Randomization will be accomplished by assigning patients to precoded medication supplies. The CSPCC will prepare a randomized, non-sequential list of patient numbers with assigned treatment codes 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) which will then prepare medication supplies for each patient based on the treatment assignment on the list.

Investigators will telephone the CSPCC between 7:30 AM and 4:00 PM Eastern time to randomize (phase 1) and enroll (phase 2) 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, buprenorphine/naloxone, and matching placebo 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

- Phase 1

Patients will receive their first dose of study medication on Mondays through Wednesdays only. Thereafter, they will come to the clinic daily (Monday through Friday) and will be administered their medication on-site. Take-home Saturday and Sunday doses will be dispensed on Fridays; take-home doses will also be provided with respect to those holidays on which study sites would not normally provide medication services. Individuals who miss three consecutive doses of medication will be re-inducted onto the study medication. Thus, patients who fail to receive a Friday dose and do not receive that weekends' Saturday and Sunday doses will be re-inducted onto the study medication. Patients who miss one, or two consecutive doses, will continue on their assigned dosage; i.e., no re-induction procedure will be utilized.

Patients assigned to placebo will receive placebo throughout the entire first phase of the study. Individuals assigned to buprenorphine 16 mg or buprenorphine 16 mg/naloxone 4 mg will receive buprenorphine 8 mg on day 1 and buprenorphine 16 mg on day 2. Study patients will then receive buprenorphine 16 mg or buprenorphine 16 mg/naloxone 4 mg, depending upon

group assignment, on days 3 through 28.

All patients will be compensated at a rate of \$10 per day for each day they attend the clinic and complete the requisite assessments, questionnaires, etc. as specified for this phase of the study. Individuals will be compensated regardless of whether they continue to receive study medication. It is emphasized that individuals will be compensated for time spent completing study-mandated assessments; they will not be paid for receiving treatment or taking study medication.

Patients who cannot tolerate the study medication or who desire not to continue receiving it for any reason will be compensated for their providing of study data as described above. These individuals may also, if desired, continue to receive the psychosocial intervention described below, or receive a referral to other, available treatment services.

In order to keep psychosocial intervention as consistent as possible across treatment groups, all patients will receive one 1-hour session of individualized counseling per week (see *Psychosocial Treatment Services*), in addition to initial HIV counseling. The amount of psychosocial intervention provided in the context of the study, as well as any that patients may be receiving outside of the study paradigm, will be documented.

- Phase 2

Patients will not receive financial compensation during this phase of the 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 in both study phases (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-inducted 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 to the end of phase 2 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

- Phase 1 (See also Figure 1A for a schedule of data collection.)

Selection of Primary Outcome Measures

The primary outcome measures were selected to provide an efficacy assessment of the study

medications with regards to both objective (i.e., urine samples negative for opiates), and patient-based assessment (i.e., patient-reported craving for opiates). Regarding the first measure, the most direct method to ascertain the frequency and amount of illicit opiate use would be through the use of patient self-reports. However, these reports may not always be reliable or accurate (Zanis et al., 1994). Thus, as noted below, the analysis of urine samples for specific drugs or drug metabolites is typically used as an objective criterion for assessing illicit drug use. With respect to the second measure, the term craving was initially applied in reference to the strong urge for opiates experienced by opiate-dependent individuals during acute drug withdrawal (Wikler, 1948). It has since been utilized to describe an individual's desire to use any substance at any time, and the assessment of craving has been utilized extensively in the evaluation of therapeutic outcome with respect to the treatment of opiate, cocaine, and alcohol dependence (Wise, 1988; Bauer, 1992).

In addition to their use described above, the primary outcome measures have been utilized (either singly or in combination with other measures) in many efficacy assessments of buprenorphine (for review, see Fudala and Johnson, 1995), including two trials identified as pivotal (Johnson et al., 1992; Study #999A) with respect to the support of an NDA for the buprenorphine/ naloxone combination product. The inclusion of these outcome measures in the present protocol will enhance the evaluation of the combination product in consideration of the results from previously conducted clinical trials.

Primary Outcome Measures

1. Urine samples negative for opiates. Samples will be collected under observation (*amended 070896, using Franklin Collectors*) on Mondays, Wednesdays, and Fridays. If a patient fails to give a sample on the day it is due, it will be recorded as missing. Urine samples will be sent to a central laboratory (Northwest Toxicology, Inc., Salt Lake City, UT) to be analyzed for morphine and corresponding metabolites. A sample will be considered negative if the amount of drug or metabolite in the sample is less than 300 ng/ml. All Monday samples (or the first sample collected in a given week) will be analyzed additionally for amphetamines, barbiturates, benzodiazepines, cocaine, and methadone. Urine samples negative for assayed substances other than opiates will be considered as secondary efficacy measures (see below). Approximately one-

half of each urine sample will be frozen at the sites until the samples have been obtained and the results recorded at the central laboratory. Results will not be provided to the individual sites prior to all sites' completion of this study phase. Sites are prohibited from analyzing samples locally.

2. Patient-reported craving for opiates. This measure will be assessed at each clinic visit using a 100 mm visual analog scale assessing peak craving for opiates that occurred over the previous 24 hours.

Secondary Outcome Measures and Assessments

The first two measures indicated below, clinician and patient global impression/improvement ratings, have been used to assess therapeutic outcome in opiate-dependence treatment trials (e.g., Soler-Insa et al., 1987), as well as in psychiatric treatment studies of various disorders and therapeutic interventions (Feigner, 1987; Bech, 1989; Goodman and Price, 1992; Gottfries et al., 1992). They are considered the principal, secondary outcome measures in the present protocol.

1. Patient global impression rating. This patient-rated measure will be assessed on Mondays, Wednesdays, and Fridays using a 100 mm visual analog scale measuring the patient's status at the time of the rating.

2. Clinician global impression rating. This clinician-rated measure will be assessed on Mondays, Wednesdays, and Fridays using a 100 mm visual analog scale measuring the patient's status at the time of the rating.

3. 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.

4. Assessment of HIV-associated risk behaviors using the Risk Assessment Battery (RAB). 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.

5. Adverse medical events.

6. Urine samples negative for amphetamines, barbiturates, benzodiazepines, cocaine, and methadone. Results will not be provided to the individual sites prior to all sites'

completion of this study phase. Sites are prohibited from analyzing samples locally.

7. Medical evaluation results, including those from physical examinations, pregnancy tests, and clinical chemistry and hematology panels.

8. 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).

9. 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.

- Phase 2 (See also Figure 1B 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 previously, risk behaviors will be assessed using the 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. Assessments of HIV-associated risk behaviors using the RAB (assessed monthly).

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 070696, 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 TSR.
4. Population pharmacokinetic assessments of buprenorphine and naloxone.

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. The board will be blind to patients' actual treatment assignments during the first study phase, but will review the data with respect to blinded group assignments (i.e., treatment "1," "2," or "3").

Interim 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 to 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. When repeated significance tests are performed on accumulating outcome data as part of a periodic monitoring function, the overall Type I error rate can change dramatically. This consideration has received much attention in the statistical literature (Pocock, 1983; Friedman et al., 1985; DeMets, 1987). At its initial meeting, a safety data monitoring board develops guidelines for terminating a study or a portion thereof. It will be proposed to this study's Data Monitoring Board that Haybittle-Peto horizontal boundaries using criteria of ± 3 standard deviations as described by DeMets (1987) be utilized for interim tests so that final analyses would be performed at the $\alpha = 0.05$ level of significance.

Patient Safety Monitoring

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 cease to receive medication (phase 1) or will be administratively discharged from the protocol (phase 2) 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

In phase 1, all patients will receive one, 1-hour session of individualized counseling per week, in addition to initial HIV counseling. During these sessions, emergency counseling and referral services will be provided (Childress et al., 1991). However, no privileges or service

contingencies based on urine results, nor extra services such as family or employment counseling will be offered. Study participants will not be encouraged to participate in any additional therapy.

In phase 2, 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 as described above will be available. 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

- Phase 1

The objective of this study phase is to compare, as described below, the three treatment groups (placebo, buprenorphine 16 mg, and buprenorphine 16 mg/naloxone 4 mg) with respect to the primary and secondary outcome measures and assessments. A total of 384 patients will be enrolled at eight sites over a period of approximately 24 weeks. Thus, each site will enroll 48 patients (16 patients per treatment group per site) at a rate of about 2 patients per week.

- Primary Outcome Measures

The two primary outcome measures were used in the estimation of requisite sample size for the study. No adjustment of the Type I error α level will be made for the analyses of these measures, and only one of the three possible pairwise treatment comparisons, buprenorphine/naloxone versus placebo, will be considered as primary. Results of the other two pairwise comparisons will be of secondary interest. The mean percentages of "clean" urine samples (see below) for all three treatment groups will be compared by pairwise normal (approximation to the binomial) Z-tests. For the other primary outcome measure (as well as for the principal secondary outcome measures - see below), repeated-measures analysis of variance or covariance procedures (as appropriate) will be used. All statistical analyses of primary outcome measures will be performed using "intent to treat" methodology (i.e., all randomized patients will be included in the analyses) and will incorporate the pooled data from all study sites. Subanalyses will also be performed to identify treatment by site interactions and potential differences related to gender.

Where appropriate, imputational methods will be used to estimate missing data. Primary, repeated-measures analyses will use software such as the BMDP-5V procedure (Schluchter, 1988) which allows for the use of incomplete data sets. All available data can be used for analyses with this or related procedures (see Gornbein et al, 1992 and Laird, 1988 for a discussion of the assumptions related to the appropriate use of this and other procedures). Additional analyses will include only those patients with complete data sets.

1. Urine samples negative for opiates ("clean" samples). Since the incidence of opiate use is not directly measurable, a urine sample containing ≥ 300 ng/ml opiates or opiate metabolites will be considered positive ("dirty") and indicative of an episode of opiate use; < 300 ng/ml will be considered negative ("clean"). Urine samples will be collected three times weekly on Mondays, Wednesdays, and Fridays.
2. Patient self-reported craving for opiates. This measure will be assessed at each clinic visit using a 100 mm visual analog scale (anchored with "no craving" on one end and "most intense craving I ever had" on the other) measuring peak craving for opiates that occurred

over the previous 24 hours.

- Secondary Outcome Measures and Assessments

For the two principal, secondary outcome measures (patient and clinician global impression ratings), repeated-measures analysis of variance or covariance procedures (as appropriate) will be used. Patient retention data will be analyzed by comparing the survival curves of the three treatment groups. Estimates of the survival distribution function will be calculated using the Kaplan-Meier method (Kaplan and Meier, 1965). The homogeneity of the survival function across groups will be assessed using the log rank test (Peto and Peto, 1972). The potential influence of covariates (e.g., age, gender) on patient retention will be assessed using the Cox proportional hazards model (Cox, 1972). The analytical methodology for the other secondary outcome measures is described in the Biostatistical Review and Data Processing appendix (Appendix E).

1. Patient global impression rating. This measure will be assessed on Mondays, Wednesdays, and Fridays using a 100 mm visual analog scale (anchored with "much worse" on one end, "no change" in the middle, and "much better" on the other end) measuring a patient's overall status since the previous observation and since entering the study
2. Clinician global impression rating. This measure will be assessed on Mondays, Wednesdays, and Fridays using a 100 mm visual analog scale (anchored with "much worse" on one end, "no change" in the middle, and "much better" on the other end) measuring a patient's overall status since the previous observation and since entering the study.
3. 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.
4. Assessment of HIV-associated risk behaviors using the Risk Assessment Battery (RAB).
5. Adverse medical events.
6. Urine samples negative ("clean") for amphetamines, barbiturates, benzodiazepines, cocaine, and methadone.

7. Medical evaluation results, including those from physical examinations, pregnancy tests, and clinical chemistry and hematology panels.
8. Amount of psychosocial treatment services provided using the Treatment Services Review (TSR).
9. Population pharmacokinetic assessments of buprenorphine and naloxone.

- Sample Size

Sample size estimations were derived using effect sizes and variances observed in Study #999A ("A multicenter trial of buprenorphine in treatment of opiate dependence") in which the effects of 8 mg and 1 mg buprenorphine, both given as sublingual solutions, were compared. The effects obtained from the 16 mg tablet formulation in the present study are expected to be analogous to those from the 8 mg solution. However, the 1 mg dosage used in the previous trial is expected to be at least as efficacious as placebo in the present study. Sample size estimates based on these results are, therefore, conservative (i.e., larger than required) since differences in treatment effect sizes are expected to be larger in the present study. In consideration of the above, the following action plan has been developed. Interim analyses (see *Interim Monitoring* described previously) under the guidance of the Data Monitoring Board will be conducted. If efficacy of the buprenorphine/naloxone treatment is demonstrated prior to the completion of phase 1 enrollment, the Data Monitoring Board will consider recommendations regarding whether phase 1 of the study should be terminated and all subjects enrolled in phase 2. This would modify patient recruitment in phase 2 in order to reach the FDA-targeted sample size required for the evaluation of safety. The above plan was introduced to reduce the number of individuals exposed to a placebo treatment to the minimum necessary to achieve the study goals.

Opiate clean urine samples was the first primary outcome measure used in the estimation of requisite sample size for phase 1. Estimates were obtained using software and procedures as described for a two-group, one-factor analysis of variance in Cohen (1977). A minimum detectable difference of 10 percentage points between the buprenorphine/naloxone and placebo groups was chosen. Data from the first four weeks of Study #999A indicated that the 8 mg

buprenorphine treatment group was associated with $25.4 \pm 30.2\%$ (mean \pm SD) and the 1 mg with $14.8 \pm 25.8\%$ opiate clean urine samples. In order to detect a significant difference of 10% with a Type I error rate of 0.05 and a power of 0.9, 84 patients per group (252 total) would be required. Since only clean urine samples provided will be considered (missing and dirty samples are considered "not clean"), no adjustment of sample size due to missing data is required.

Additional

estimates based on $\alpha = 0.05$ are shown in the table below.

MINIMUM DETECTABLE DIFFERENCE	POWER		
	80	85	90
5%	248	284	332
10%	63	71	84
15%	28	32	37
20%	16	18	21

Patient self-reported craving for opiates was the second primary outcome measure used in the estimation of requisite sample size for phase 1. A minimum detectable difference of 10 points between the buprenorphine/naloxone and placebo groups was chosen. Data from the first four weeks of Study #999A indicated that the 8 mg buprenorphine treatment group was associated with craving scores of 30.0 ± 31.2 (mean \pm SD) and the 1 mg with 42.7 ± 34.7 . In order to detect a significant difference of 10 points with a Type I error rate of 0.05 and a power of 0.8, 86 patients per group (258 total) would be required.

Assuming that 86 patients are required for each of the three treatment groups (see tables below) and allowing for approximately 30% (i.e., 33%) attrition, a total of about 128 patients per group (384 total) would be required.

MINIMUM DETECTABLE DIFFERENCE	POWER		
	80	85	90
5	342	392	458
10	86	98	115
15	38	44	51
20	22	25	29

Number and percentage of patients completing between one and four weeks of Study #999A.

TREATMENT GROUP	NUMBER OF PATIENTS RANDOMIZE D	NUMBER (PERCEN TAGE) OF PATIENT S COMPLE TING WEEK NUMBER			
		1	2	3	4
Buprenorphine 1 mg	184	166 (90.2)	151 (82.1)	140 (76.1)	130 (70.7)
Buprenorphine 8 mg	186	168 (90.3)	157 (84.4)	149 (80.1)	145 (78.0)
TOTAL	370	334 (90.3)	308 (83.2)	289 (78.1)	275 (74.3)

- Phase 2

The objective of this study phase is to assess the safety of the buprenorphine/naloxone combination product in 300 patients who have taken the medication for at least eight weeks. A total of 524 individuals will be enrolled to obtain this 300-patient sample. These individuals will be enrolled through this phase of the present protocol, as well as through CSP study #1008B conducted at an additional four 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 CSP 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 CSP study #999A an enrollment of 500 individuals would be required to achieve the necessary sample of 300 (about 70% retention through week 4 and 60% through week 8 of the present study). 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 #1008B contingent upon their approval by the Department of Veterans Affairs Cooperative Studies Program:

Paul Casadonte, M.D. (New York, NY)
Walter Ling, M.D. (Los Angeles, CA)
Usha Malkerneker, M.D. (Hines, IL)
Laura McNicholas, M.D., Ph.D. (Philadelphia, PA)
John A. Renner, Jr., M.D. (Boston, MA)
Eugene Somoza, M.D. (Cincinnati, OH)
Susan Stine, M.D., Ph.D. (West Haven, CT)
Donald J. Tusel, M.D. (San Francisco, CA)

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.

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