

LAATRC/VA/NIDA Study #999a
A Multicenter Clinical Trial of
Buprenorphine in Treatment of Opiate Dependence

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February 7, 1992
TABLE OF CONTENTS

	Page
STUDY OBJECTIVE.....	1
BACKGROUND	1
Study Sponsor	1
Prior Studies of Buprenorphine in Treatment of Addiction	1
Buprenorphine Pharmacology	2
METHOD	3
Inclusion Criteria	4
Exclusion Criteria	4
Patient Screening, Recruitment, and Informed Consent	4
Randomization	5
Study Medications	5
Buprenorphine Induction and Maintenance Procedures	5
Reinduction After Lapse in Dosing	5
Measures and Measurement Instruments	6
Major Efficacy Measures	6
Other Measures	6
Patient Safety Monitoring	8
Data Monitoring Board	8
Psychosocial Treatment Services	8
Termination of Patients from the Study	8
DATA MANAGEMENT	9
STATISTICAL CONSIDERATIONS	9
Efficacy Variables	10
Statistical Methods	10
Analysis of the Incidence of Opiate Abuse	10
Analysis Primarily for FDA Statistical Review	11
Analysis Primarily for FDA Medical Review	13
Exploratory Analyses to Identify Subgroups	14
Analysis of Dropout Rates	14
Analysis of Opiate Craving Scores and Global Rating Scores	14
Secondary Variables	14
Sample Size Consideration	15
Summary of Assumptions Made in Sample Size Calculations	16
Interim Monitoring	16
PATIENT RIGHTS	17
PARTICIPATION	17
REFERENCES AND BIBLIOGRAPHY	18
APPENDIX A - Informed Consent	21
APPENDIX B - Curricula Vitae	27
APPENDIX C - Study Budget	37
APPENDIX D - Study Forms	55
APPENDIX E - Biostatistical and Research Data Processing Procedures	85

STUDY OBJECTIVE

The primary purpose of this 16-week maintenance study is to determine the safety and effectiveness of 8 mg per day sublingual buprenorphine as compared to 1 mg per day sublingual buprenorphine in decreasing illicit opiate use as measured by urine testing 3 times a week, retention rates, and opiate craving and global rating scores in patients who meet DSM-III-R criteria for opiate dependence. A secondary purpose of the study is to gather more experience with two other doses of buprenorphine, 4 mg per day and 16 mg per day, regarding safety in the same population. Because the data will be used to support an NDA for buprenorphine in the treatment of opiate dependence, the data will be collected using FDA guidelines for good clinical practices.

BACKGROUND

Study Sponsor

NIDA is the study sponsor. This protocol will be conducted under IND #35877.

Prior Studies of Buprenorphine in Treatment of Addiction

Buprenorphine, a partial agonist analgesic, with both agonist and antagonist effects, has been undergoing clinical investigation for treatment of opioid dependence for over a decade (Jasinski, Pevnick, Griffith, 1978). Although a parenteral form of buprenorphine (Buprenex) has been approved by the FDA for relief of moderate to severe pain, the use of buprenorphine for treatment of opioid dependence is investigational.

The pharmacological profile and clinical studies of buprenorphine suggest that buprenorphine will be useful for treatment of opiate dependence. Early studies with opiate addicts showed that buprenorphine blocked the effects of morphine. Unlike the opiate agonist blockade produced by methadone, blockage of opiate agonist effects by buprenorphine induces a low level of opiate physical dependence. Naloxone administration did not precipitate acute withdrawal in patients treated with buprenorphine. Abrupt discontinuation after eight weeks of buprenorphine treatment resulted in only a mild morphine-like withdrawal. In another study, 2 mg of buprenorphine was given subcutaneously to 8 patients in place of their daily dose of methadone (mean daily dose of 36 mg). Only mild discomfort resulted, and after 28 days of buprenorphine administration, abrupt placebo substitution resulted in a mild withdrawal syndrome of several days duration (Jasinski, Henningfield, Hickey, et al., 1982).

Studies of buprenorphine in opiate abusers have found that patients stopped self-administration of heroin (Jasinski, Pevnick, Griffith, 1978; Mello, Mendelson, Kuehnle, 1982). In a double-blind short-term study, 2 mg of sublingual buprenorphine was found to be comparable to 30 mg of methadone (Bickel, Stitzer, Bigelow, et al., 1988). Interpretation of the results of this study is ambiguous because there was no placebo group. Illicit opioid use in this study was common and suggests a need for higher dosage.

In a 30-day, outpatient, open-label clinical trial, buprenorphine in doses of 2, 4, and 8 mg, sublingually, was effective in maintaining abstinence and keeping patients in treatment. At the conclusion of the trial, buprenorphine was abruptly discontinued. Patients maintained on the 8 mg dose had substantial increase of withdrawal symptoms. Those on 2 and 4 mg doses had only minimal withdrawal, and seven of the 16 patients were successfully started on naltrexone (Kosten and Kleber, 1988).

These clinical trials involved small numbers of patients, and they need to be confirmed with controlled studies of larger numbers. The results thus far, however, are promising and suggest that buprenorphine could be an effective agent for detoxification as well as for maintenance.

Buprenorphine is not entirely free of abuse liabilities although it may be less addictive than methadone. Some buprenorphine abuse by addicts has been reported in Europe and Australia where the drug is available in a tablet form (e.g., O'Connor, Maloney, Travers, et al., 1988; Quigley, Bredemeyer, Seow, 1984).

The proposed study extends research on buprenorphine recently completed at NIDA's Addiction Research Center. That study, conducted by Rolley E. Johnson, found 8 mg of buprenorphine superior to 20 mg of methadone and comparable to 60 mg of methadone in a 180-day detoxification study.

Buprenorphine Pharmacology

Buprenorphine hydrochloride is classified as a μ -opiate partial agonist. It is structurally related to morphine but it has a longer duration of action and its analgesic activity is 25 to 40 times more potent than morphine (Jasinski, Pevnick, Griffith, 1978). The exact mechanism by which buprenorphine produces analgesia is unknown, but it appears to result from a high affinity binding of CNS opiate receptors. Buprenorphine has a high affinity for the μ -opiate receptors and dissociates from them slowly, which may contribute to its long duration of action (Jasinski, Pevnick, Griffith, 1978; Jasinski, Fudala, Johnson, 1989). Buprenorphine may appear to act as both an opiate agonist and antagonist; however, this is due to its partial agonist properties, not necessarily the antagonist properties. It produces only a limited maximal effect even when a maximally effective dose is given, so although buprenorphine shows a high affinity for the μ -opiate receptor, it has only low to moderate intrinsic activity (Martin, Eades, Thompson, Huppler, Gilbert, 1976).

Buprenorphine is pharmacologically active when given by the subcutaneous, sublingual and oral routes of administration. In 1982, Jasinski et al. reported the onset of action, time to peak, and duration of effect to be similar among the three routes of administration. The relative potency ratio between these three routes of administration has been reported to be 15:10:1, respectively (Lange, Fudala, Dax, Johnson, 1990). When administered sublingually, buprenorphine is readily absorbed with approximately 50% of a dose absorbed systemically (Reckitt and Colman, 1987).

Buprenorphine generally produces few cardiovascular effects. A usual analgesic dose of buprenorphine may depress respiration to the same degree as 10 mg of parenteral morphine sulfate in nonopiate tolerant individuals. The onset of buprenorphine-induced respiratory depression when it does occur is slower than that of morphine-induced respiratory depression and the duration appears to be more prolonged. Like opiate agonists, buprenorphine has been shown to decrease plasma concentrations of luteinizing hormone (LH) and increase plasma concentration of prolactin (Mendelson, Ellingboe, Mello, Kuehnle, 1982). The most common adverse effects reported with the sublingual administration of buprenorphine include drowsiness, dizziness, nausea, and vomiting (Lange, Fudala, Dax, Johnson, 1990).

METHOD

This is a multicenter, randomized, clinical trial that will involve a minimum of 480 opiate abusers seeking opiate maintenance treatment. The study will be conducted at 10-12 sites with a maximum of 60 patients enrolled per site. Patients will be recruited at a rate of about 2 per week at each study site. Patient recruitment will last 30 weeks. Patients will remain on study medication for 16 weeks. After eligibility screening and signing a written informed consent, patients will be randomly assigned to one of four treatment groups: buprenorphine 1, 4, 8, or 16 mg/day. About 120 patients will be assigned to each group. Each site will enroll 15 patients into each group.

Patients will be administered their buprenorphine dose daily. No takeout dosages of medication will be allowed. Study sites will dispense buprenorphine 7 days per week.

After patients complete the 16-week protocol, they may be continued on the study drug under a new protocol or offered other treatment available at clinic. Patients who wish to be tapered from buprenorphine will be administered the induction schedule in reverse. If resources are available at the site, eligible patients can be switched to methadone or other treatments available after they are tapered from the buprenorphine. Otherwise, they will be tapered off the drug.

Inclusion Criteria

1. DSM-III-R diagnosis of current *opiate dependence* with daily use for past month.
2. Male and non-pregnant, non-nursing female, ages 18 or older.
3. Mentally competent to give informed consent.
4. Agreeable to being in protocol (signs informed consent).
5. Permanent residence within commuting distance of clinic.
6. Urine negative for methadone.

Exclusion Criteria

1. Acute hepatitis or any other acute medical condition that would make participation in the study medically hazardous for the patient, e.g., active tuberculosis, unstable cardiovascular or liver disease, unstable diabetes, or AIDS (not HIV-positive alone). Patients with elevated liver enzymes (SGOT or SGPT greater than 5 times the upper limit of normal) require more frequent clinical and laboratory monitoring than those specified in the schedule of data collection. Those with liver enzymes exceeding 8 times the upper limit of normal require at least weekly clinical and laboratory examinations and consultation from a specialist in liver disease before enrollment.
2. DSM-III-R diagnosis of current *alcohol dependence or sedative-hypnotics dependence*.
3. Current daily use of anticonvulsants, Antabuse, or neuroleptics.
4. Patient not expected to remain available to attend clinic for duration of study (e.g., those with criminal charges).
5. Patient enrolled in a methadone maintenance program within the past 30 days.
6. Has been a patient in a prior buprenorphine trial for treatment of drug addiction.
7. Currently participating in another research project.
8. Female patient of childbearing potential who refuses birth control.

Patient Screening, Recruitment, and Informed Consent

Patients will be recruited from among opiate dependent patients who apply for treatment at the participating clinics. Figure 2 shows the number of patients that would be active at each site if the patients are recruited at a rate of 2 per week. The top curve shows the number of patients who would be active if all patients remained in the study for the full 16 weeks. The bottom curve is a computer simulation that assumes an overall dropout rate of 30 percent. It will be important for each participating facility to enter a substantial number of female patients. NIDA strives to have at least a third of the patients in their studies be female and requires that at least 25% of study patients are females. Each facility must develop a plan to ensure that sufficient females are entered at their site. This plan might include providing contra-ceptive information and supplies to those women who lack the resources to purchase these supplies themselves.

Screening information needed to ascertain inclusion/exclusion criteria will be collected and recorded on the Study Admission Record (Form 11).

A physician investigator will review the case report forms (Forms 01 to 10) and meet with the potential patient. If the physician determines that the patient satisfies inclusion/exclusion criteria, the physician will discuss the study consent form with the patient. Eligible patients who sign the consent form will become patients in the study when they receive their first dose of buprenorphine.

Randomization

The randomization will be accomplished by assigning patients to precoded medication supplies. The Pharmacy Coordinating Center (VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center at the Albuquerque VA Medical Center) will provide medication supplies already packaged in unit doses. Eligible patients who have signed a consent form will be randomized to one of the prepackaged boxes of medication just before they receive their first dose of buprenorphine and become a participant in the study. To randomize a patient, the investigator will telephone the Data Coordinating Center (VA Cooperative Studies Program Coordinating Center at the Perry Point VA Medical Center), who will assign the patient to the appropriate nonsequential patient number.

Study Medications

The buprenorphine doses will be supplied to the study sites in prepacked unit doses consisting of 1 ml liquid containing 1, 2, 4, 8, 12 or 16 mg of buprenorphine. Each dose is in a triangular plastic pack with a breakaway top. The blinding of medication will be done at the Pharmacy Coordinating Center.

All staff at participating sites will be blind to patients' doses. Medications will be administered by a dispensing nurse. Patients will hold medication under their tongue for 5 minutes following the sublingual dosage to assure absorption. No takeout doses of buprenorphine will be allowed under this protocol.

Buprenorphine Induction and Maintenance Procedures

Before the first dose of medication, patients will be examined by a staff physician. Patients assigned to 1 mg of buprenorphine will receive 1 mg per day for the 16 weeks. Patients assigned to 4 mg of buprenorphine will receive 2 mg on day one, and 4 mg per day for the remainder of the study. Patients assigned to 8 mg of buprenorphine will receive 2 mg on day one, 4 mg on day two, and 8 mg per day for the remainder of the study. Patients assigned to 16 mg of buprenorphine will receive 2 mg on day one, 4 mg on day two, 8 mg on day three, 12 mg on day four, and 16 mg per day for the remainder of the study.

Reinduction After Lapse in Dosing

Patients who miss 4, 5 or 6 sequential days of dosing will be reinducted on buprenorphine. Patients' medication supplies will contain supplies for 3 reinduction cycles. The reinduction dose schedule is the same as the initial induction.

Measures and Measurement Instruments

Major Efficacy Measures

1. *Urine samples for drugs of abuse* will be collected under observation on Monday, Wednesday, and Friday for each patient. If 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 (University of Utah) to be analyzed for morphine and cocaine or metabolites. An opiate positive will be morphine greater than 300 ng/ml; a cocaine positive will be a cocaine or metabolite greater than 300 ng/ml. All Monday samples (or the first sample collected in a week) will be analyzed additionally for amphetamine, methadone, and benzodiazepines. Study sites will not receive urine results from the University of Utah and study sites are prohibited from locally analyzing urines for drugs of abuse. About half of each urine sample will be frozen at the facilities until the results have been obtained and recorded at the central laboratory.
2. *Days of retention in treatment* is an important measure of treatment effectiveness. If a patient is terminated for any reason, the date of the last buprenorphine dose will be considered the termination date. The *reason for protocol termination* will be determined as precisely as possible (e.g., medication side effects, arrested, moved from area) and recorded on the study Termination Form (Form 18).
3. *Opiate and cocaine craving scores* (Form 13) will be measured with a visual analogue scale. The patient will be instructed to record the peak craving that has occurred during the past 7 days. Patients will record their estimate on a 100 mm line designated no craving on one end and maximum craving ever experienced on the other.
4. *Global Rating Scores* (Forms 04 and 05) are an overall rating of the patient's status at the time of the rating and in comparison to both his/her status at the previous rating and upon entering the study. These scores will be completed by both the patients and the staff. The current status portions of the rating are based on a scale of 0 to 100 with 0 representing an absence of drug problems and 100 representing the worst ever case. The ratings comparing status from the previous rating period are based on a five-point scale where 5 is "much better" and 1 is "much worse."

Other Measures

1. *Serum plasma levels of buprenorphine* will be collected at weeks 2 and 8. The sample will be drawn 24 hours after the previous dose and before administration of the next buprenorphine dose. The plasma will be frozen and sent to a central laboratory for analysis.
2. *Missed doses* Each site will keep records (Coordinators Weekly Report - Form 12 and Dose Administration Record - Form 19) documenting the administration of each dose. The number of missed doses will be computed from these records.
3. *Adverse experiences* will be evaluated at screening (Medical History and Status - Form 06) and weekly thereafter (Adverse Events - Form 16). The questions to elicit this information are open ended. The signs, symptoms or life-events need not necessarily be caused by buprenorphine. The study sites must report within 24 hours serious adverse experiences (i.e., death, experience resulting in permanent disability or hospitalization) to the sponsor (NIDA), the IRB, and the

Clinical Coordinating Center. (The sponsor will report the reaction to FDA.) Form 17 (Serious Adverse Event Form) must be completed for all serious adverse experiences.

4. A complete physical examination will be done at baseline and termination and recorded on the medical monitoring form. An abbreviated physical examination (Form 09) will be done monthly. More frequent medical evaluations may be conducted as clinically indicated.
5. The amount of psychosocial treatment provided patients will be recorded weekly on Form 14 - Psychosocial Services Received. This measure is to monitor comparability of groups on the amount of psychosocial services received.

Schedule of Data Collection

Instruments	Screen	Week of Study															
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Form 01 - Background Information	x																
Form 02 - Drug Use History	x																
Form 03 - DSM-III-R Criteria for Diagnosis of Opiate Dependence	x																
Form 04 - Global Rating (Staff)	x				x				x				x				x
Form 05 - Global Rating (Patient)	x				x				x				x				x
Form 06 - Medical History and Status	x																
Form 07 - Craving Scale	x																
Form 08 - Laboratory Report	x		x		x				x				x				x
Form 09 - Physical Exam	x				x				x				x				x
Form 10 - Electrocardiogram	x				x												x
Form 11 - Study Admission	x																
Form 12 - Coordinators Weekly Report		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Form 13 - Weekly Self-Report of Drug Use and Craving Scale		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Form 14 - Psychosocial Services Received		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Form 15 - Concomitant Medication		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Form 16 - Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Form 17 - Serious Adverse Events*																	
Form 18 - Termination																	x
Form 19 - Dose Administration Record ?																	
Locator Information	x																
Informed Consent	x																
* To be completed only as necessary. ? To be completed daily beginning with the first dose of buprenorphine.																	

6. Pregnancy testing of women of childbearing potential will be done by serum pregnancy test during screening, and monthly. Women of childbearing potential must agree to use adequate contraception while in the study. Should pregnancy occur, her participation in the protocol will be terminated. Results will be recorded on Form 08, Laboratory Report.

7. Laboratory data CBC, UA, SMA-12 (to include BUN, creatinine, SGOT, SGPT, GGT, alkaline

phosphatase and bilirubin, total protein and albumin, and glucose) and EKG will be collected as indicated on the table. These will be performed at each site and the results recorded on Form 08, Laboratory Report, except for the EKG which is recorded on a separate form (Form 10).

Patient Safety Monitoring

The study site physicians, who are blind to buprenorphine dose, will be responsible for the day-to-day clinical monitoring of patients. If the physician observes significant signs or symptoms of buprenorphine toxicity, the physician will order the dispensing nurse to not dispense the patient's buprenorphine dose for that day. If this occurs on three successive occasions, the P.I. will terminate the patient from the study. A patient whose liver enzymes, SGOT and/or SGPT, rise above 8 times the upper limit of normal requires filing of an Adverse Events Form (Form 16) and a Serious Adverse Event Form (Form 17). An immediate telephone report to MDD/NIDA is also required. To remain in the study, such patients must have weekly clinical and laboratory follow-up examinations, more often if necessary, and consultation from a medical specialist in liver disease.

Data Monitoring Board

The group safety data will be monitored monthly by the Study Chairman and periodically reviewed by the Data Monitoring Board.

Psychosocial Treatment Services

Local sites will have some variability in the amount of psychosocial services provided; however, all sites should include at least one session of AIDS education. Psychosocial services are those given in addition to regular contact with staff to complete the case report forms. In general, formal counseling and other psychosocial services should not exceed one hour per week and not be less than one hour/month.

If a patient requires further counseling for significant life-crisis problems (e.g., death, loss of job, divorce), the investigator may increase the amount of counseling at his/her discretion. This shall be well-documented.

Termination of Patients From the Study

Once a patient has been assigned a randomized number from Perry Point, he/she shall not be replaced if terminated early. Patients are in the study voluntarily and can terminate their participation at any time. In addition, the investigators shall terminate a patient's participation for any of the following reasons:

1. Medication Toxicity (e.g., excessive sedation).
2. Missing 7 consecutive days of dosing.
3. Buprenorphine toxicity, evidenced by significant signs or symptoms, that warrants drug dosing to be withheld on three successive occasions.
4. When a patient requires a fourth induction (i.e., patient has already been reinducted 3 times for missing 4, 5 or 6 sequential days of dosing).
5. Termination by clinic physician because of intercurrent illness or medical complications precluding safe administration of buprenorphine.
6. Administrative termination (e.g., moved from area, violence or threats of violence within clinic, excessive drinking).
7. Pregnancy.

DATA MANAGEMENT

The data management for NDA purposes will be done by the VA Cooperative Studies Program Coordinating Center at Perry Point, Maryland. At the study sites, data will be collected on triplet NCR forms supplied by the Data Coordinating Center at Perry Point. Completed Case Report Forms (CRF) for each patient will be retained at the study site until reviewed by an authorized study project monitor. The monitor will send one copy to the VA Cooperative Studies Program Coordinating Center at Perry Point; and one copy will be sent to the NIDA project director. All other Case Report Forms and source documents will be retained at the study site.

Principal investigators at each site must agree to data audits by NIDA's Medications Development Division's quality control staff and comply with directions from the Clinical Coordinating Center with regard to protocol compliance and data quality control.

STATISTICAL CONSIDERATIONS

The objective of the proposed study is solely to compare the efficacy of the 8 mg dose of buprenorphine with the 1 mg dose of buprenorphine. The purpose of including the 4 and 16 mg doses of buprenorphine in the trial is to provide additional information about the adequacy of the 8 mg dose and not to prove the efficacy of the 4 mg and 16 mg doses. It is believed that in order to have a successful NDA, information concerning doses other than 8 mg will be required by FDA. Therefore, data on these two additional doses, such as estimates of efficacy parameters and side effects, will be collected to complement the 8 mg versus 1 mg dose comparison.

However, since doses other than 8 mg may be more appropriate for certain subgroup of patients, exploratory analyses as described later will be conducted to identify these subgroups.

Efficacy Variables

Four major efficacy variables will be analyzed. No adjustment in α levels will be made for multiple efficacy variables. These variables will be:

1. Incidence of opiate abuse: Since, the incidence of opiate abuse is not directly measurable, a urine sample testing positive for the presence of opiates will be indicative of an episode of opiate abuse. The urine samples will be collected three times a week on Mondays, Wednesdays and Fridays.
2. Retention rates: The time from entry in the study to the last dose of buprenorphine administered will be the second major efficacy variable. The reason for termination will be recorded as accurately as possible.
3. Opiate craving scores will be measured with a visual analogue scale. The patients will be instructed to record the peak craving that has occurred during the past 7 days. Patients will record their estimate on a 100 mm line designated "no craving" on one end to "most intensive craving I ever had" on the other.
4. Global Rating Scores are overall ratings of the patients' status at the time of rating (on a scale of 0 meaning no drug problem to 100 meaning worst case ever). These ratings are completed at screening and every four weeks thereafter. The patients are also rated on a scale from 1 (much worse) to 5 (much better) as compared to the previous rating. Both types of ratings are completed separately by the staff as well as the patients. The staff will also be asked to rate the patient at termination in comparison to how the patient was at the time of entry into the study using the five-point scale.

Statistical Methods

Analysis of the Incidence of Opiate Abuse

As mentioned earlier, the incidence of opiate abuse will be estimated by the urine samples obtained and analyzed three times a week, i.e., on Mondays, Wednesdays and Fridays. Thus, in this 16-week maintenance study, up to 48 urine samples will be collected for each patient in the study. However, given the experience with the ARC 090 Study which had as high as 80% dropout rate in the low dose methadone group, the dropout rates are likely to be high and even those who stay in the study are likely to miss a substantial number of clinic visits and, thus, there are likely to be a lot of missing urine samples. In the ARC 090 study, on the average, 20% of the urine samples were missing. Consequently, in order to handle missing values and to simplify statistical analysis, a weekly index of urine positivity for opiates has been developed, or in other words, 48 data points will be reduced to 16 weekly data points. For a given patient, his first study week will be days 1-7 in the study, second study week will be days 8-14 in the study, etc.

Analysis Primarily for FDA Statistical Review

The following **data reduction** algorithm will be used:

1. If there is at least one positive urine during a given study week, that week will be considered positive for opiates (a *positive week*).
2. If all three samples during a week are found to be missing, that week will be considered a *positive week*.
3. If conditions 1 and 2 above are not met, the week will be considered to be a *negative week*.

In a 25-week (17 weeks of maintenance and 8 weeks of detoxification treatment), three-arm study conducted by Addiction Research Center (ARC 090 study), the efficacy of 8 mg buprenorphine was compared with a 20 mg dose of methadone which was considered as a placebo treatment and with 60 mg dose of methadone which was considered as an active control group. It was seen that percents of positive urines observed for buprenorphine were consistently (i.e., over each time point) lower for the maintenance phase of the study than for either the 20 mg or 60 mg methadone groups. The order in which percents positive urines were observed was: (buprenorphine 8 mg) < (methadone 60 mg) < (methadone 20 mg). Even though analysis of variance does not permit analysis of censored observations (as is the case for both ARC 090 and the proposed study), the data for each patient was pooled over time and three treatment groups were compared for percent positive urines. Statistically significant differences were observed for the buprenorphine and methadone 20 mg comparison ($p < .001$) in favor of buprenorphine. However, no statistically significant differences were observed ($p = .78$) for the comparison between methadone 60 mg and buprenorphine treatments. This is contrary to what would be expected since buprenorphine treatment resulted in consistently lower percent of positive urines when compared to 60 mg methadone treatment. Obviously, analysis of variance did not result in a test powerful enough to capture the differences between buprenorphine and 60 mg methadone treatment groups. In addition, as mentioned earlier, analysis of variance does not permit the analysis of censored observations. **Consequently, analysis of variance will be used to analyze data from the proposed study for medical review only.**

As an alternative to the (parametric) analysis of variance considered above, data for each patient can be scored, e.g., 0 for a negative urine and 1 for a positive urine and the sum of scores for each patient can be calculated. These sum of scores can be ranked and a (non-parametric) analysis of variance for these ranks can be used. However, there are several problems with this approach. Firstly, this approach also does not permit censored observations. It was suggested by Dr. Harter of FDA that the missing and censored data points should be scored as 1, i. e., all urine samples for which data are not available be considered positive. Since, based on the dropout rates in ARC 090 study (60% to 80%), we expect a high dropout rate in this study too, this analysis will be based on more unreal, i.e., made up data than the real observed data. This certainly would not be advisable. Secondly, these sum of scores obscure the pattern of positive and negative urines, e.g., a score of 25

does not inform whether these 25 positive urines came from first half of the study or second half of the study. Thirdly, the differences in ranks are not directly interpretable for a clinician. For example, mean rank for a group A may be 22.2 and group B, 28.2, but this difference of 6 in mean ranks is not interpretable in terms of percent positive urines. For these reasons, it was decided that (non-parametric) analysis of variance based on ranks would not be a suitable procedure for the proposed study.

Since each positive urine is considered to be indicative of an episode of drug abuse and as such a possible treatment failure, these data can be analyzed by using one of the multiple failure models proposed in the literature. In this study, 48 urine samples will be collected from each patient and as such, a patient can experience up to 48 failures. Many methods to analyze multiple failures have been proposed but the one based on Cox's proportional hazards model by Wei and others (JASA, 84, 1065-1073, 1989) imposes least restrictive structure on the data and is proposed to be used for this multicenter study. The computer program given in Lin (1990) will be used.

The reduced data, i.e., 16 data points as explained earlier, one for each week will be used for this analysis. Since, treatment assignment will be the only covariate used, 16 regression coefficients will be estimated. A common regression coefficient estimated as $\hat{\alpha} = \sum c_i \hat{\alpha}_i$ where $\hat{\alpha}_i$ is the regression coefficient for failure i ($i=1, \dots, 16$) will be tested for statistical significance and the common hazard ratio $HR = e^{\hat{\alpha}}$ will be estimated.

The estimate of common $\hat{\alpha}$ (common HR), if found to be statistically significantly different from zero (one) for the data pooled for all study centers for buprenorphine 8 mg versus buprenorphine 1 mg analysis only at $\alpha=.05$, will be indicative of the superiority of one drug over the other for FDA approval purposes.

This model was successfully used to analyze the ARC 090 study using a 17 dimensional model using the same data reduction algorithm as proposed for this study and buprenorphine was found to be statistically significantly better than both methadone 20 mg ($p=.015$) and methadone 60 mg ($p=.037$). The common hazard ratio was found to be .746 for the buprenorphine/60 mg methadone comparison and .706 for the buprenorphine/20 mg methadone comparison.

The common hazard ratio estimable from this model has an easy clinically understandable interpretation. For example, a common hazard ratio of .746 for the buprenorphine/60 mg methadone comparison means that the conditional probability of a buprenorphine treated addict, on the average, has a 25.4% less chance of abusing drug (opiate) compared to a methadone 60 mg treated addict provided none of them have yet used opiate. In other words, after the treatment begins, a buprenorphine treated addict has, on the average, 25.4% less chance of using opiate the first time compared to 60 mg methadone treated addict. In addition, the hazards ratios or comparative conditional probabilities for using the opiate the first time, the second time etc. are also estimable from $\hat{\alpha}_1, \hat{\alpha}_2$, etc. The relationship between the first, second positive urines etc. can also be studied by variance-covariance matrix of $\hat{\alpha}$'s. Consequently, use of this model has the following advantages:

? This model can be used for censored data.

- ? Hazard ratios estimable from this model have easy clinically understandable interpretations.
- ? The relationship (pattern) between various positive urines can be studied.

The time to first failures, second failures, etc., will be counted from the beginning of the study in days. For example, for the first positive week, if the first positive urine during study week seven was observed on day 45, the time to first failure will be 45 days. For the second positive week if the first positive urine during study week ten was observed on day 66, the time to second failure will be 66 days. If the week was considered positive because all samples during that week were missing, the time to first missing urine during that week will be the time to failure.

The **main** analysis for FDA approval purposes will be done by pooling data from all study centers and by computing $\hat{\alpha}$ and HR. A subanalysis will be done for each study center to study treatment-center interaction. Subanalyses will also be done on the pooled data for males and females separately.

Common hazard ratios for 8 mg vs. 1 mg, 4 mg vs. 1 mg and 16 mg vs. 1 mg analysis will be plotted and displayed for comparison purposes only. Hazard ratios for each study week for each analysis will also be displayed.

Analysis Primarily for FDA Medical Review

For the analyses specified below, the following data reduction algorithm will be used:

1. If two or more urine samples for a given study week are found to be missing for a given patient, that week will be considered to be a missing week for that patient.
2. If at least two urine samples were available and analyzed for a given patient during a given week and if at least one urine sample was found to be positive for opiates, that week will be considered to be positive for opiates or a positive week. Otherwise, it will be considered to be a negative week.

The data for the missing weeks will be excluded from the following analyses:

1. Percent positive urines for each study week will be computed and plotted for each treatment group. For the data pooled for the total study period, a z statistic will be calculated and four preplanned *a priori* comparisons will be made between the proportions of positive urines for 1 mg vs. 4, 8 and 16 mg treatments respectively and for 1 mg vs. 4+8+16 mg comparison. Each of these *a priori* comparisons will be considered to be statistically significant at p value of .05 or below. Histograms will be plotted for percent positive urines for each of the four treatment groups for the total study period. No adjustment will be made for multiple comparisons.

Percent positive urines will also be calculated for each urine testing opportunity and displayed.

2. The total number of positive urines for each patient will be rank ordered according to an algorithm specified by Dr. Harter and four preplanned *a priori* comparisons will be made between the number of positive urines for 1 mg vs. 4, 8 and 16 mg treatments respectively and for 1 mg vs. 4+8+16 mg comparison. Each of these *a priori* comparisons will be considered to be statistically significant at *p* value of .05 or below. No adjustment will be made for multiple comparisons.

3. ROC curves will be drawn for percent positive urines for each study week for each of the four pairs of treatment groups viz., 1 mg vs. 4, 8 and 16 mg and for 1 mg vs. 4+8+16 mg. No statistical analysis will be performed.

Exploratory Analyses to Identify Subgroups

Subgroups classified by body size/weight, sex and any other quantifiable factor as agreed to by FDA and the sponsor that may affect the suitability of one dose over another will be identified. Percent positive urines for each of these subgroups will be determined to identify which dose may be best for them. Urine sample profiles for all patients will also be displayed to determine which subgroup does better on what dose.

Analysis of Dropout Rates

Cox's single failure proportional hazards model will be used to analyze these data. Treatment assignment, age, sex and study center will be covariates used in the model.

The estimate of $\hat{\alpha}$ (hazard ratio) for treatment assignment adjusted for all other covariates, if found to be statistically significantly different from zero (one) for buprenorphine 8 mg versus buprenorphine 1 mg analysis only at $\alpha=.05$, will be indicative of the superiority of one drug over the other for FDA approval purposes.

Regression coefficients $\hat{\alpha}$ and hazard ratios for 4 mg vs. 1 mg, 16 mg vs. 1 mg and 1 mg vs. 4+8+16 mg will also be estimated and plotted and displayed for comparison purposes only.

Analysis of Opiate Craving Scores and Global Rating Scores

These data will be analyzed by two factor analysis of variance of difference scores $\ddot{A}_1, \ddot{A}_2, \ddot{A}_3$, etc., where \ddot{A}_1 is the difference in e.g., opiate craving scores at time t_1 and baseline, etc. If no treatment-score interaction is found, four preplanned *a priori* pairwise comparisons will be made between 1 mg and 4 mg, 8 mg, 16 mg and 4+8+16 mg treatments. Separate analyses will be performed for patient and staff ratings.

Secondary Variables

The secondary variables will analyzed using the appropriate statistical methodology. Included in these secondary analyses will be analyses of the number of medical events occurring between the treatment groups. The number of patients reporting any medical events and the number reporting

various specific types of events in each treatment group will be compared using chi-square techniques. Background characteristics of the patients in the treatment groups will be compared using analyses of variance techniques for continuous variables (e.g., age) and chi-square techniques for discrete variables (e.g., gender).

Sample Size Consideration

In the study conducted by the Addiction Research Center (ARC 090 study), the safety and efficacy of buprenorphine 8 mg dose was compared with 20 mg and 60 mg doses of methadone. The 20 mg dose of methadone was assumed to act as a placebo. In the proposed multicenter buprenorphine study, 1 mg dose of buprenorphine will be *assumed* to act as a placebo for statistical purposes. Hence, all sample size calculations will be based on the results obtained from ARC 090 study from buprenorphine 8 mg comparison with 20 mg methadone treatment. Further, since the proposed study intends to compare the safety and efficacy of 1 and 8 mg doses of buprenorphine only, the sample size calculations will be restricted to estimating the group sizes for these two groups only. The purpose of including 4 and 16 mg buprenorphine treatments in the proposed study is to provide additional information regarding the adequacy of 8 mg buprenorphine treatment.

Since each urine sample found to be positive for opiates can be considered to be a treatment failure, up to 51 failures were observable in the 17-week (maintenance) ARC 090 study and up to 48 failures will be observable in the proposed 16-week study. Consequently, the analyses of data from these trials constitute analysis of multiple failures. Many methods to analyze multiple failures have been proposed but the one based on Cox's proportional hazards model by Wei and others (1989) imposes the least restrictive structure on the data and was used to analyze ARC 090 data and is proposed to be used for the multicenter study.

Briefly, this model estimates a regression coefficient between log hazard rate (dependent variable) and the treatment assignment (independent variable) for each failure. Tests of hypotheses to draw inference for each regression coefficient are available. A test of hypothesis to draw inference for a common regression coefficient which is a linear combination of individual regression coefficient is also available. Since the primary interest of the proposed study would be to compare the overall efficacy of the two treatments, the sample size calculations were based on the ability to draw inference for the common regression coefficient.

Since the parameter estimation may be mathematically extremely difficult for a 51- or a 48-dimensional model, the data will be reduced to 16 dimensions by deriving the index of weekly failures described earlier.

In the ARC 090 study, the sample sizes were 53 and 55 for the 8 mg buprenorphine and 20 mg methadone groups, respectively. The estimate of common regression coefficient was found to be 0.348 ($p=.015$) indicating superiority of buprenorphine over 20 mg methadone treatment. The sample sizes of 120 for each treatment group in the proposed study are more than double of what they were for the ARC 090 study and should provide sufficient cushion against the unexpected. However, the formal sample size/power calculations were still performed using the sample size calculation methods for multiple regression and correlation analyses given in Cohen (1988) using

Table 9.3.2 in this book.

Using Table 9.3.2, the following powers values were obtained for various values of f

f^2	\ddot{e}	Correlation r	Power
.02	4.8	.14	60%
.15	36.2	.36	99%
.35	84.4	.50	99%

Hence, unless the correlation between treatment assignment and (log) hazard rates is too small, a power of well above 80% should be obtainable. To achieve a power of 80% with N=240, an effect size of about .033 or a correlation of about .18 would be required. This size of correlation amounts to a small to medium size relationship between hazard rates and treatment assignment.

Summary of Assumptions Made in Sample Size Calculations

1. One mg dose of buprenorphine will act similar to 20 mg dose of methadone. In other words, if 1 mg dose of buprenorphine happens to be a treatment superior to 20 mg methadone treatment, the expected outcome of the proposed study is likely to be jeopardized.
2. Since the proposed study is a 12 center study vis-a-vis ARC 090 study which was a single center study, any unexpected variations across different study centers and deviations from ARC 090 study, e.g., in protocol compliance, collection of urine samples, dropout rates, etc., may render the proposed sample sizes inadequate and thus the expected outcome of the proposed study is likely to be jeopardized.
3. The statistical model to be used for analyzing these data assumes proportional hazard rates for the two treatment groups. However, the model is robust to the violation of the proportionality assumption and is probably the most used model to analyze failures. The additional comfort is drawn from the fact that the use of this model for analysis of ARC 090 data did not lead to any unexpected outcomes and proved all clinical expectations to be true.

Interim Monitoring

The study as currently planned consists of a 30-week recruitment period and a 16-week follow-up period. Thus, it would be expected that only one interim report would need to be produced for this study. Because of concerns by NIDA about unblinding of the data prior to the NDA being submitted to the FDA, efficacy data will not be included in the one interim report. That report will

give information on patient recruitment and retention, sample description, data quality and patient safety. If the safety data, however, give an indication of a serious problem that requires the efficacy to be looked at, then analyses of the efficacy data will be performed prior to the final analyses. The decision to review efficacy data in conjunction with a safety problem will be made by the study's Data Monitoring Board.

PATIENT RIGHTS

This protocol will be reviewed by the IRB of the Grantee Organization, Friends Medical Science Research Center, Inc., and the IRB of the VA Cooperative Studies Program. The principal investigators at each performance site will secure approval of the protocol and consent form from their local IRB. Before patients are entered into the protocol, they must sign the informed consent. A sample informed consent can be found in Appendix A.

PARTICIPATION

The study is to be performed at 12 facilities. Each facility will be expected to enter two patients per week for 30 weeks for a total of 60 patients. If each facility recruits its required number of patients, then there would be 720 patients entered into the trial. This is above the 480 patients required for the study as given in the sample size section. These additional projected patients will give some protection against one or two facilities not producing or a larger than expected loss rate. They would also provide increased power for the study results if all facilities do produce and the loss rate is not excessive.

In addition to providing sufficient patients, each facility must also get IRB or R&D Committee (in the case of VA facilities) approval, be able to administer treatment seven days a week and guarantee to follow all aspects of the study protocol. Facilities not functioning properly may be removed from the study.

The following facilities have agreed to participate in this study:

VAMC, Hines, Chicago, IL
Milwaukee Co. Mental Health Complex
VAMC, West Haven, CT
New York ARTC
Philadelphia, PA
Pizarro Treatment Center, L.A.
San Francisco General Hospital
VAMC, San Francisco
VAMC, San Juan, PR
West L.A. Treatment Program

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Kay Kintaudi, M.D.

VAOPC, Boston
VAMC, New York

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Paul Casadonte, M.D.

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VA/NIDA Study #999a EXT
Long Term Extension of
A Multicenter Clinical Trial of
Buprenorphine in Treatment of Opiate Dependence

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Final Version: October 9, 1992

Reprinted: December 4, 1992

TABLE OF CONTENTS

	Page
1.0 SYNOPSIS	1
2.0 INTRODUCTION	3
2.1 Background: Preclinical	3
2.2 Background: Clinical	3
2.3 Rationale/Disease Review	3
3.0 OBJECTIVES	4
4.0 STUDY DESIGN	4
5.0 SUBJECTS	6
5.1 Source/Description of Study Group	6
5.2 Inclusion Criteria	6
5.3 Exclusion Criteria	6
5.4 Termination Criteria	6
5.5 Concurrent Medication	6
6.0 DRUG INFORMATION	6
6.1 Formulation	6
6.2 Packaging/Storage Information	7
6.3 Labeling	7
6.4 Preparation of Drug for Administration	7
6.5 Stability	7
7.0 STUDY EXECUTION	8
7.1 Treatment	8
7.2 Study Procedures	12
7.3 Clinical Observations	12
8.0 CRITERIA FOR RESPONSE	14
9.0 STATISTICS	14
10.0 REFERENCES	16
11.0 HUMAN SUBJECT PROCEDURES	16
11.1 Informed Consent	16
11.2 IRB Approval	16
11.3 Pregnancy	16

TABLE OF CONTENTS (cont'd)

Page

12.0	REGULATORY ISSUES	17
12.1	Adherence to Protocol	17
12.2	Protocol Amendment Procedures	17
12.3	Study Monitoring Procedures	17
12.4	Case Report Forms	17
12.5	Drug Accountability	18
12.6	Investigator Agreement	18
12.7	Records Retention	18
12.8	Confidentiality/Publication	18
13.0	PROCESSING AND SHIPMENT OF BIOLOGIC SAMPLES	18
	APPENDIX A - Drug Handling Protocol	19
	APPENDIX B - Study Forms	39
	APPENDIX C - Informed Consent	53

1.0 SYNOPSIS

This amendment to Protocol #999a seeks:

1. to collect longer term safety data during an aggregate of 52 weeks of continuing double blind and open buprenorphine treatment. This extension protocol will be available to subjects continuously receiving buprenorphine who successfully completed the initial study and any current continuations of that study,
2. to permit certain modifications to the parent protocol. These modifications will reduce subject burden from participation compared to the parent protocol. Previous studies have indicated these modifications to be safe, and
3. to collect information for "directions for use" to be included in labeling language as part of an NDA.

Upon conclusion of the parent protocol and applicable continuation for any given subject, this amendment will permit:

1. the study sites to collect and analyze urine specimens for drug screening proposes. These results will be used by the investigators for dose modification and counseling purposes.
2. dose modification to the next higher or lower dose. This modification may be made at any time during the course of this amendment. An additional dose of 32 mg will be added to the dosage range to permit escalation from the current highest study dose in the parent protocol.
3. continuation of buprenorphine dosing for up to 52 weeks total [i.e., parent, continuation (if any), and extension].
4. reduction of clinic attendance to 5 or 6 days per week at the request of study site personnel. Because take home doses will not be permitted, a double dose not to exceed 32 mg will be administered on day 5 or 6 of the clinic schedule.
5. reduction of frequency and extensiveness of assessment.

All patients who enroll in this extension will be maintained on buprenorphine in a double blind status until the last eligible patient at all sites has completed 12 additional weeks of dosing under the extension protocol.

In order to provide a comparison group for safety measures included in this study, "scooped" data from methadone patients treated at the individual sites will be gathered during the course of this extension protocol. This information will reflect the number of patients followed at the clinic, the demographic descriptors of those patients, the dose of methadone received, numbers of program drop outs/terminations, and adverse events. It is anticipated that adverse event reporting for the methadone patients may not be as extensive as it is for the study patients. To the extent methadone adverse experience data are available for reporting, they will be used for comparison to the experience of patients participating in this extension amendment. No patient identifiers will be reported with these data; only the aggregate data normally reported to governmental agencies will be utilized for this comparison.

There are several compelling reasons to collect longer term safety data on buprenorphine in opiate addicts:

1. the safety data derived from buprenorphine analgesia patients may not be applicable to this population because opiate addicts may require higher buprenorphine doses than used for analgesia and longer duration of dosing compared to analgesia patients;
2. opiate abusers often take a variety of other street drugs and prescription medications, increasing chances of unanticipated drug-drug interactions compared to pain patients; and
3. many opiate abusers have pre-existing liver disease or other chronic illnesses. Hence prior safety data of buprenorphine in pain patients is not entirely relevant for opiate addicts.

In addition to long term safety data, this protocol amendment permits the gathering of limited self report and observer reported data with regard to the dose modification including the newly added 32 mg dose. This information is not intended as efficacy data, but will be reported in labeling language descriptively characterizing the dosing experience among these patients during the extension amendment.

It is also expected that amending this protocol to provide for extended dosing will enhance retention in the original protocol. It could be expected that compliance will increase because:

1. subjects will be less likely to terminate if a regular methadone treatment slot were to become available to them
2. subjects who prefer buprenorphine to other opiate-dependence treatment (i.e., naltrexone or methadone), will perceive the opportunity to remain on buprenorphine to be a personal advantage and health benefit.

Attrition due to the above factors, which is not related to the study medication, tends to erode the strength of drug abuse treatment studies.

Only modifications to the parent protocol will be explicitly identified in this amendment. Unless specified, methods identified in the parent protocol will maintain in this amendment.

This amendment will begin at each participating site as quickly as possible after obtaining IRB approval. In order to permit complete development of this extension amendment, a continuation amendment at some, but not all sites has been filed. Where implemented, the continuation amendment included all procedures from the parent protocol in order to obtain expedited approval. Certain data not specified in this present extension amendment were gathered during the continuation phase of this study. Those data not identified in this extension amendment will be retained for archival purposes at the individual sites, but will not be analyzed as part of the NDA document.

Should a given site wish to continue to gather data relevant to the parent protocol but not specified for the extension amendment, they may do so, including the use of case report forms developed for the parent protocol. If this choice is made, the data will be stored at the site for archival purposes, but will not be reported for inclusion in the data analysis phase of this amendment.

INTRODUCTION

Background: Preclinical

See Parent Protocol

Background: Clinical

See Parent Protocol

Rationale/Disease Review

See parent protocol

3.0 OBJECTIVES

The objectives of this study are:

1. to provide an opportunity to collect longer term safety data on buprenorphine;
2. to permit certain modifications to the parent protocol in dosing, schedule, and assessment to reduce subject burden from protocol participation;
3. to increase subject incentive to complete successfully the parent protocol;
4. to give subjects who did well on buprenorphine continued access to the treatment medication for a total of 52 weeks; and,
5. to perform a descriptive analysis of the experience associated with modifications in methods; see "2." above for inclusion in "directions for use" language in an NDA for buprenorphine.

4.0 STUDY DESIGN

This extension amendment provides drug dosing to all patients who successfully complete the original protocol 999a and any applicable continuation of that parent protocol for an aggregate total of 52 weeks. Compared to the parent protocol and applicable continuations, this amendment permits:

1. the study sites to collect and analyze urine specimens for drug screening purposes. These results will be used by the investigators for dose modification and counseling purposes.
2. dose modification to the next higher or lower dose. This modification may be made at any time during the course of this amendment. An additional dose of 32 mg will be added to the dosage range to permit escalation from the current highest study dose (16 mg) in the parent protocol. There are no limits to the number of dose modifications that can be made during the extension (no more than one dose change per day). At the time of enrollment or any time thereafter patients in the extension protocol and their treating physician may choose to double or to halve the individual's dose. These modifications may occur as

frequently as deemed clinically indicated, but in no instance will the dose increase beyond 32 mg/day or decrease to less than 1 mg/day.

3. reduction of clinic attendance to 5 or 6 days per week depending upon the decision of study site personnel. Because take home doses will not be permitted, a double dose not to exceed 32 mg will be administered on clinic day 5 or 6.
4. reduction of frequency and extensiveness of assessment.

Previous studies indicate that doses up to 32 mg/day have been safely tolerated even in normal volunteers (Walsh, et al, 1992a). Prior work has also indicated that withdrawal symptoms from fixed doses of 8 mg. of buprenorphine appear after 48-72 hours (Fudala, et al, 1990). Hence doubling doses is expected to provide coverage from withdrawal symptoms during the weekend dosing schedule.

All patients who enroll in this extension will be maintained on buprenorphine in a double blind status until the last eligible patient at all sites has completed 12 additional weeks of dosing after the parent protocol or has been terminated. At that time the study can be opened for an investigator to know the dose of buprenorphine being administered to any given patient.

Assessment frequency is modified and reduced as reflected in the Schedule of Data Collection (see Appendix B - Study Forms). During the extension, the sites will have access to the urine drug screen results to enable the staff to better deal with the addicts' behaviors. Urine drug screening should be performed by the individual sites to provide information for clinical decisions regarding dose modification and protocol eligibility. Urine drug screen results will not be used as an efficacy measure; therefore results will not be reported to nor collected by the sponsor.

Data analysis in the extension study will assess the safety variables by dose, dose modification, and presence of other drug use.

Initiation of this study shall begin after local site approval of the amendment. Once in effect, this extension amendment supersedes any continuation amendments in place at that site.

5.0 SUBJECTS

5.1 Source/Description of Study Group

All subjects who successfully complete Study #999a and any additional dosing during a continuation of that protocol, if applicable, are eligible to enter the #999a Extension protocol. All subjects who participate in this extension will be required to sign a new consent form.

5.2 Inclusion Criteria

Successful completion of the parent protocol (#999a) and any applicable continuation of that protocol without interruption of study participation.

5.3 Exclusion Criteria

No additional exclusionary criteria specific for this extension study are identified.

5.4 Termination Criteria

The termination criteria in this amendment are modified to permit longer absences from the study than in the parent protocol (see pages 11-12).

5.5 Concurrent Medication

Any concomitant medications used by the subject, including over-the-counter preparations, shall be recorded monthly on Form 05 in this Extension protocol.

6.0 DRUG INFORMATION

6.1 Formulation

See Drug Handling Protocol section of Protocol #999a.

Packaging/Storage Information

See Drug Handling Protocol section of Protocol #999a.

For the extension phase, the buprenorphine doses will be in the same prepackaged unit dose formulations as in the parent protocol, consisting of 1 ml liquid containing 1, 2, 4, 8, 12, 16, or 32 mg of buprenorphine.

Subjects in the Extension Protocol will not have individual dose therapy kits as they have in the parent protocol. Rather, each site will have a 36-drawer drug cabinet that will contain the study drug (see Appendix A - Drug Handling Protocol for more details).

In addition, each subject will have a dosing schedule that will specify:

1. which coded drug he/she should receive on Mondays through Thursdays or Mondays through Fridays--depending upon whether the clinic is operating on a 5 or 6 day study regimen, respectively
2. which coded drug should be received on Fridays or Saturdays.

Each time a subject is required to have a dose adjustment, the Pharmacy Coordinating Center (PCC), Albuquerque must be notified by FAX (505-256-5749). PCC will FAX a dose assignment to the site so the subject can be dosed without delay. To accomplish this, PCC requires one day's notice to implement this change in dose. (See Appendix A - Drug Handling Protocol, for more details.)

Labeling

See Drug Handling Protocol section of Protocol #999a.

Preparation of Drug for Administration

See Drug Handling Protocol section of Protocol #999a.

Stability

See Drug Handling Protocol section of Protocol #999a.

7.0 STUDY EXECUTION

7.1 Treatment

Number of subjects:

All subjects at each of 12 centers who have been receiving buprenorphine continuously and successfully completed parent protocol (#999a) and any applicable continuation.

Subject replacement/addition:

None

Premature Withdrawals:

If a subject either leaves the study voluntarily prior to completion or is terminated by the staff, the circumstances, if known, will be documented in the subject's study record and recorded on Form 08. In addition, PCC will be notified by each site when a subject is terminated.

Method of drug administration:

Medications will be administered by dispensing personnel, exactly as in the parent protocol. All staff at participating sites will remain blind to the subjects' doses except as discussed previously. As in the parent protocol, subjects will hold the medication under their tongue for 5 minutes following the sublingual dosage to assure maximal absorption.

Dose Schedule:

The number of dosing adjustments will be at the investigators' discretion, but each time a dosing change is made, the reason must be fully documented in the case report form. The doses available are: 1, 2, 4, 8, 16, and 32 mg. (A 12 mg dose also is available, but this dose only occurs in the reinduction and taper paradigms and is not a maintenance dose.) *The highest maintenance dose available is 32 mg and the lowest is 1 mg.*

As in the parent protocol, no take home doses will be allowed. Subjects must attend the clinic either Monday through Friday or Monday through Saturday, depending upon at which site the subject is enrolled.

The following sites will operate on a Monday through Friday schedule:

Hines VA
Boston VAOPC
New York VA

San Juan VA
San Francisco General
San Francisco VA

Those operating on a Monday through Saturday schedule are:

Milwaukee County Medical Complex
West Haven VA
Philadelphia VA

Subjects will receive a double dose of their study medication on either Fridays or Saturdays to eliminate the need for a Saturday and Sunday or a Sunday clinic visit, respectively. This is expected to "hold" the subject until Monday, but the results of this study will be more definitive in this regard.

Even though double doses are administered on Fridays or Saturdays, subjects who regularly are on 32 mg will still receive 32 mg on that day. This dose is assumed to be high enough that it will hold the subject for 70 hours or more (Walsh, et al, 1992b). Only 1 vial of medication will be given to a subject at any one time. Even on Saturdays, the double dose will be incorporated into the one unit dose vial assigned to the subject.

In order to assure the safety of individuals receiving dose increments either for weekend dosing or for dose escalations, the following procedures must be available at sites participating in this extension protocol:

1. Initiation of weekend doses for the first time in any given patient must occur during a period when the clinic has weekend "on call" medical staff available for or is open seven days per week with medical staff available for consultation during the weekend.
2. Increased doses, other than that described in #1 above, should occur during Monday through Wednesday or Monday through Thursday, depending upon whether clinic is open 5 or 6 days a week, respectively, unless the clinic provides medical staff available for consultation throughout the week. In this case, limitations on dose increment scheduling are not required.

Dose Escalation/Reduction:

Subjects who successfully complete the 16-week parent protocol and applicable continuation dosing will be offered the opportunity to continue buprenorphine at their present dosage, or if necessary, at the investigator's discretion, have their present dose

either doubled (maximum 32 mg/day) or halved (minimum 1 mg/day) as discussed below. Double-blind dosing will be maintained (as described above).

Adjustment of Dose:

This amendment will allow for an adjustment of dosing, at the investigator's discretion. When a subject completes the parent protocol, the investigator may keep the subject on the same dose that he/she was on during the parent protocol, or the dose may be increased (doubled) or decreased (halved). Only one adjustment may be made at any one time, which is either twice or one half the current dose. There is no limit to the number of dose adjustments that may occur during the study extension, providing that only one adjustment is effected on any given day. Regardless, *the protocol must still remain double blinded except as provided for above (see page 1).*

Dose Assignment Schedule:

All dose assignments will be made by the Pharmacy Coordinating Center (PCC), Albuquerque. PCC must be notified at least 5 days before a subject is eligible to enter the extension protocol. PCC will provide the site with the appropriate dose assignment information. It is anticipated that most subjects will continue on the same maintenance dose that was used in the parent protocol. However, if in the investigator's judgment, at any point in time, a dose adjustment would be advantageous for the subject, this may be effected by selecting the appropriate dose adjustment (either twice or one half current dosage) as listed on the "Patient Enrollment/Dose Adjustment/Termination Notification" (DHP-1/EXT) form. This form must be FAXed to the PCC no later than 4PM EST the day before a dosage change is to be initiated.

Drug Discontinuation Criteria:

The likelihood of a subject developing buprenorphine toxicity or side effects (see parent protocol) after successful completion of the parent protocol is remote. Should such a toxicity develop, however, the physician has the option of decreasing the dose by one-half. This procedure may be effected repeatedly until the dose is deemed satisfactory. The subject may be terminated at any time if the investigator deems it prudent to do so.

Modification and Definition of Toxicity Levels:

In the parent protocol #999a, lab tests to monitor safety are indicated monthly. The extension allows for safety blood chemistries and urinalyses to be performed every three months, unless health concerns prompt more frequent testing.

If a subject has liver function tests [SGPT (ALT), GGT, AlkPhos, SGOT (AST)] five times normal values or greater, "safety" blood chemistries will be done more frequently than the every-3-month testing specified in this protocol (see section Clinical Evaluations, page 12), and at least monthly. If a liver function test increases to eight times normal or higher, this will automatically prompt a serious adverse event report (Form 07) as in the parent protocol. Note that these criteria do not apply to bilirubin determinations.

The investigator must individualize these safety analyses to each subject's needs. If signs or symptoms suggest hepatotoxicity, more frequent testing based on the investigator's clinical judgment, will be required even if the above criteria are not reached.

Pregnancy:

If a subject becomes pregnant while on the study, she must be discontinued from the study and treated appropriately (see section Human Subjects Procedures, Pregnancy, page 16).

Treatment Duration:

Up to one year including time spent in the Parent Protocol and applicable continuation dosing after the Parent Protocol.

Dependent upon a number of factors, further dosing with buprenorphine may be contemplated at the conclusion of this extension amendment. If offered, such dosing would be addressed in a subsequent protocol. If accessibility to buprenorphine for subjects in this study is either not feasible or not indicated, all appropriate medical options will be reviewed with subjects in this study prior to termination from this study.

Treatment Termination:

The investigator shall terminate a subject from participation in this study for any of the following reasons:

1. Medication toxicity, evidenced by significant signs or symptoms, that does not respond to halving the dose on repeated, successive occasions.
2. Missing 9 consecutive calendar days without study drug during the blinded portion of the extension. Once the study becomes unblinded, exceptions may be made for hospitalizations and excused absences as provided for in clinic policy.
3. Requiring a sixth reinduction in the extension protocol (i.e., subject has already been reinducted 5 times during the extension study for missing 4, 5, 6, 7, or 8 consecutive days of dosing).
4. Intercurrent illness or medical complications precluding safe administration of buprenorphine.
5. Administrative termination (e.g., moved from area, violence or threats of violence within clinic, excessive drinking or toxicity resulting from illicit drug abuse).
6. Pregnancy

7.2 Study Procedures

Psychosocial Services:

Psychosocial services are those given to the subject in addition to regular contact with staff for dosing, urine collection, or to complete the case report forms. NIDA encourages such support for this protocol, and recommends that formal counseling and other psychosocial services not be less than one hour/month. Reporting of these services to the sponsor is not required during this amendment.

Schedule of Events:

All measures will remain as they were in the parent protocol, except when noted (see section Clinical Observations, below).

7.3 Clinical Observations

Physical Exams/Vital Signs:

at 12 weeks, 24 weeks, 36 weeks, or whenever termination occurs

The physical exams, performed every third month, may be abbreviated on the clinical judgment of the on-site physician based on the subject's relative good health. More frequent and more thorough examinations will be performed as necessary.

Laboratory Tests: clinical blood chemistries (CBC, SMA-12) and routine urinalyses: at 12 weeks, 24 weeks, 36 weeks, or whenever termination occurs

Clinical Measurements: Self report of drug use: weekly
Electrocardiograms: will be performed at 24 weeks after the parent protocol is completed and at termination
Concomitant medications will be recorded: monthly

Adverse Experiences including Reporting: see original protocol

Pharmacokinetic Measurements:

Although pharmacokinetic studies will not to be performed under this amendment, paired *trough* plasma samples will be collected whenever a change of dose is planned: a baseline trough sample will be collected just prior to the dose adjustment (and **before the subject is actually dosed**); and again two weeks thereafter, on the same day of the week as the baseline sample, if possible, another trough sample will be collected. This second trough sample should reflect steady state blood levels. The procedure for collecting steady state blood samples is listed as an amendment to the Parent #999a Protocol:

"Attempt to collect blood as soon as possible after the 14th day of dosing (day 15 would be ideal). Please note, however, that if the subject requires a reinduction during the first two weeks, the 14-day count should re-start with the 1st day of reinduction. Also, do not draw blood on the day after a dose has been missed. The subject must have received dosing for **at least three consecutive days prior to drawing blood levels**. It is conceivable, that in the case of subjects with many absences, the plasma levels might not be drawn until the fourth week or even later. Similarly, apply the same procedures for the eighth week sample."

"In occasional instances, it may be impossible to collect blood under the conditions and restrictions described above."

Plasma samples should also be collected whenever a significant or serious/unexpected adverse event occurs. These samples should be taken as closely as possible to the event in question.

PLEASE NOTE: Plasma samples will still be sent to the University of Utah.

Urine Collection for Drug Screen Analysis:

Because this is a safety study, urine drug screens will not be an outcome measure in the extension protocol as they were in the parent protocol. Consequently, the sponsor will not collect urine drug screen results. Individual sites are advised, however, to monitor drug usage by screening urine samples as per clinic policy at that site. It is expected that information gathered from the drug screen tests will be used by standard clinical practice to determine the potential utility of drug dosage modification, continued protocol participation, and for psychosocial counseling purposes.

8.0 CRITERIA FOR RESPONSE

Measures and Measuring Instruments:

Those variables used primarily to evaluate safety are:

1. Adverse experiences will be evaluated at the time of entry into the extension protocol and weekly thereafter as in the parent protocol.
2. Laboratory data CBC, UA, SMA-12 will be collected every twelve weeks and EKGs will be taken 24 weeks after the completion of the parent protocol and at the termination.

Those variables which will be used primarily to provide descriptive analyses of method modifications (dose adjustments, dosing schedule, doubled weekend doses) for inclusion in "directions for use" label language are:

1. Self reported frequency of illicit drug and ethanol use will be obtained every week.
2. Abbreviated self report including reports of opiate side effects and withdrawal symptoms.

9.0 STATISTICS

This extension is intended primarily to gather longer term safety data. Safety parameters to be analyzed both descriptively and as group and paired t-tests utilizing all data generated on participating patients are:

1. All safety parameters (adverse events, protocol discontinuation, laboratory studies)
2. Dose adjustment, dose schedule modification, and doubled weekend doses compared to parent protocol data for safety variables (#1 above)

Analysis of safety data will include both relevant data from the extension amendment period as well as the prior parent protocol and applicable continuation amendments. Thus, the period of analysis for all subjects will be for up to one year, or until the point of termination from the study.

Modifications of methods in this extension amendment will also permit consideration of data relevant to these modifications. These modifications are:

1. unblinding of the results of urine toxicology tests, allowing each site to perform its own drug screening to monitor illicit drug use
2. adjustment of dosage including a new 32 mg dose
3. reduction of clinic attendance to 5 or 6 days per week depending upon the decision of study site personnel
4. doubling of weekend dosage in place of take home dosages.

A descriptive analysis of these modifications relevant to safety and outcome will be completed, dependent in part of the number of patients who opt to modify their dose. This extension amendment provides data for the following analyses:

1. Percent patients experiencing opiate withdrawal including craving or side effects by dose and dosing pattern (5 or 6 day dosing)
2. Percent missed doses by day of the week and by dose level of buprenorphine.

All comparisons with the parent protocol will be made by displaying the measures graphically and by using simple t-tests. The comparisons with the parent protocol will be made using the data for all patients from the parent protocol as well as for only those patients who were allowed to enter the extension protocol. The latter comparison will enable us to evaluate the usefulness of the extension protocol for those patients who crossed over to the extension protocol.

10.0 REFERENCES, additional to parent protocol

1. Fudala, PJ, Jaffe, JH, Dax, EM, et al. (1990) Use of buprenorphine in the treatment of opioid addiction. Clin Pharm Ther, 47:525-34.
2. Walsh, SL, Preston, KL, Stitzer, ML, et al. (1992a) The acute effects of buprenorphine and methadone in non-dependent humans. Clin Pharm Ther, 51:167.
3. Walsh, SL, Preston, KL, Stitzer, ML, et al. (1992b) The acute effects of high dose buprenorphine in non-dependent humans. CPDD Monograph, 119:245.

11.0 HUMAN SUBJECT PROCEDURES

11.1 Informed Consent

Each subject eligible to enter this extension study must first sign a new consent form. Because the consent process emphasizes being informed, the form should be written in the subject's native tongue or one in which she/he has considerable facility. The Sponsor and IRB must approve this form before it is used.

11.2 IRB Approval

The protocol that extends the parent #999a study must be approved by each site's institutional review board prior to initiation of the research. Each site must obtain written approval that describes the protocol as "#999a Extension."

11.3 Pregnancy

Women of child bearing potential will be tested monthly for pregnancy and will be urged to use an approved method of birth control. If a subject should become pregnant while on the study, she should be terminated from this protocol. Because detoxification is considered to be potentially dangerous in pregnant addicts (increases the risk of spontaneous abortion in the first trimester), the subject should be transferred to another opiate agonist treatment program including routine prenatal care.

.0 REGULATORY ISSUES

.1 Adherence to Protocol

No changes may be made to this extension protocol without prior approval from both the sponsor and the IRB. Failure to follow this procedure constitutes a protocol deviation(s) and are considered violations of federal regulations.

.2 Protocol Amendment Procedures

See parent protocol.

.3 Study Monitoring Procedures

See parent protocol.

.4 Case Report Forms

For each subject, the tests and evaluations that were completed for week 16 in the parent protocol will double as the baseline values for the Extension Protocol. In the instance of patients who have been on a continuation protocol prior to entering the extension protocol, the last assessment in the continuation protocol that recorded lab testing and a physical exam will serve as the baseline for the extension amendment.

Although the reporting requirements for this phase of the study are substantially reduced, a given site may choose to continue to use case report forms from the parent protocol if it meets their clinical needs. When used, the case report form will be stored archivally by the site should reference to it at some future date be necessary. Use by the site of a CRF from the parent or continuation protocol not specified by the extension amendment will not be analyzed for reporting in an NDA application.

A xerox copy of each Case Report Form (CRF) from the parent protocol, numbered Form 04, 05, 08, 09, 10, 12, 13, 14, 15, 16, 18, and if applicable, 17, should be entered into the CRF book as the baseline data for each subject in the Extension. The schedule of data collection is found in Appendix B - Study Forms.

12.5 Drug Accountability

See Drug Handling Protocol section of Protocol #999a.

12.6 Investigator Agreement

The legal agreement between each principal investigator and the sponsor (VA/NIDA) that was signed prior to initiating the parent protocol, #999a does not apply to protocol #999a EXT. A new agreement covering #999a EXT will be developed and forwarded to each site prior to the initiation of the trial.

12.7 Records Retention

Each investigator is responsible for maintaining her/his complete study records for a period of two years after the NDA has been approved for the indication for which it is being investigated, or for two years after the IND has been discontinued and FDA is notified. In either case, NIDA, the study sponsor, shall notify each principal investigator when the required two-year period has expired.

12.8 Confidentiality/Publication

VA/NIDA and each participating site agree to the terms described in the legal agreement referenced under the "Investigator Agreement" paragraph on page 17.

13.0 PROCESSING AND SHIPMENT OF BIOLOGIC SAMPLES

Sera will be shipped to the University of Utah as in the parent protocol #999a, although on a different schedule. Shipping instructions for sera will be sent to each site.

APPENDIX A

Drug Handling Protocol

VA/NIDA Study #999a Extension

**"Long Term Extension of
A Multicenter Clinical Trial of
Buprenorphine in Treatment of Opiate Dependence"**

DRUG HANDLING PROTOCOL

Prepared by

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July 7, 1992

[Revised: December 1, 1992]

TABLE OF CONTENTS

Drug Handling Protocol

	Page
RESPONSIBILITIES FOR DRUG ACCOUNTABILITY	21
DESCRIPTION OF EXTENSION STUDY DRUG SUPPLIES	21
CUSTODY AND STORAGE REQUIREMENTS	22
INITIAL SHIPMENT OF STUDY MATERIALS	22
ORDERING STUDY DRUGS AND OTHER SUPPLIES FROM THE PHARMACY COORDINATING CENTER (PCC)	22
ADMINISTERING STUDY DRUG	23
6.01 <u>Entrance Procedure</u>	23
6.02 <u>Clinic Visit Schedule</u>	24
6.03 <u>Dose Adjustment Procedure</u>	24
6.04 <u>Reinduction Period</u>	25
6.05 <u>Dose Tapering Period</u>	27
6.06 <u>Labeling</u>	28
SHIPMENT OF RETURNS TO PCC	28
DHP FORMS	29
STUDY AIDS	33

RESPONSIBILITIES FOR DRUG ACCOUNTABILITY

Each principal investigator is responsible for a complete and accurate accounting of all study drugs received by the center. The VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (PCC) in Albuquerque, New Mexico, will provide forms, instructions and assistance as necessary to assure proper use and accountability of all study drug. The PCC will monitor the performance of each participating center in this regard. In addition each center must observe local policies and applicable state and federal regulations concerning custody, dispensing and possession of drugs. Each participating Department of Veterans Affairs (VA) Medical Center will be provided with all documents needed to comply with VA regulations.

Following completion of the extension protocol, the PCC will submit to NIDA (National Institute on Drug Abuse) a comprehensive report of all drugs received, dispensed and returned from each participating center.

DESCRIPTION OF EXTENSION STUDY DRUG SUPPLIES

Seven different strengths of buprenorphine will be used in the extension study. Since this is a double blind study, the study drug will be labeled, ordered and referred to as "B-999AE". A separate supply of study drug is provided for the extension study. **DO NOT USE STUDY DRUG FROM THE PARENT PROTOCOL (LAATRC/VA/NIDA Study #999a) FOR THE EXTENSION PROTOCOL (VA/NIDA Study #999a Extension) OR VICE VERSA.** The study drug is supplied in clear triangular-shaped unit dose containers. Each unit contains 1 ml of buprenorphine in 30% ethyl alcohol. The different strengths of buprenorphine that will be provided in the extension study are outlined below:

VA/NIDA Study #999a Extension Study Drug

Study Drug	Strengths	Code Name
Buprenorphine	1mg, 2mg, 4mg, 8mg	B-999AE
	12mg, 16mg or 32mg	

A 36-drawer cabinet will be provided to each center for storage of the extension study drug. This cabinet is 3 feet long x 3 feet high x 1 foot deep. Each drawer contains two individual sections and is identified with a two digit number; i.e., #01 - 36. Each drawer contains one of the seven strengths of buprenorphine, B-999AE (1mg, 2mg, 4mg, 8mg, 12mg, 16mg, or 32mg). Each unit within a drawer is labeled with an unique 5-digit Unit ID number (e.g., "19019") in addition to the two-digit drawer number (e.g. "32"). All units in a drawer are the same strength. Multiple drawers are available for each strength of buprenorphine. The extension study drug will be provided in ziplock bags containing 28 units/bag. Each bag will be labeled with the corresponding drawer number in which it should be placed. Initially each center will receive two bags for each drawer. The center is instructed to open only one bag at a time. Open one bag and place the 28 labeled units in the first section of the drawer. The second bag should be used as a back-up and placed in the second section of the drawer.

Replacement bags for each drawer will be sent automatically from the PCC after the contents of one bag have all been dispensed. Each replacement bag will bear the two digit drawer number (e.g., "32") identifying the drawer into which it should be placed. The replacement bag should be placed in the second section of the appropriate drawer. Do not empty the contents of the replacement bag into the first section of the drawer until all doses in that section have been administered. Each unit within the bag will bear an unique 5-digit Unit ID number in addition to the two-digit drawer number. When replacement units are received, they should be placed immediately in the appropriate section of the corresponding drawer.

3. CUSTODY AND STORAGE REQUIREMENTS

The study drug (B-999AE) should be stored at room temperature in a secure area. It may be stored either in the study clinic or pharmacy depending on local policy. Each participating center will initially receive one 36-drawer storage cabinet and 72 separate ziplock bags (2 bags/drawer) of study drug. The level of study drug available in each drawer will be monitored and automatically replenished by PCC.

4. INITIAL SHIPMENT OF STUDY MATERIALS

The Pharmacy Coordinating Center (PCC) will send each center that will be participating in the VA/NIDA Study #999a Extension protocol an initial shipment of study materials. This shipment will include the following items:

- A. One "VA/NIDA Study #999a Extension Study Drug" 36-drawer cabinet
- B. 72 separate ziplock bags of study drug
(28 units/bag; 2 bags/drawer)
- C. Study Aids (medical alert cards, chart labels, etc.)
- D. DHP Forms

5. ORDERING STUDY DRUGS AND OTHER SUPPLIES FROM THE PHARMACY COORDINATING CENTER (PCC)

Centers need not routinely order drug from the PCC; inventory levels and drug needs at each center will be monitored by the PCC and drugs will be shipped automatically as needed. PCC will provide each site with a supply of "Receiving & Dispensing Study Drug Inventory" (DHP-2/EXT) forms. Sites are not required to use these forms if they have similar forms already in use. These forms have been designed to assist the site in maintaining a perpetual inventory of study drug on hand.

The information needed for monitoring drug needs will be obtained from each center. Maintaining the same schedule established during the parent protocol, each center is required to fax all "Dose Administration Record" (Form # 9) forms for each

patient to the PCC every Wednesday or Thursday. This will enable the PCC to keep up to date on where each patient is in the study, which doses have been administered and when additional medication will be needed. Study drug supplies will be shipped straight to each center. The PCC will notify the clinic of each shipment.

Individual centers will be responsible for ordering additional study materials. A special form, "Pharmacy Coordinating Center (PCC) Order Form" (DHP-4/EXT), has been developed to assist the centers in ordering additional supplies. These forms can be mailed, phoned in, or faxed depending upon the urgency of the request. If a drug supply question or problem arises or additional study drug is needed this form may be used. An order for additional drug should be made either by telephone or fax at least 10 days before the drug is needed.

ADMINISTERING STUDY DRUG

Extension Procedure

Patients who have successfully completed the parent protocol (LAATRC/VA/NIDA) and any applicable continuation without interruption will be allowed to enter the extension protocol and receive up to 12 months in aggregate of treatment. This extension protocol will remain double blinded until the last site has completed 12 additional weeks after the parent.

When the investigator anticipates that a patient will enter the extension protocol, he/she must notify the PCC (by faxing a "Patient Enrollment/Dose Adjustment/Extension Notification" form, DHP-1/EXT) **AT LEAST 5 DAYS** before a patient is eligible to enter the extension protocol. PCC will provide the appropriate dose assignment information to the site within 5 days after notification. The investigator may keep the patient on the same dose that he/she was receiving during the parent protocol. The dose may be doubled or halved. **No other adjustments may be made at any time.** The PCC will provide the center with a copy of the dosage assignment by sending a "Dose Assignment Notification Form" for the appropriate patient(s). There may be two or three dose assignments on one page. The clinic is instructed to remove the appropriate dose assignment for each patient and place it in that patient's chart.

As stated previously when a patient is eligible and has agreed to enter the extension study, the center notifies the Pharmacy Coordinating Center (PCC) via fax (DHP-1/EXT form) or by telephone: (505) 265-1711 Ext. 2580 AT LEAST FIVE days before the patient is eligible to enter the extension protocol. The patient retains his/her randomization number (e.g., 501-123) from the parent protocol. When informed the dose this patient will be starting on, the PCC will generate a dosage scheme identifying the specific drawers that doses for this patient should be taken from. A copy of the patient's dosage assignment will be faxed to the center prior to the day that patient will enter the extension protocol. If, for example, patient 501-123 completed the parent

study on 8mg of buprenorphine and the investigator chooses to leave the patient on this dose.

A random dosing scheme such as the following would be generated for this patient's treatment during the extension protocol:

DOSE ASSIGNMENT NOTIFICATION FORM		
PATIENT RANDOMIZATION NUMBER	DRAWER NUMBER ASSIGNMENT	
	WEEKDAY DOSE	WEEKEND DOSE
501-123	32	3

This information will be faxed to the center from PCC. If this patient continues on this dose then each dose Monday through Thursday (or Friday depending on the hours of the clinic) will be taken from drawer #32 and the Friday/Saturday dose will be taken from drawer #3. Contrary to the parent protocol in which a patient received a dose every day, during the extension protocol these patients will be dosed either Monday through Friday or Monday through Saturday. Thus a double dose will be administered to hold the patient over the 1 or 2-day interval on either Friday or Saturday.

6.02 Clinic Visit Schedule

The study medication is given daily Monday through Thursday or Friday with a double dose administered on Friday or Saturday depending upon the clinic. No takeout doses of study medication (B-999AE) are allowed under this protocol. Patients must return to clinic five or six days a week (Monday through Friday or Saturday) to receive the appropriate dose.

6.03 Dose Adjustment Procedure

The extension protocol will allow flexible dosing. The doses available are: 1mg, 2mg, 4mg, 8mg, 16mg, and 32mg. The highest maintenance dose available is 32mg and the lowest maintenance dose is 1mg. A 12mg dose is also available; however, it is not a maintenance dose. The 12mg dose is only used in the Reinduction or Taper Periods. There is no limit to the number of dosing adjustments that may be made; these will be made at the investigator's discretion. Each time a dosage change is required, the center must contact PCC **24 hours (ONE DAY)** in advance to receive the appropriate dosage assignment. PCC must be notified **no later than 4:00 PM EST** the day before a dosage change is required in order to allow adequate time for PCC to process the order and fax the appropriate "Dose Assignment Notification Form" to the clinic. This should be done by completing and faxing a "Patient Enrollment/Dose Adjustment/Termination Notification" form (DHP-1/EXT) to PCC. The new dosage

signment will be faxed to the center within 24 hours.

DOSE ASSIGNMENT NOTIFICATION FORM		
PATIENT RANDOMIZATION NUMBER	DRAWER NUMBER ASSIGNMENT	
	WEEKDAY DOSE	WEEKEND DOSE
501-123	3	12

The reason for a dosage change must be fully documented on the "Dose Administration Record" (Form # 9). If this patient continues on this dose then each Monday through Thursday (or Friday depending on the hours of the clinic) will be taken from drawer #3 and the Friday/Saturday dose will be taken from drawer #12.

No dosage adjustments are allowed on the last two days of the dosing week. For clinics open Monday through Friday dosage adjustments may be made on Monday or Wednesday if the PCC is notified on Monday or Tuesday, respectively. In clinics that are open Monday through Saturday, dosage adjustments can be made on Tuesday, Wednesday or Thursday, providing PCC was notified on Monday, Tuesday or Wednesday, respectively.

Reinduction Period

If the patient misses 4, 5, 6, 7, or 8 calendar days, he/she will need to go through a four-day (four-dose) reinduction period. The reinduction regimen is obtained by calling PCC to receive the correct dosage assignments. The dose assignment for the first day of the reinduction period will be given verbally over the telephone. The last three days will be obtained from the faxed "Dose Notification Form" which will be faxed to the center within 24 hours after the initial assignment.

If the site anticipates that a subject who has been absent for four to eight consecutive days may be coming to the clinic for a reinduction dose over the weekend, it is imperative to call PCC on **Friday** for possible dose assignment. PCC will not be available to make dose assignments over the weekend.

Reinduction doses should be available for subjects at the clinics on Saturdays and Sundays even though the maintenance dose schedule will only be operational five or six days a week.

An example of the "Dose Notification Form" is shown below:

Date:		DOSE ASSIGNMENT NOTIFICATION FORM			
PATIENT RANDOMIZATION NUMBER	DRAWER NUMBER ASSIGNMENT REINDUCTION REGIMEN				
	Dose #1	Dose #2	Dose #3	Dose #4	
501-123	2	14	23	4	

After completion of the four day (4-dose) Reinduction Period, doses should be obtained from the drawers indicated on the previous Dose Assignment Notification Form.

This document must be placed in the patient's clinic chart. After the patient completes the reinduction period, he/she will resume the previous dose assignment (e.g., for patient 057-028 the weekly doses will be obtained from Drawer # 32 and the weekend dose will be obtained from Drawer #3. The reinduction dosing schedule is outlined below:

REINDUCTION DOSING SCHEDULE				
Dosage Level	Dose #1	Dose #2	Dose #3	Dose #4
1 (32mg)	2mg	4mg	8mg	16mg
2 (16mg)	2mg	4mg	8mg	12mg
3 (8mg)	2mg	4mg	8mg	8mg
4 (4mg)	2mg	4mg	4mg	4mg
5 (2mg)	1mg	2mg	2mg	2mg
6 (1mg)	1mg	1mg	1mg	1mg

If a patient misses one, two or three days during a reinduction period, he/she will be given the next dose (no doses will be skipped), i.e., if the patient begins reinduction on Study Day #151, then misses Day #153 and Day #154 of treatment, on Day #155 when he comes to the clinic he will be given Dose #3 and on Day #156 he will receive Dose #4, then on Day #157 the dose administered will be taken from the appropriate drawer previously assigned to that patient. If a patient misses 4, 5, 6, 7 or 8 days during a reinduction period, the next dose administered will be Dose #1 from the drawer indicated for Dose #1 (e.g., "3") on the "Dose Assignment Notification Form" provided for the Reinduction Regimen for this patient. A patient is allowed 5 reinduction periods during the extension protocol.

5 Dose Tapering Period

If a patient requests being tapered off study drug, the clinic must contact PCC to obtain the correct 4-dose tapering regimen (Dose #1, Dose #2, Dose #3, and Dose #4) assignments. The dose assignment for the first day of the dose tapering period will be given verbally over the telephone. The last three days will be obtained from the completed "Dose Assignment Notification Form" which will be faxed to the center within 24 hours after the initial assignment. An example of this form is shown below:

DOSE ASSIGNMENT NOTIFICATION FORM				
PATIENT RANDOMIZATION NUMBER	DRAWER NUMBER ASSIGNMENT TAPERING REGIMEN			
	Dose #1	Dose #2	Dose #3	Dose #4
501-123	4	23	12	3

After completion of the four day (4-dose) Dose Tapering Period the patient has completed his/her participation in the study.

This document must be placed in the patient's clinic chart. The taper schedule, which will be the reverse of the reinduction dosing schedule, is dependent upon which dosage level the patient is being maintained on. The six different dose tapering schedules used in the extension are outlined below:

DOSE TAPERING SCHEDULE				
Dosage Level	Dose #1	Dose #2	Dose #3	Dose #4
1 (32mg)	16mg	8mg	4mg	2mg
2 (16mg)	12mg	8mg	4mg	2mg
3 (8mg)	8mg	8mg	4mg	2mg
4 (4mg)	4mg	4mg	4mg	2mg
5 (2mg)	2mg	2mg	2mg	1mg
6 (1mg)	1mg	1mg	1mg	1mg

6.06 Labeling

Each triangular-shaped unit of study drug is labeled with the following information:

- A. VA/NIDA Study 999a EXT
- B. Study Drug [DRUG: B-999AE Buprenorphine 1mg, 2mg, 4mg, 8mg, 12mg, 16, or 32mg] 1ml/unit
- C. Drawer # [e.g., "32"]
- D. Unit ID # [e.g., "19019"]
- E. Name: _____

To avoid confusion with the study drug used in the parent study, each unit of study drug used in the extension study will be labeled with a small green flag label. These units will also NOT be enclosed in a plastic bag. In order to avoid errors or confusion, when removing a unit of study drug from one of the drawers, immediately write the patient number or name on that unit label.

7. SHIPMENT OF RETURNS TO PCC

Each center must ship all unused study drug to the Pharmacy Coordinating Center (PCC) for disposition at the end of the study. The pharmacist or study coordinator is responsible for the completion of the "Returned Study Drug Inventory" (DHP-3/EXT) and the return of all study drug.

Both the green and blue copies of this form should be enclosed in the box prior to shipment to the PCC. The pink copy should be retained by the local clinic. The PCC will return the blue copy to the clinic acknowledging receipt of the returned box or kit. Upon receipt from PCC, the blue copy should be stapled to the pink copy and retained by the local clinic. Returns should be sent via registered mail. When returning study drug, each site must retain proof of shipment which must include:

- 1. Date shipped
- 2. Carrier's name
- 3. A list of all units returned ["Returned Study Drug Inventory" (DHP-3/EXT)]

PATIENT ENROLLMENT/DOSE ADJUSTMENT/TERMINATION NOTIFICATION

Date: _____

FAX To: NIDA Pharmacy Coordinating Center (PCC)

FAX: (505)256-5749

From: _____
(Name)_____
(Center #)

ENROLLMENT: Notify PCC at least 5 days before a patient is eligible to enter the extension protocol. PCC will provide the appropriate dose assignments to the clinic within 5 days after notification.

Patient Randomization Number	B-999AE Dose Requested			First Dose Needed	
	1/2 Dose	Parent Protocol Dose	2 x Dose	Date	Day of Week

DOSE ADJUSTMENT: PCC must be notified no later than 4PM EST the day preceding the dosage change. PCC will provide the appropriate dose assignments to the clinic within 24 hours after notification.

Patient Randomization Number	B-999AE Dose Requested		First Dose Needed		
	1/2 Dose	2 x Dose	Date	Time	Day of Week

TERMINATION: Notify PCC ASAP!

Patient Randomization Number	Date Terminated	Reason

COMMENTS:

Page:

DEPARTMENT OF VETERANS AFFAIRS COOPERATIVE STUDIES PROGRAM

"RETURNED STUDY DRUG INVENTORY"
(Returned Drug/Device Inventory)

NIDA STUDY #: 999a Extension CENTER #: _____ CENTER NAME: _____

STUDY TITLE: Long Term Extension of a Multicenter Clinical Trial of Buprenorphine
in Treatment of Opiate Dependence

STUDY DRUG IDENTIFICATION INFORMATION:

<u>EXTENSION STUDY DRUG</u>	<u>MANUFACTURER</u>	<u>LOT #</u>	<u>RECALL DATE</u>
BUPRENORPHINE 1mg, 2mg 4mg, 8mg, 12mg, 16mg or 32mg (Drug Code Name: B-999AE)	NIDA		Monitored by PCC

Drawer Number	Total Number of Units	Drawer Number	Total Number of Units
01		19	
02		20	
03		21	
04		22	
04		23	
06		24	
07		25	
08		26	
09		27	
10		28	
11		29	
12		30	
13		31	
14		32	
15		33	
16		34	
17		35	
18		36	

Signature of Person Completing this Form:

Name: _____ Date: _____

Green: PCC - Blue: PCC Acknowledgement of Returns - Pink: Local Records

PHARMACY COORDINATING CENTER (PCC)

ORDER FORM

CENTER (include Name/Address): _____

CENTER NUMBER: _____

TELEPHONE NUMBER: _____

Person Initiating Order: _____

Date: _____

Instructions: Mail or fax this order to the PCC. Retain a copy for your records.

NIDA Pharmacy Coordinating Center (151-l)
2100 Ridgecrest Drive, SE
Albuquerque, NM 87108.

Telephone: Commercial (505) 265-1711 EXT. 2580 FAX: Commercial (505) 256-5749

ITEM

QUANTITY

Study Aids:

- | | |
|--|-------|
| 1. Medical Alert Cards | _____ |
| 2. Chart Alert Labels | _____ |
| 3. Investigator Information Cards | _____ |
| 4. Case Report Form Book Labels | _____ |
| 5. "Patient Enrollment/Dose Adjustment/Termination Notification"
(DHP-1/EXT) - 50/pad | _____ |
| 6. "Receiving & Dispensing Study Drug Inventory"
(DHP-2/EXT) - 50/pad | _____ |
| 7. "Returned Study Drug Inventory" (DHP-3/EXT) | _____ |
| 8. PCC Order Forms (DHP-4/EXT) - 25/pad | _____ |
| 9. Other _____ | _____ |

Request for additional study drug:

<u>Drawer #</u>	<u># Bags</u> (28 units/bag)
_____	_____
_____	_____
_____	_____
_____	_____

This form should be mailed or faxed to the PCC. Allow at least ten working days for preparation and shipping of supplies.

[illegible]

Patient's Name _____ Randomization # _____

Address _____ Phone Number _____

I am taking an investigational medication as a participant in
a clinical trial. IN AN EMERGENCY or if I require medical
attention at any time, please contact the study site physician
listed below:

Physician: _____ Telephone # _____

_____ Telephone # _____

IN AN EMERGENCY ONLY, If unable to contact the study site physician, call 800-843-2237. (Please keep this card with you at all times and show it to any physician or dentist treating you.)

[illegible]

(COLOR: LIGHT GREEN)

PHARMACY COORDINATING CENTER (PCC)

Carol Fye, R.Ph., M.S. - Pharmacist

Kathy Thomas - Study Coordinator

Hours: 9AM - 5:30PM (EST)

Phone: (505) 265-1711 Ext. 2580

FAX: (505) 259-2878

Hours: 24-hour SkyPager

Dial 1-800-759-8235

Enter Pin #: 5469220

After the tone, leave your voice message.

For help call SkyTel (1-800-SKY-USER)/(1-800-759-8737)

Drug Issues

Unblinding

INVESTIGATOR INFORMATION CARD

VA/NIDA Study #999a Extension

**"A Multicenter Clinical Trial of Buprenorphine
in Treatment of Opiate Dependence"**

This is a double blind investigational drug trial conducted by the VA Cooperative Studies Program and the National Institute on Drug Abuse (NIDA). The study drug, BUPRENORPHINE (Code Name: B-999AE), an opiate partial agonist, is available in seven strengths: 1mg, 2mg, 4mg, 8mg, 12mg, 16mg, or 32mg. Each dose is administered sublingually.

COORDINATING CENTER PERSONNEL**Whom To Call****NIDA MEDICATION DEVELOPMENT DIVISION**

Doralle Segal, M.S.

Project Director

Hours: 8AM - 5PM (EST)

Phone: (301) 443-6270

FAX: (301) 443-2599

Type of Question

Protocol Questions

Regulatory Issues

Special AE Reports

Medical Problems

Complications

MDD/NIDA 24 hr Emergency Hotline: 800-NIDA-ADR (or 800-843-2237)

(Ask for Buprenorphine person on call.)

DATA COORDINATING CENTER (DCC)

Joe Collins, Sc.D. - Biostatistician

Susan Stinnett - Project Manager

Karen Jones - Statistical Programmer

Hours: 8AM - 8PM (EST)

Phone: (410) 642-2411 Ext. 6154/6281

(410) 642-2411 Ext. 5288

FAX: (410) 642-1129

Data Collection Forms

IRB Issues

CENTRAL LABORATORY - NW Toxicology Inc.

Hours: 10AM - 7PM (EST)

Phone: (801) 288-2431

FAX: (801) 283-3805

Lab Supplies

(COLOR: WHITE BACKGROUND WITH GREEN PRINT)

PATIENT CHART ALERT LABEL

**Participant In
VA/NIDA Study #999a Extension**

**"A Multicenter Clinical Trial of Buprenorphine
In Treatment of Opiate Dependence"**

Patient taking buprenorphine (sublingual)
1mg, 2mg, 4mg, 8mg, 12mg*, 16mg, or 32mg.

For consult, contact Dr: _____, ext. __

Study Coordinator: _____, ext. __

* For Reinduction or Taper Only.

[Adhesive-backed label]

(COLOR: FLUORESCENT GREEN)

CASE REPORT FORM BOOK LABELS

**Participant In
VA/NIDA Study #999a Extension**

**Buprenorphine
VA/NIDA Study #999a
Extension**

**"A Multicenter Clinical Trial of Buprenorphine
In Treatment of Opiate Dependence"**

Patient Initials:

Patient Initials:

Randomization #:

Randomization #:

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PRESCRIPTION RUBBER STAMPS

VA/NIDA STUDY #999a Extension

DRUG CODE NAME: B-999AE (Buprenorphine 1, 2, 4, 8, 16, or 32mg)

Patient Randomization #: _____

WEEKDAY DOSE: [Monday through Thursday or Friday]

Drawer #: _____

Units Dispensed: ONE dose daily during the week.

Directions: Place contents of one container under the tongue daily.

VA/NIDA STUDY #999a Extension

DRUG CODE NAME: B-999AE (Buprenorphine 1, 2, 4, 8, 16, or 32mg)

Patient Randomization #: _____

WEEKEND DOSE: [Friday or Saturday]

Drawer #: _____

Units Dispensed: ONE dose every weekend.

Directions: Place contents of one container under the tongue daily.

VA/NIDA STUDY #999a Extension

DRUG CODE NAME: B-999AE (Buprenorphine 1, 2, 4, 8, 12, 16, or 32mg)

Patient Randomization #: _____

Drawer #: _____

Circle Regimen: Reinduction, OR Taper

Circle Dose Dispensed: Dose #1; Dose #2; Dose #3; Dose #4

Directions: Place contents of one container under the tongue daily.

APPENDIX B

Study Forms

LAATRC/VA/NIDA STUDY # 001-99-0006
**"A Multicenter Clinical Trial of Buprenorphine
in Treatment of Opiate Dependence"**

Schedule of Data Collection

Instruments	Week of Study																																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Form 01 - Laboratory Report												x												x												x
Form 02 - Physical Exam												x												x												x
Form 03 - Electrocardiogram*																								x												x
Form 04 - Weekly Self-Report of Drug Use	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Form 05 - Concomitant Medication				x				x				x				x				x				x				x			x				x	
Form 06 - Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Form 07 - Serious Adverse Event Form‡																																				
Form 08 - Termination																																				x
Form 09 - Dose Administration †																																				
* EKG to be performed 24 weeks after Parent Protocol is completed and at termination. ‡ To be completed only as necessary. † To be completed daily beginning with the first dose of buprenorphine.																																				

VA/NIDA STUDY 999a EXT

A Long Term Multicenter Clinical Trial of Buprenorphine in Treatment of Opiate Dependence

Patient Initials

Center No.

Patient No.

SUMMARY OF LENGTH OF TIME IN 999a PROTOCOL:

PARENT: _____ *weeks*

CONTINUATION: _____ *weeks*

EXTENSION: _____ *weeks*

STUDY FORMS FOR 999a EXT

FORM 01 - Laboratory Report

FORM 02 - Physical Exam

FORM 03 - Electrocardiogram

FORM 04 - Weekly Self-Report of Drug Use

FORM 05 - Concomitant Medication

FORM 06 - Adverse Events

FORM 07 - Serious Adverse Event Form

FORM 08 - Termination

FORM 09 - Dose Administration Record

VA/NIDA STUDY 999a EXT

A Long Term Multicenter Clinical Trial of Buprenorphine in Treatment of Opiate Dependence

Patient Initials

Center No.

Patient No.

Date of Visit

 - -
month - day - year

FORM 01 - LABORATORY REPORT

RATING PERIOD:

☐ 12 wk

☐ 24 wk

☐ 36 wk/termination

☐ other _____

DATE SAMPLE DRAWN:

month day year

TIME SAMPLE DRAWN:

 :
(24 hour clock)

HEMATOLOGY

- | | | | |
|-------------------------------------|--|--------------------|--|
| 1. Total WBC ($\times 10^3$ cu mm) | <input type="text"/> <input type="text"/> • <input type="text"/> | 6. Neutrophils (%) | <input type="text"/> <input type="text"/> • <input type="text"/> |
| 2. Total RBC ($\times 10^6$ cu mm) | <input type="text"/> <input type="text"/> • <input type="text"/> | 7. Lymphocytes (%) | <input type="text"/> <input type="text"/> • <input type="text"/> |
| 3. Platelet count (/cu mm) | <input type="text"/> <input type="text"/> | 8. Monocytes (%) | <input type="text"/> <input type="text"/> • <input type="text"/> |
| 4. Hemoglobin (gm/dl) | <input type="text"/> <input type="text"/> • <input type="text"/> | 9. Eosinophils (%) | <input type="text"/> <input type="text"/> • <input type="text"/> |
| 5. Hematocrit (gm/dl) | <input type="text"/> <input type="text"/> • <input type="text"/> | 10. Basophils (%) | <input type="text"/> <input type="text"/> • <input type="text"/> |

BLOOD CHEMISTRY

- | | | | |
|---------------------------|--|------------------------------|--|
| 11. Glucose (mg/dl) | <input type="text"/> <input type="text"/> <input type="text"/> | *16. SGOT or AST (U/L) | <input type="text"/> <input type="text"/> <input type="text"/> |
| 12. Total protein (gm/dl) | <input type="text"/> • <input type="text"/> | *17. SGPT or ALT (U/L) | <input type="text"/> <input type="text"/> <input type="text"/> |
| 13. Albumin (gm/dl) | <input type="text"/> • <input type="text"/> | *18. GGT (U/L) | <input type="text"/> <input type="text"/> <input type="text"/> |
| 14. BUN (mg/dl) | <input type="text"/> <input type="text"/> | *19. Alk. phosphatase (U/L) | <input type="text"/> <input type="text"/> <input type="text"/> |
| 15. Creatinine (mg/dl) | <input type="text"/> • <input type="text"/> | *20. Total bilirubin (mg/dl) | <input type="text"/> • <input type="text"/> |

21. If any liver function test values (*) are 8 times or greater than normal, were Forms 06 and 07 completed and the Sponsor and the IRB notified? 1 ☐ Yes 2 ☐ No

URINALYSIS

- | | |
|---|---|
| 22. Specific gravity | <input type="text"/> • <input type="text"/> <input type="text"/> <input type="text"/> |
| 23. Reaction (record actual Ph value) | <input type="text"/> • <input type="text"/> |
| 24. Albumin (0=Negative, 1=Present) | <input type="text"/> |
| 25. Glucose (0=Negative, 1=Trace, 2=1+, 3=2+, 4=3+, 5=4+) | <input type="text"/> |
| 26. Acetone (0=Negative, 1=Present) | <input type="text"/> |
| 27. WBCS/HPF (1=None, 2=Few, 3=Moderate, 4=Heavy) | <input type="text"/> |
| 28. RBCS/HPF (1=None, 2=Few, 3=Moderate, 4=Heavy) | <input type="text"/> |
| 29. Epithelial Cells (1=None, 2=Few, 3=Moderate, 4=Heavy) | <input type="text"/> |

RATING PERIOD:

☐

12 wk

☐

24 wk

☐

36 wk/termination

☐

other

30. Were any clinically significant abnormal results observed?

☐

Yes

☐

No

If yes, please give details:

PREGNANCY TEST (To be done only on women of childbearing potential.)

31. Serum Pregnancy Test:

☐

Positive

☐

Negative

☐

Not Applicable

BUPRENORPHINE BLOOD LEVELS (To be done just prior to and 2 weeks after dose change and when a Serious Adverse Event occurs.)

32. Was blood drawn?

☐

Yes

☐

No

33. Date:

month

day

year

COMMENTS:

FORM COMPLETED BY

INVESTIGATOR'S SIGNATURE

Date

VA/NIDA STUDY 999a EXT

A Long Term Multicenter Clinical Trial of Buprenorphine in Treatment of Opiate Dependence

Patient Initials

Center No.

Patient No.

Date of Visit

 - -
month day year

FORM 02 - PHYSICAL EXAM

Rating Period:

☐

12 wk

☐

24 wk

☐

36 wk/termination

☐

other _____

VITAL SIGNS

1. Height (ins.)

4. Blood Pressure - sitting (mmHg) /

2. Weight (lbs.)

5. Pulse Rate (/minute resting)

3. Temperature (°C) .

6. Respiration (/minute resting)

PHYSICAL EXAMINATION	Normal (1)	Abnormal (2)	Not Done (3)	Describe Abnormality
7. HEENT	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
8. Sublingual Mucosa	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
9. Pupil Size	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
10. Heart	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
11. Lungs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
12. Abdomen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
13. Extremities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
a. Fresh Needle Marks	1 <input type="checkbox"/> Yes	2 <input type="checkbox"/> No		
b. Available Veins	1 <input type="checkbox"/> Yes	2 <input type="checkbox"/> No		
14. Skin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
15. Lymph Nodes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
16. Other _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other physical findings: _____				

FORM COMPLETED BY _____

INVESTIGATOR'S SIGNATURE _____

Date _____

VA/NIDA STUDY 999a EXT

A Long Term Multicenter Clinical Trial of Buprenorphine in Treatment of Opiate Dependence

Patient Initials

Center No.

Patient No.

Date of EKG

 - -
month day year

FORM 03 - ELECTROCARDIOGRAM

Electrocardiogram to be performed 24 weeks after Parent Protocol is completed and at termination.

ENTER STUDY WEEK NUMBER:

Please answer each question by placing an "X" in the appropriate box.

	Present	Absent		Present	Absent
1. Left Atrial Hypertrophy	1 <input type="checkbox"/>	2 <input type="checkbox"/>	16. Ventricular Premature Beat	1 <input type="checkbox"/>	2 <input type="checkbox"/>
2. Right Atrial Hypertrophy	1 <input type="checkbox"/>	2 <input type="checkbox"/>	17. Supraventricular Tachycardia	1 <input type="checkbox"/>	2 <input type="checkbox"/>
3. Left Ventricular Hypertrophy	1 <input type="checkbox"/>	2 <input type="checkbox"/>	18. Ventricular Tachycardia	1 <input type="checkbox"/>	2 <input type="checkbox"/>
4. Right Ventricular Hypertrophy	1 <input type="checkbox"/>	2 <input type="checkbox"/>	19. Atrial Fibrillation	1 <input type="checkbox"/>	2 <input type="checkbox"/>
5. Acute Infarction	1 <input type="checkbox"/>	2 <input type="checkbox"/>	20. Atrial Flutter	1 <input type="checkbox"/>	2 <input type="checkbox"/>
6. Subacute Infarction	1 <input type="checkbox"/>	2 <input type="checkbox"/>	21. Other Rhythm Abnormalities	1 <input type="checkbox"/>	2 <input type="checkbox"/>
7. Old Infarction	1 <input type="checkbox"/>	2 <input type="checkbox"/>	22. Implanted Pacemaker	1 <input type="checkbox"/>	2 <input type="checkbox"/>
8. Myocardial Ischemia	1 <input type="checkbox"/>	2 <input type="checkbox"/>	23. 1st Degree A-V Block	1 <input type="checkbox"/>	2 <input type="checkbox"/>
9. Digitalis Effect	1 <input type="checkbox"/>	2 <input type="checkbox"/>	24. 2nd Degree A-V Block	1 <input type="checkbox"/>	2 <input type="checkbox"/>
10. Symmetrical T-Wave Inversions	1 <input type="checkbox"/>	2 <input type="checkbox"/>	25. 3rd Degree A-V Block	1 <input type="checkbox"/>	2 <input type="checkbox"/>
11. Poor R-Wave Progression	1 <input type="checkbox"/>	2 <input type="checkbox"/>	26. LBB Block	1 <input type="checkbox"/>	2 <input type="checkbox"/>
12. Other Nonspecific ST/T	1 <input type="checkbox"/>	2 <input type="checkbox"/>	27. RBB Block	1 <input type="checkbox"/>	2 <input type="checkbox"/>
13. Sinus Tachycardia	1 <input type="checkbox"/>	2 <input type="checkbox"/>	28. Pre-excitation Syndrome	1 <input type="checkbox"/>	2 <input type="checkbox"/>
14. Sinus Bradycardia	1 <input type="checkbox"/>	2 <input type="checkbox"/>	29. Other Intraventricular Cond. Block	1 <input type="checkbox"/>	2 <input type="checkbox"/>
15. Supraventricular Premature Beat	1 <input type="checkbox"/>	2 <input type="checkbox"/>			

30. EKG OVERALL RESULTS: 1 ☐ Normal 2 ☐ Abnormal

31. Do any items listed as "present" exclude the patient from continuing with the study? 1 ☐ Yes 2 ☐ No

READ BY: _____

Date _____

INVESTIGATOR'S SIGNATURE _____

Date _____

VA/NIDA STUDY 999a EXT
A Long Term Multicenter Clinical Trial of Buprenorphine in Treatment of Opiate Dependence

Patient Initials

Center No.

Patient No.

Date of Visit
 - -
 month - day - year

FORM 04 - WEEKLY SELF-REPORT OF DRUG USE

ENTER STUDY WEEK NUMBER:

THIS REPORT IS FOR THE WEEK OF TO
 month day year month day year

DRUG	USED DRUG?	WHAT DAYS OF THE WEEK DID YOU USE DRUGS AND <u>HOW MANY TIMES?</u>				TOTAL DOLLAR AMOUNT SPENT	Primary Mode of Abuse 1=Oral 2=I.V. 3=Snorting 4=Smoking 5=Sublingual 6=Other
		Fri. Sat. Sun.	If Yes: # of Times	Mon. thru Thurs.	If Yes: # of Times		
1. Heroin or other opiate	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	\$ <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>
2. Cocaine	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	\$ <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>
3. Methamphetamine	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	\$ <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>
4. Alcohol	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	\$ <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>
5. Tranquilizers	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	\$ <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>
6. Marijuana or other forms of THC	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	\$ <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>
7. PCP	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	\$ <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>
8. Other, specify: _____	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	<input type="text"/> <input type="text"/>	\$ <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>

FORM COMPLETED BY _____

INVESTIGATOR'S SIGNATURE _____

Date _____

VA/NIDA STUDY 999a EXT

A Long Term Multicenter Clinical Trial of Buprenorphine in Treatment of Opiate Dependence

Patient Initials

Center No.

Patient No.

Date of Visit

 - -
 month day year

FORM 05 - CONCOMITANT MEDICATION

ENTER STUDY WEEK NUMBER:

1. Did the patient take any prescription or over-the-counter medications in the past month? 1 ☐ Yes 2 ☐ No

IF YES, list drug(s) and give indication(s) below. Record the strength (mg) and doses per day, the dates the drug(s) were taken, and check (✓) if continuing the medication.

Drug Name (Generic Preferred)	Strength (mg)	Doses /Day	Indication	FROM			TO			Check (✓) if continuing
				Mo	Day	Yr	Mo	Day	Yr	
a.	----	--		--	--	--	--	--	--	
b.	----	--		--	--	--	--	--	--	
c.	----	--		--	--	--	--	--	--	
d.	----	--		--	--	--	--	--	--	
e.	----	--		--	--	--	--	--	--	
f.	----	--		--	--	--	--	--	--	
g.	----	--		--	--	--	--	--	--	
h.	----	--		--	--	--	--	--	--	

FORM COMPLETED BY _____

INVESTIGATOR'S SIGNATURE _____

Date _____

VA/NIDA STUDY 999a EXT
A Long Term Multicenter Clinical Trial of Buprenorphine in Treatment of Opiate Dependence

Patient Initials

Center No.

Patient No.

Date of Visit
 - -
month day year

FORM 06 - ADVERSE EVENTS

STUDY WEEK NUMBER: FOR THE WEEK OF TO
month day year month day year

1. "How have you been feeling this last week?" _____
2. "Have you had any problems in the last week such as an accident or hospitalization?"
(Including those present or unresolved at entry.) 1 ☐ Yes 2 ☐ No
3. "Has your drug dose been holding you ok?" 1 ☐ Yes 2 ☐ No
If NO, describe: _____

I. Type of Report	II. Relatedness	III. Severity	IV. Action Taken	V. Outcome
1=Anticipated adverse event 2=Unanticipated adverse event 3=Intercurrent illness 4=Withdrawal symptom †5=Development of clinically significant abnormal lab value	1=Study drug related 2=Probably study drug related 3=Possibly study drug related 4=Unrelated to study drug	1=Mild 2=Moderate 3=Severe	1=None 2=Prescription or OTC drug therapy required *3=Inpatient hospitalization required or prolonged *4=Prescription drug therapy and hospitalization required 5=Dropped from study due to effect 6=Medical specialty consultation	1=Resolved; No sequelae 2=Not yet resolved *3=Resulted in chronic condition, severe and/or permanent disability *4=Deceased 5=Unknown

Considering the patient's responses to questions 1, 2, and 3 above and any other pertinent information (i.e., lab results, etc.), please describe, in the investigator's own words, each Adverse Event, Intercurrent Illness or Clinically Significant Abnormal Lab Value and associated information below.

Nature of Illness, Event or Abnormal Lab Value	Date of Onset (mo day yr)	Date of Resolution (mo day yr)	I. Type of Report	II. Relatedness	III. Severity	IV. Action Taken	V. Outcome
a.	-----	-----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b.	-----	-----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c.	-----	-----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d.	-----	-----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e.	-----	-----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f.	-----	-----	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

†May require completion of Form 07 - Serious Adverse Event Form

*Requires completion of Form 07 - Serious Adverse Event Form

4. Is a Serious Adverse Event Form (Form 07) required? 1 ☐ Yes 2 ☐ No

FORM COMPLETED BY _____

INVESTIGATOR'S SIGNATURE _____

Date _____

FORM 07 - SERIOUS ADVERSE EVENT FORM

STUDY NO. 999a EXT

CENTER NO.

PATIENT NO.

I. ADVERSE EVENT

STUDY WEEK NO.

PATIENT INITIALS

2-4. EVENT ONSET

Month: Day: Year:

5. Age: (yrs)

SEX

7. HEIGHT (in)

8. WEIGHT (lb)

A. PROVIDE A NARRATIVE DESCRIPTION OF EVENT: _____

ACTION TAKEN				
B. GREATEST SEVERITY	C. STUDY DRUG RELATED	D. DOSE CHANGE	E. TREATMENT	F. OUTCOME
1 = Mild	0 = No	0 = No Change	0 = No Treatment	0 = Unknown
2 = Moderate	1 = Possible	1 = Reduced	1 = Outpatient Tx	1 = Resolved
3 = Severe	2 = Probable	2 = Temp. Dc'd	2 = Hospitalization	2 = Ongoing
<input type="text"/>	<input type="text"/>	3 = Perm. Dc'd	<input type="text"/>	3 = Died
		<input type="text"/>		<input type="text"/>

G. If Died, List Primary Cause of Death:

Relevant Tests/Laboratory Data:

II. SUSPECT DRUG(S) INFORMATION

1. Suspect Drug(s) (Give Trade/Generic Name(s), Manufacturer):

2. Daily Dose:

13. Route of Administration:

14. Dates of Administration: (from/to)

5. Indication(s) for Use:

16. Duration of Administration:

III. CONCOMITANT DRUG(S) AND HISTORY

7. Concomitant Drug(s) and Date(s) of Administration (Exclude those used to treat reaction)

8. Other Relevant History (e.g. diagnoses, allergies, etc.)

IV. INITIAL REPORTER

19-20. Name, Title, and Address of Reporter (Include Zip Code)

21. Telephone No. (Include area code)

Date Completed:

VA/NIDA STUDY 999a EXT

A Long Term Multicenter Clinical Trial of Buprenorphine in Treatment of Opiate Dependence

Patient Initials

Center No.

Patient No.

Date Terminated

 - -
month day year

FORM 08 - TERMINATION

1. USING THE LIST BELOW, PLEASE INDICATE THE PRIMARY REASON PATIENT TERMINATED FROM THE STUDY. (If 3, 7, 10, or 12 are given as the primary reason for termination, please specify reason where indicated below.)

- ☐ 1. Completed protocol
- ☐ 2. Toxicity or side effects related to buprenorphine
- ☐ 3. Medical reason unrelated to buprenorphine; or termination by clinic physician because of intercurrent illness or medical complications precluding safe administration of buprenorphine
IF YES, specify reason: _____
- ☐ 4. Drug not "holding"
- ☐ 5. Missed 9 consecutive calendar days of dosing
- ☐ 6. Required a 6th reinduction
- ☐ 7. Patient's request
IF YES, specify request: _____
- ☐ 8. Moved from area
- ☐ 9. Incarceration exceeding 8 days
- ☐ 10. Administrative discharge
IF YES, specify incident: _____
- ☐ 11. Death (termination date is date of death if patient is dosed up until death, or date of last dose of buprenorphine if patient is not dosed up until death; complete Serious Adverse Event Form (07))
IF YES, specify cause of death if known: _____
- ☐ 12. Other
IF YES, specify: _____

2. BRIEFLY DESCRIBE THE EVENTS WHICH LED TO TERMINATION (be specific): _____

3. SINCE THE PATIENT ENTERED THE STUDY, IS HE/SHE:

5 ☐ Much Better 4 ☐ A Little Better 3 ☐ No Change 2 ☐ Slightly Worse 1 ☐ Much Worse

FORM COMPLETED BY _____

INVESTIGATOR'S SIGNATURE _____

Date _____

"A Long Term Multicenter Clinical Trial of Buprenorphine in Treatment of Opiate Dependence"

FORM 09 - DOSE ADMINISTRATION RECORD

Center Number: _____

Patient Number: _____

Patient's Initials: _____

Study Drug: B-999AE (Buprenorphine 1mg, 2mg, 4mg, 8mg, 12mg, 16mg, or 32mg)

Date FAXed (Mo/Day)	Bupre- norphine Day Number	Day of Week	Date (Mo/Day/Yr)	No Dose Given		Extension Study Drug		Dose Administered (Please Check Appropriate Box)												Dosed By	Comments (Record dose changes here)
				Missed Dose	Day Off	Drawer Number	Unit ID Number	Weekly Dose		ReInduction Regimen				Taper Regimen							
								Weekday Dose	Weekend Dose	Dose #1	Dose #2	Dose #3	Dose #4	Dose #1	Dose #2	Dose #3	Dose #4				
		Su																			
		Mo																			
		Tu																			
		We																			
		Th																			
		Fr																			
		Sa																			
		Su																			
		Mo																			
		Tu																			
		We																			
		Th																			
		Fr																			
		Sa																			
		Su																			
		Mo																			
		Tu																			
		We																			
		Th																			
		Fr																			
		Sa																			

Signature of Person(s) Administering Dose:

Initials

Name

Initials

Name

Initials

Name

APPENDIX C

Informed Consent

Buprenorphine Study #999a EXTENSION

[Please attach to this Consent Form a copy of each patient's signed Consent Form from the Parent #999a study when obtaining consent.]

.....

VA/NIDA Study #999a EXTENSION Consent Form "A Multicenter Clinical Trial of Buprenorphine in Treatment of Opiate Dependence"

Study #999a EXT

You have successfully completed a 16-week study (#999a) of the investigational drug, buprenorphine, being evaluated for safety and effectiveness in treating opiate addiction. You were offered to participate in that study originally because you were dependent upon opiates. At the time that you signed your consent form (see attached), you were told that at the end of the study, buprenorphine might be available to you in a new protocol.

A continuation of the above study, #999a, for up to an additional 16 weeks, was available *until* a long-term "Extension Protocol" went into effect. Now, the Extension Protocol is available and is being offered to you. This protocol will be at least of 20 weeks duration, with a maximum of 36 weeks. Your doctor will explain to you how long you may be eligible to stay in the study. In general, the 16-week study, the continuation portion of that study (if applicable), and the Extension phase, combined, will be one year in length.

The Extension Protocol is designed to evaluate the long-term safety of the drug, buprenorphine, and to obtain more information for the labeling instructions if and when the drug does get marketed. If you choose to continue receiving buprenorphine and to enroll in the extension study (#999a EXT), you will be treated and evaluated in a similar, yet different manner from how you had been treated.

Your dose of buprenorphine may be adjusted during the extension phase if your doctor thinks that is indicated for your treatment. However, dose changes may only be made during the first part of each week. No take home doses will be allowed and you must come to the clinic for dosing either 5 *or* 6 days a week. However, you will receive a double dose of buprenorphine on Fridays (if your clinic is operating on a Monday through Friday schedule), or on Saturday (if your clinic is operating on a Monday through Saturday schedule). *[Sites: please choose what's applicable for your site]*. Results from previous studies seem to suggest that buprenorphine, when given on alternate days, may have "holding power" for some 70 hours. The doses of buprenorphine will be 1, 2, 4, 8, 16, and 32 mg daily with a maximum dose of 32 mg, including on weekends, and a minimum of 1 mg.

continued next page

No additional procedures will be incorporated into the extension protocol that were not part of the original or parent #999a study. However, some procedures, tests, and forms completion will be done with less frequency or even eliminated in this extension phase:

You will have blood samples drawn and physical exams done every 3 months, except if your physician feels more frequent follow-up is indicated. An EKG will be taken 6 months after you complete the #999a study, and again when you terminate from the extension study. You will continue to give urines (sites: spell out the details of how often and whether it'll be under observation, please). Also, you must continue to complete certain forms with the study staff, although some will be less frequent. For example, you must still report your weekly drug use and how you have been feeling, but you will not be asked to complete the craving scale, nor the "patient's global rating scale."

Risks and discomforts, benefits, other treatments available, confidentiality, and your rights as a study patient are all exactly the same as in the parent #999a study (see attached consent form).

COMPENSATION FOR INJURY: *[This paragraph is for non-VA sites. VA sites: please modify for your specific needs].* If you have been injured as a result of this study, emergency medical treatment will be provided. The cost of the treatment will be paid for by your insurance carrier or by yourself *[or by the clinic if your site is so structured.]* It is not the policy of this clinic, however, to provide compensation, as such. If you believe that you have sustained injury by participating in this research, you should speak with Dr. _____, the physician in charge of the study *[or whomever else the site designates]* by calling _____.

TERMINATION FROM THE STUDY: Should you decide to discontinue your participation at any time during the study, you may do so by notifying a member of the research staff of your decision. If you terminate, you may participate in other studies or continue to receive other appropriate services of the clinic. We will help you taper from the medication or assist you with a referral to another clinic.

As in the parent study, if you leave the study early, we may want to contact you to see how you are doing. If you sign this consent, you are agreeing that we may contact you. You previously gave us names of people we may contact to find you. You may withdraw this consent at any time by notifying us in writing.

Research staff may terminate your participation in the study if you fail to comply with the study procedures or if you continue to put yourself at risk by using street drugs. Reasons for termination in this extension phase (#999a EXT) are slightly different from the #999a study. The differences are:

continued next page

1. Missing 9 consecutive calendar days without study drug . Exceptions may be made later in the study for hospitalizations and excused absences, according to clinic policy.
2. If you require a 6th reinduction in the extension study (that is, you have already been reinducted 5 times during the extension phase for missing 4, 5, 6, 7, or 8 consecutive days of dosing), you will not be allowed to continue.

If you are a woman, you must continue to use adequate contraception to avoid pregnancy; should you become pregnant, your participation in the study will be terminated. We will then assist you in arranging appropriate treatment and prenatal care.

As in the parent study, we urge you not to drink alcohol or use other drugs while you are in this study. The effects of combining buprenorphine with alcohol or other drugs is still unknown.

COMPLETION OF THE STUDY: If/when you complete this extension study, several options will be available to you at this clinic. If you and your doctor agree, you may opt to be tapered from buprenorphine and go "drug free" in a medically-supervised withdrawal program. Other medications may be available, such as naltrexone or methadone. Or, you may have an opportunity for ongoing maintenance on buprenorphine in another dosage form or on another dosage schedule; in this event, a new study proposal would be in effect. Your study doctor will discuss these possibilities with you at the end of this extension study.

I understand that I do not have to take part in this study, and my refusal to participate will involve no prejudice as to my ongoing care or my rights. I may withdraw from this study at any time without penalty or loss of any benefits to which I am entitled.

CONFIDENTIALITY: A Certificate of Confidentiality has been applied for from the Department of Health and Human Services. This certificate will protect the investigators from being forced to release any research data in which you are identified, even under a court order or subpoena. This protection, however, is not absolute. It does not, for instance, apply to any state requirement to report certain communicable diseases or to disclosure of medical information in cases of medical necessity. In addition, the investigator(s) may choose to voluntarily report certain cases of child abuse to the appropriate authorities. Also, because this research is regulated by the Food and Drug Administration (FDA) and sponsored by the National Institute on Drug Abuse (NIDA), staff from these and other DHHS agencies may review records that identify you. However, it is the policy of these agencies and this investigator(s) that every attempt will be made to resist demands to release information that identifies you. When results of this study are published, your name will not be used.

continued next page

In case there are medical problems or questions about an injury, I have been told I can call:

Dr. _____ at _____

during the day, and

Dr. _____ at _____ after
hours.

If I have any questions about this study or about my rights as a research patient, I may contact:

_____ at _____.

My rights as a research patient have been explained to me, and I voluntarily consent to participate in this study. I have been told what the study is about and how and why it is being done. I will receive a signed copy of this consent form.

I have been informed that because this study involves a medication regulated by the FDA (Food and Drug Administration), the FDA and NIDA, the sponsor, may choose to inspect records identifying me as a patient in this investigation.

Patient's Signature

Date

Signature of Witness

Witness (print)

Signature of Investigator