I. ABSTRACT

Currently, lofexidine hydrochloride (HCl) (Britlofex, Britannia Pharmaceuticals, Ltd.), an alpha-2-adrenergic agonist, is the most commonly used nonopiate medication for detoxification from opiates in the United Kingdom (UK). There is no nonopiate medication approved by the Food and Drug Administration (FDA) for the same indication in the United States (U.S.).   The only medication currently approved by the FDA for opiate detoxification is methadone, an opiate agonist. The value of having an approved nonopiate in this medication class is to offer patients and their physicians a medication suitable for the alleviation of opiate detoxification with no to low abuse liability. Clonidine, also an alpha-2-adrenergic agonist, is often used "off-label" for this indication in the U.S. In addition to the nonapproved status of clonidine for this indication, a significant limitation of clonidine is that it induces significant hypotension at doses that are effective at alleviating some of the symptoms of opiate withdrawal. Results of recent double-blind (DB) studies suggest that lofexidine has less hypotensive effects than clonidine at equally effective doses for the alleviation of opiate withdrawal in opiate dependent individuals. Based upon the advice of the FDA, a panel of external scientific and medical consultants to the National Institute on Drug Abuse (NIDA), and results of an extensive Phase 2 multi-site dose-response tolerability study, the proposed study is the first Phase 3 multi-site trial designed to assess the efficacy of lofexidine compared with placebo in a DB design for the alleviation of opiate withdrawal symptoms in opiate dependent individuals. The choice of the 3.2 mg dose of lofexidine for the PIII trial is based upon results of the Phase 2 study, which indicates that this is the optimal therapeutic dose (efficacy: side effects).   Such a placebo-controlled, DB assessment is an essential major first step in the evaluation and approval process of lofexidine as an agent for assisting opiate dependent individuals who wish to have a nonopiate agent for the alleviation of their withdrawal symptoms.

II. SUMMARIES

IIA. IMPACT STATEMENT
The value of this pivotal Phase 3 efficacy trial is to investigate if a nonopiate such as lofexidine, an alpha-2-adrenergic agonist, is an effective medication for the alleviation of opiate detoxification symptoms in opiate dependent individuals. **Ultimately, if lofexidine is approved by the FDA based upon this and subsequent studies, a new nonopiate medication (with no or low abuse liability) will then be available to opiate dependent patients and their physicians in the U.S. to assist in the detoxification from opiates.**

IIB. SYNOPSIS OF RESEARCH PLAN
The proposed study is a 11 day inpatient placebo-controlled (PC), DB study of 96 opiate dependent, treatment-seeking individuals randomized to two medication groups: lofexidine (3.2 mg/day, n=48) and placebo (n=48), to be conducted in inpatient units at three treatment sites. The primary outcome measure is the Modified Himmelsbach Opiate Withdrawal Scale (MHOWS), an objective assessment of the severity of opiate withdrawal symptoms, obtained on the second opiate detoxification day. It is hypothesized that the MHOWS scores will be significantly lower in the lofexidine as compared with the placebo group. Subjects will be medically discharged on the morning of the 11th day.

IIC. SYNOPSIS OF METHODOLOGY
There are three major phases of the study. Morphine will be used to stabilize participants on a fixed dose of opiate agonist before the evaluation medication/detoxification phase begins. An initial morphine agonist phase is a prerequisite in the use of the MHOWS (Kolb & Himmelsbach, 1937; Jasinski, 1977; Jasinski, Johnson and Kocher, 1985), and the MHOWS

has been approved by the FDA (April 7, 1999) as the primary outcome measure for this Phase III trial based upon its long standing success as an objective and reliable efficacy measure in opiate detoxification trials. Standardizing participants on an identical dose of morphine may reduce the variability in withdrawal symptoms observed and enable the comparison of lofexidine <u>versus</u> placebo to occur with the lowest variability possible. In turn, this will maximize the detection of a statistically significant effect of lofexidine in the alleviation of opiate withdrawal symptoms.

(1) Opiate Agonist Stabilization Phase:
Days 1-3, 100 mg/day of subcutaneous (s.c.) morphine sulfate),

(2) Detoxification/Medication or Placebo Phase:
Days 4-8, withdraw from morphine sulfate and medicate with lofexidine (Lofex) or placebo. A plateau dose of Lofex (3.2 mg/day, p.o.) will be administered on Days 4-7, and the dose of Lofex (1.6 mg/day, p.o.) will be halved on day 8. The reduction in Lofex dose on day 8 is because a reduced amount of medication is needed when withdrawal is at a minimum, and also to decrease the probability of possible rebound hypertension,

(3) Post Detoxification/Medication Phase:
Days 9-10, all subjects receive placebo. All subjects are discharged on the morning of Day 11, and do not receive any placebo or Lofex on that day.

The **primary outcome measure** is the **MHOWS (study day 5 or 2nd opiate detoxification day)**.

The **secondary outcome measures** include the following: (1) Day to Drop Out, (2) MHOWS (peak effect during the detoxification/medication phase – days 4-8), (3) Objective Opiate Withdrawal Scale (OOWS), (4) Short Opiate Withdrawal Scale (SOWS, Gossop), (5) Modified Clinical Global Impressions Scales (NIMH, MCGI – rater), (6) Modified Clinical Global Impressions Scales (NIMH, MCGI – patient), (7) Subjective Opiate Withdrawal Scale (SOWS, Handlesman), (8) Visual Analog Scale: Efficacy of Medication for the Alleviation of Withdrawal Sickness (VAS-E), and (9) Number of Concomitant Medications Related to Opiate Withdrawal, Study Days 4-8 inclusive. Some of these other secondary measures may have potential as primary outcomes in future trials that may not employ an opiate agonist lead-in.

There will also be **two secondary outcome measures** that provide an important assessment of the **potential abuse liability** of lofexidine: (1) Addiction Research Center Inventory (ARCI) - euphoria (MBG) subscale, and (2) one visual analogue scale (VAS) for "Drug High" that assesses potential abuse related liability aspects of lofexidine. The importance of these latter two abuse liability assessments is per the request of the FDA and in anticipation of potential labeling issues if the product is approved.

The broad array of secondary measures reflects the importance of this study (and its exploratory nature) in providing the first available evidence as to the relative efficacy of Lofex <u>versus</u> placebo on measures with the potential to assess the efficacy of a medication in the alleviation of various aspects of opiate withdrawal.

A variety of **safety measures** will also be obtained including: (1) sitting vital signs including heart rate, systolic and diastolic blood pressure (BP), oral body temperature, and respiratory rate, (2) standing heart rate, systolic and diastolic BP, (3) effects on the electrocardiogram (ECG), (4) physical examination (any abnormal clinical sign), (5) effects on laboratory

chemistries (abnormalities, cf. Appendix V), (6) urine toxicology (for drugs of abuse), (7) adverse events, and (8) Abnormal Vitals Resolution and Termination Event Log.

Additional assessments will include (1) analyses of plasma levels of Lofex ~~and~~ (2) quantitative urine toxicology assays of drugs of abuse, and (3) tobacco withdrawal symptoms.

III. INTRODUCTION and BACKGROUND

The aim of this clinical trial is to evaluate the efficacy of lofexidine, an alpha-2-adrenergic agonist, as a medication for the alleviation of opiate withdrawal symptoms in opiate dependent individuals. The present trial was designed as a Phase 3 pivotal efficacy trial and utilizes a placebo-controlled, double-blind multi-site design. Currently, there is no nonopiate medication approved by the Food and Drug Administration (FDA) for this indication in the United States (U.S.). If this trial demonstrates clinical efficacy of lofexidine for opiate withdrawal, then a substantial clinical development accomplishment will be made paving the way for regulatory approval. Contingent upon the review and approval of the FDA, this will then permit the rapid clinical development of lofexidine and depending upon the success of these other clinical trials (possibly two) may lead to a New Drug Application (NDA) for lofexidine for the indication of opiate detoxification. Therefore, the current trial has the potential of greatly facilitating the regulatory approval of the first nonopiate medication for the alleviation of opiate withdrawal symptoms. The "no" or "low" abuse liability of such an agent is its primary advantage, offering a new nonopiate medication to patients and their physicians in treatment issues surrounding opiate addiction.

IIIA. Medications Therapies for Opiate Addiction: Medically Supervised Maintenance, Withdrawal, and Relapse Treatment. It is valuable to place this effort in the context of the general treatment issues surrounding opiate addiction. There are three well-defined indications for the development of new medications for the treatment of opiate addiction: maintenance, withdrawal, and relapse (Herman et al., 1995; Herman & O'Brien, 1997). These targets can be viewed as a developmental progression of pharmacotherapies representing the initial, middle, and final stages of treating an individual with a severe opioid dependency. A majority of individuals may benefit from remaining in the maintenance phase for an indefinite period of time (Kreek, 1997), while others may be able to transfer directly to medically supervised detoxification and relapse therapy without the need for maintenance therapy.

The indication being targeted in the current study is the alleviation of the abstinence distress associated with opiate withdrawal. Clinical research evaluating such medications for this indication has been reviewed elsewhere (e.g., Herman et al., 1995; Herman & O'Brien, 1997; Kleber & Riordan, 1982; Mattick and Hall, 1996). The only U.S. FDA approved medication for the treatment of opiate withdrawal is methadone. Detoxification is one of the indications where nonopioids medications have shown efficacy when administered as "off-label" treatments (cf. Herman and O'Brien, 1997). Clonidine, also an alpha-2-adrenergic agonist, has successfully been used "off-label" to assist opiate detoxification, but its clinically significant hypotensive effects and nonapproved status are drawbacks in its medical use.

Though medications development for opiate detoxification is valuable (Mattick & Hall, 1996), it is only one small facet in the larger picture of treatment issues for a chronically, relapsing disorder such as opiate addiction (O'Brien & McLellan, 1996). Developing medications for this disorder is analogous to developing medications for other chronic, relapsing "medical" disorders, including diabetes or hypertension. Accordingly, for the majority of affected individuals, it is unrealistic to contemplate that short-term pharmacotherapy will permanently

reverse opiate addiction any more than can common, approved medications of today reverse diabetes or hypertension (O'Brien & McLellan, 1996; Sees et al., 2000). However, with the purity of street heroin at an all time high in the U.S. (cf. Herman & Iversen, 1997, p. 69), detoxification with a nonopiate may be a particularly valuable alternative for individuals with a newly acquired addiction to opiates or to individuals with a more entrenched addiction who finally have a more supportive social and medical environment to encourage the success of detoxification.

IIIB. Structure of Lofexidine and Receptor Binding Characteristics. (+)-Lofexidine, 2-(- [2,6-dichlorophenoxy]ethyl)-∆2-imidazoline, resembles clonidine in structure as indicated in Figure 1 below.
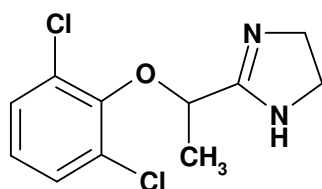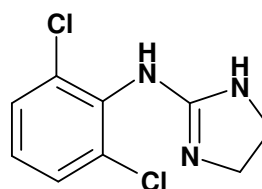
Lofexidine   **Clonidine**

Figure1 – Structure of lofexidine and clonidine.

IIIC. Alpha-2 A, B, and C Receptor Subtyping and Possible Implications for Efficacy: Side Effects Profile of Lofexidine and Clonidine. *Note: this section contains highly confidential unpublished research, cite only with the permission of Britannia Pharmaceuticals, Ltd.* Three subtypes of the alpha-2-adrenergic receptor have been cloned: 2A, 2B, and 2C (Marjamaki et al., 1993; Uhlen & Wikberg, 1991). In the early 1990's, it was reported that clonidine was a nonspecific alpha-2-adrenergic agonist with equal affinity for all three subtypes of receptors (*ibid*). Herman et al. (1996, unpublished) (Herman & O'Brien, 1997; Herman et al., 1999) hypothesized that the relative binding affinity of lofexidine to the various alpha-2-adrenergic receptor subtypes must be different than clonidine based upon its reported different efficacy: side effects profile for the alleviation of opiate withdrawal relative to producing hypotensive effects. Of greatest interest, was the relative binding affinities of these agents to the 2A receptors relative to the other receptors. Higher affinity 2A subtype agents have been shown in nonhuman primates to have less hypotensive effects while retaining functional efficacy on processes such as memory enhancement in aged animals than more nonspecific agents such as clonidine (Arnsten et al., 1988; Herman & O'Brien, 1997). This hypothesis led to the in vitro evaluation of the relative binding affinities of lofexidine and clonidine to the various alpha-2 receptor subtypes. In 1998, MDS Panlabs conducted research on behalf of Britannia Pharmaceuticals, Ltd. comparing the relative affinities of lofexidine and clonidine to these receptor subtypes using human recombinant clones. As noted previously, the binding affinity of clonidine to the 2A and 2B receptors was virtually identical. In contrast to the previous results, the affinity of clonidine to the 2C receptor was about 20-fold lower than that to the 2A or 2B receptors. As predicted, the relative binding affinity of lofexidine showed that lofexidine had the highest affinity for the 2A receptor, followed by the 2B receptor, and then the 2C receptor (about 10-fold lower than 2B). These are the first receptor data providing a potential pharmacological explanation for the purported similar efficacy of lofexidine relative to clonidine in the alleviation of opiate withdrawal coupled with a relatively lower incidence of hypotensive effects. However, the magnitude of the enhanced affinity of lofexidine: clonidine

for 2A <u>versus</u> 2C was about 3-fold, suggesting further <u>in vitro</u> receptor characterization is needed to fully explain the pharmacological differences between these agents in humans.

IIID. Preclinical Evidence that Alpha-2-Adrenergic Agonists Decrease Opiate Withdrawal through the Inhibition of Brainstem Norepinephrine Activity. Preclinical research suggests that chronic exposure to opiates leads to a tonic inhibition of brain nor epinephrine (NE) and to an inhibition in the activity of noradrenergic cells in the locus coeruleus (LC) of the brainstem (Aghajanian, 1982; Aston-Jones et al., 1993) and elsewhere in the brain (Aston-Jones, ref needed about 1999). Abrupt withdrawal of opiates from an opiate-dependent individual appears to result in disinhibition (hyperactivity) of NE cells in the LC and elsewhere which then leads to the expression of numerous symptoms associated with the opiate-withdrawal syndrome (Aghajanian, 1982; Aston-Jones et al., 1993, new ref needed; Gold et al., 1981; Roth, 1982). This hypothesis suggests that medications which reduce brain noradrenergic activity should decrease symptoms of opiate withdrawal. Indeed, many preclinical and clinical studies support this hypothesis. For example, clonidine, an alpha -2-adrenergic agonist, decreases electrophysiological, behavioral, and physical symptoms of opiate withdrawal symptoms in rats (e.g., Aghajanian, 1982; Aston-Jones et al., 1993; Roth et al., 1982; for review cf. Nestler, 1997) and in nonhuman primates (e.g., Roth et al., 1982). Lofexidine inhibits opiate-withdrawal symptoms in morphine-dependent rats after either abrupt withdrawal from chronically infused morphine or precipitating opiate withdrawal using naloxone (Sherman et al., 1980).   Therefore, preclinical research provides a basis for exploring the efficacy of alpha2-adrenergic agents as treatments for opiate withdrawal.

IIIE. Clinical Evidence that Alpha-2-Adrenergic Agonists Decrease Opiate Withdrawal.

Clinical Evidence: Clonidine Alleviates Opiate Withdrawal. The efficacy of clonidine in the treatment of opiate withdrawal in humans has been tested (cf. Gold, 1993; Gold et al., 1978; for a review see Herman & O'Brien, 1997 and Jaffe, 1995). Typically, outpatient administration of clonidine involves starting with a low dose on the first day (0.1-0.3 mg, tid) and increasing to 1.2 mg (Jaffe, 1995). Several placebo-controlled, double-blind trials confirm the efficacy of clonidine in alleviating some (but not all) opiate withdrawal symptoms. A distinction commonly made in these studies is the relative efficacy of clonidine in alleviating the "physical" (autonomic nervous system) signs of withdrawal <u>versus</u> the "psychological" (e.g., anxiety, panic, insomnia) symptoms of withdrawal. Indeed, one of the first placebo-controlled, double-blind studies reported that clonidine (Gold et al., 1980) decreased the physical signs of opiate withdrawal. In agreement with these findings, results of other studies have suggested that clonidine significantly alleviates the physical signs of opiate withdrawal but not the psychological symptoms (e.g., Charney et al., 1981; Uhde et al., 1980). Clonidine has not proved to be effective as an adjunct treatment in enhancing detoxification using gradual methadone dose reduction (e.g., Ghodse et al., 1994; Washton and Resnick, 1981).

There has also been placebo controlled, double-blind studies examining the efficacy of clonidine in reducing heroin or morphine withdrawal. In one of the most elegant studies in the medication/ opiate withdrawal literature, Jasinski et al. (1985) reported that clonidine reduced physical signs much more than psychological symptoms of following abrupt withdrawal from morphine (but see Gold et al., 1980 who did report effects on some psychological symptoms).

The chief limitation of clonidine is clinically significant hypotensive effects at doses required to alleviate opiate withdrawal in an inpatient setting (cf. Charney et al., 1981), with sedation a second common side effect (*ibid*). In addition, clonidine appears to be without efficacy in alleviating the "restlessness" and "insomnia" that accompanies either abrupt withdrawal from

methadone (Ghodse et al., 1994, Kahn et al., 1997) or morphine (Jasinski et al., 1985). In brief, the clinical experience of both Karen Miotto, M.D. (LA) and Elmer Yu, M.D. (Phil) in the Phase 2 lofexidine study suggested that the hypotensive effects of lofexidine were less notable in comparison to clonidine, and the "recovery" from hypotension was more rapid with lofexidine <u>versus</u> clonidine. Systematic research will be needed to test the validity and reliability of this seeming qualitative difference between lofexidine <u>versus</u> clonidine for the opiate withdrawal indication.

<u>Rapid Detoxification Using Clonidine and an Opiate Antagonist in Awake Individuals</u>. A variant of the clonidine technique is a method of rapid detoxification in awake individuals utilizing combinations of alpha-2-adrenergic agonists with opiate antagonists (RDA, rapid detoxification with alpha-2 agonists). Opiate antagonists are used to precipitate opiate withdrawal and thereby shorten the duration of the most intense phase and symptoms of opiate withdrawal (cf. Jaffe, 1995). Gold et al. (1978) was the first to demonstrate the efficacy of clonidine in blocking acute naloxone-precipitated opiate withdrawal symptoms. A chief limitation of this procedure is compliance issues with opiate dependent individuals who frequently will not participate in medical care utilizing opiate antagonists, because of their concerns of the discomfort associated with precipitated withdrawal using opiate antagonists. Although the clinical research using a combination of clonidine and naloxone does not provide significant evidence for such a concern of increased distress with the addition of an opiate antagonist (cf. Gerra et al., 1995). The RDA clonidine/naloxone technique was followed by the RDA clonidine/naltrexone technique (Charney et al., 1982, 1986; Kleber et al., 1987; Riordan & Kleber, 1980). The RDA clonidine/opiate antagonist procedure reduced the detoxification period for opiates from 10 to 5 days (or 4 days, cf. Gerra et al., 1995). Gerra et al. (1995) conducted one of the largest and best controlled studies examining the relative efficacy of placebo <u>versus</u> clonidine ($\pm$ naloxone or naltrexone) in detoxification of 152 heroin-dependent individuals. The efficacy of clonidine in treating opiate withdrawal was confirmed, and the addition of an opiate antagonist to clonidine had both desirable effects (shortening the duration of expression of opiate withdrawal signs to 2 days compared with clonidine alone) and undesirable effects (increasing symptoms on Day 2 of detoxification in comparison with clonidine alone). Detoxification with lofexidine alone can be achieved in five days (cf. Bearn et al., 1998; Herman et al., 1999, 2000; Yu et al., 2000) because relatively higher doses of alpha-2-adrenergic agonist can be administered than with clonidine given the reduced hypotensive effects of lofexidine.

<u>**Clinical Evidence: Lofexidine Alleviates Opiate Withdrawal**</u>.
Table 1

Adverse Events of Lofexidine Reported to the MCA (the UK Regulatory Body) and to Britannia Pharmaceuticals (the UK Distributor) since the Product was Launched in UK in 1992

Lofexidine was launched in the UK in 1992 and since that time, sufficient tablets for approx. **75,000 detoxifications** have been sold. Below is a summary of the adverse events reported to the MCA (the UK Regulatory Body) and to Britannia Pharmaceuticals (the UK distributor) since the product was launched:

Reports to MCA

Cardiovascular	20 (hypotension 10; bradycardia 9)
Gastrointestinal	6
General	13
Musculoskeletal	2
Neurological	7
Psychiatric	10
Respiratory	4
Skin	2
Total	64 (in 41 patients)

Reports to Britannia Pharmaceuticals Ltd

Cardiovascular	13
Ear	1
Eye	2
Gastrointestinal	6
General	1
Hepatic	1
Infections	1
Metabolic	1
Nervous system	4
Psychiatric	3
Respiratory	1
Skin	2
Total	36 (in 36 patients)

NB All of the events reported to Britannia should be included in the MCA figures, however, the MCA figures are not as up to date as Britannia's

Reported to B. Herman, DTRD, NIDA on June 30, 2000 by Mr. Keith Davies, Britannia

Table 2

**Phase 2 Lofexidine Study,
Preliminary Dose Related Efficacy on MHOWS**

Preliminary evidence of dose-related efficacy of Lofexidine (1.6 to 4.0 mg/day) in the alleviation of opiate withdrawal signs based upon dose-dependent decreases in the severity of opiate withdrawal as measured by the Modified Himmelsbach Opiate Withdrawal Scale on the second withdrawal day (peak withdrawal day). Philadelphia site.

Panel A. AM scores alone.
AM MHOWs Score (with pupils) on Study Day L2
(second day of lofexidine administration)

Dose	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum
1.6 mg/day	7	30.3	11.1	4.2	8	43
2.4 mg/day	7	22.0	6.1	2.3	17	35
3.2 mg/day	6	19.3	5.7	2.3	10	24
4.0 mg/day	3	15.7	6.8	3.9	8	21

Panel B. Combined AM & PM scores (where available).
Combined (AM & PM) MHOWs Score (with pupils) on Study Day L2
(second day of lofexidine administration)

Dose	N	Mean	Standard Deviation	Standard Error	Minimum	Maximum
1.6 mg/day	7	31.4	12.4	4.7	7	47
2.4 mg/day	7	23.1	7.8	2.9	15	39
3.2 mg/day *AM only	6	19.3	5.7	2.3	10	24
4.0 mg/day	3	18.3	7.4	4.3	10	24

By design, and for study implementation simplicity, data from Pilot I 3.2 mg/day Lofexidine were collected only in the AM, since previous data collected at the other doses (1.6, 2.4, and 4.0 mg/day) failed to show a marked difference in the sensitivity of the multiple AM & PM versus single AM MHOWS collection method in detecting dose-related efficacy. differences.

For 3.2 mg/day, Pilot I data shown

(Lofex PIII Martz MHOWS Mod BHH L2 031700 061600, revised per O'Brien and Kleber, 062000)

Table 3

**Phase 2 Lofexidine: Preliminary Dose-Related Efficacy –
Reduction of Opiate-Withdrawal-Induced Emesis**

**Doses of Lofexidine between
3.2 mg/d – 4.0 mg/d were More Efficacious than the 1.6 mg/d Dose in Decreasing
Opiate Withdrawal - Induced Emesis
in Opioid-Dependent Individuals**

Dose	Emesis	No Emesis
1.6 mg/d	5/9	4/9
2.4 mg/d	4/22	18/22
3.2 mg/d	0/6	6/6
4.0 mg/d	0/3	3/3

Fisher's Exact Test (2-tailed), p = 0.0539
(3.2 and 4.0 mg/d dose groups not combined)

Fisher's Exact Test (2-tailed), p = 0.0149
(3.2 and 4.0 mg/d dose groups combined)

Frequency table illustrating the effects of lofexidine as a function of dose in decreasing emesis during opiate withdrawal in opiate dependent participants. Data from evaluable participants are shown – i.e., those participants receiving at least one dose of lofexidine and one set of test measures. The period of observation includes the lofexidine treatment period following abrupt termination of 100 mg/s.c. morphine. Emesis was confirmed by direct observation by medical personnel. Data are combined for the two test sites and are shown for participants evaluated at the Phil site (1.6 mg/d (n=9), 2.4 mg/d (n=9), 3.2 mg/d (n=6), and 4.0 mg/d (n=3)) and those from the Long Beach site (2.4 mg/d n=13)).   Further analysis of this frequency table indicated the break point differentiating the efficacy of the various doses on emesis: 1.6 versus 2.4 mg (p = 0.0772), 1.6 versus 3.2 mg (p = 0.0440), 2.4 versus 3.2 (p = 0.5487, NS), suggesting that significantly greater efficacy of lofexidine on decreasing emesis was produced by 3.2 versus 1.6 mg/day with the comparison between 2.4 versus 1.6 mg/d approaching a conventional level of significance.

According to Kolb and Himmelsbach (1937), the most severe manifestation of opiate withdrawal is withdrawal-induced emesis, and this component of the MHOWS is weighted the most heavily (cf. Table 5 this report). Therefore, the absolute inhibition of opiate withdrawal-induced emesis in each of the participants tested at the 3.2 and 4.0 mg/day on each lofexidine day is of interest.

Original open studies of lofexidine for opiate withdrawal. The number of published controlled studies using lofexidine has been sparse, especially at the time when NIDA first considered evaluation of this agent as a treatment for the alleviation of opiate withdrawal signs and symptoms. Prior to 1997, there were a total of three published studies (total number of patients = 60) using open designs (no placebo) and found that lofexidine (0.4-2.0 mg/daily, 10-day treatment) induced significant reductions in withdrawal symptoms from methadone in comparison with "baseline" peak withdrawal while having no effects on sitting blood pressure (Gold et al., 1981; Washton & Resnick, 1982; Washton et al., 1983). Collapsing across all three studies, 46 of 60 patients showed significant reductions in opiate withdrawal symptoms, and none showed either clinical symptomatic correlates of hypotension (e.g., fainting, dizziness) or significant quantitative decreases in sitting blood pressure.

In the Gold et al. (1981) open study, data are presented on the acute effects of a single dose of lofexidine (0.2 mg) in 15 methadone maintained patients abruptly detoxified from low doses of methadone (<30 mg/day) with descriptive follow-up on the effects of an average of 1.4 mg/day (0.2 – 2.6 mg/day) of lofexidine for an average of 10 days (12-20 days) in these patients. In brief, results of this open study indicated that 2h after a single administration of 0.2 mg, p.o., of lofexidine there was about a 50% reduction in opiate withdrawal symptoms (included both signs and symptoms using an unpublished scale by Gold et al.) without any significant effects on either systolic or diastolic blood pressure at the same time points. Results of this study support the tolerability of lofexidine in doses averaging 1.4 mg/day for 10 days, and provide preliminary evidence for the safety of lofexidine using relatively low doses. Preliminary evidence for efficacy is indicated in the abrupt decline in opiate withdrawal symptoms 2h following a single dose of 0.2 mg of lofexidine without concomitant effects on sitting systolic or diastolic blood pressure.

In the Washton et al. (1983) open study, lofexidine (0.1 to 2.0 mg/day) was administered for 2 to 24 days to 30 opiate dependent individuals in an outpatient setting following abrupt discontinuation of methadone or levo-alpha acetylmethadol (LAAM). The authors conclude that lofexidine significantly reduced opiate withdrawal symptoms without the adverse sedative and hypotensive side effects that limit the usefulness of clonidine. The authors also report that there was "virtually no lowering of blood pressure, despite lofexidine doses up to 2.0 mg/day" (p. 336 of Washton et al., 1983). Results indicated that 21/30 subjects (70%) successfully completed detoxification. Successful detoxification was defined as subjects who had opiate free urines at the end of 10 days after the last dose of methadone or 14 days after the last dose of LAAM and also demonstrated no withdrawal response to a naloxone (2.0 mg IV) challenge. After the naloxone challenge test, subjects were offered naltrexone treatment to aid in relapse prevention. This study suggests the robust safety of lofexidine in doses up to 2.0 mg/day in opiate dependent individuals. The rigorous method for evaluating the opiate free state of these outpatients (clean urines and lack of response to naloxone challenge) also provides preliminary evidence of the efficacy of lofexidine in an open study in opiate detoxification from methadone or LAAM.

The other clinical evidence for lofexidine in the alleviation of signs and symptoms of opiate withdrawal is presented in chronological order below.

Double-blind comparison of lofexidine and methadone for opiate withdrawal: (detoxification from methadone, UK study) Bearn et al., 1996 compared the relative efficacy and safety profile of methadone detoxification (n=44) versus lofexidine detoxification (n=42) in the alleviation of opiate withdrawal signs and symptoms of opiate-dependent individuals, using a randomized two arm double-blind study conducted in an inpatient setting. Patients were 86

polydrug abusers with opiate dependence. The dose range of lofexidine was between 0.6 to 2.0 mg/day given for an average of 10 days. The maximum dose of lofexidine was 2.0 mg/day. In the study sample, the prior use of heroin averaged about 10.5 years, with an average of 0.46 g/day. After being brought into the inpatient unit, all patients were stabilized for a three-day period on methadone (mean dose was 64.8 mg/day) (*average dose in the U.S. is 60-80 mg/day, and climbing upwards*). After the methadone stabilization period, methadone was stopped and patients were randomly assigned to a "methadone group" (standard 10 day methadone detoxification procedure; progressive dilutions of methadone over a 10 day period using placebo syrup and placebo tablet) or the lofexidine group (placebo syrup plus lofexidine tablets). Although there was evidence that the lofexidine group experienced slightly more severe self-rated withdrawal symptoms (Short Opiate Withdrawal Scale, SOWS, Gossop) during the first 10 days of treatment, thereafter both groups showed a similar decline in symptoms. (*The SOWS, Gossop is being used as one of the secondary outcome measures of the proposed Phase 3 study, and it is a bridge measure to the UK literature*). The results suggested that both treatments were broadly clinically equivalent in terms of treatment retention (there was a lack of a significant difference in the rates of treatment completion). There were no significant differences in sitting systolic or diastolic blood pressure between the two treatment groups. However, two female patients, experienced dizziness due to postural hypotension during lofexidine treatment that was resolved when the lofexidine dose was reduced. The authors concluded that lofexidine is broadly equivalent to methadone as a detoxification treatment, although clearly such a conclusion will require further evaluation. The authors summarized that lofexidine is the first effective non-opiate treatment of opiate withdrawal without serious limiting side effects.

Methadone detoxification is viewed as the "gold standard" for the detoxification of opiate dependent individuals in the U.S., and currently, it is the only medication approved in the U.S. for opiate detoxification by the FDA. Results of this double-blind study suggested that that the doses of lofexidine used here resulted in an alleviation of opiate withdrawal symptoms that in the acute phase (first 10 days following methadone detoxification) that was somewhat less substantial than methadone, and during the chronic phase (next 10 days following methadone detoxification) resulted in patients showing a similar decline in methadone withdrawal symptoms as subjects previously treated with methadone. In comparison with previous lofexidine studies (prior to 1996), an advantage of the Bearn et al. (1996) study is its use of higher doses of methadone (today, the lower end of average doses of methadone in US methadone maintained patients which is currently 60-80 mg/day, and climbing upwards), thus presumably more closely replicating the degree of opiate withdrawal typically seen in today's US methadone maintained patients undergoing detoxification from methadone. Both an 'advantage' and 'disadvantage' of this study was that about half of the patients were co-dependent on benzodiazepines and were being simultaneously detoxified from benzodiazepines (linear dose reduction over 21 days). The advantage of this is from the perspective of safety, suggesting that co-detoxification and simultaneous administration of lofexidine and benzodiazepines did not appear to enhance the adverse events associated with the administration of lofexidine alone. The disadvantage is from the perspective of an efficacy interpretation – i.e., the difficulty of separating both benzodiazepine administration itself and benzodiazepine withdrawal from the effects observed in both treatment groups. The tolerability of lofexidine is suggested by the lack of a significant difference between lofexidine <u>versus</u> methadone in influencing sitting blood pressure (*although standing blood pressure is a more sensitive index of the potential hypotensive effects of either lofexidine or clonidine, and both sitting and standing blood pressure will be evaluated in the proposed Phase 3 study*). However, the efficacy comparisons between lofexidine <u>versus </u>methadone are impaired in part by the long half-life of methadone and not being able to assess the

impact of methadone carry-over in the alleviation of opiate withdrawal symptoms in both treatment groups. *The same criticism does not exist for the use of relatively short-acting opiates during the opiate agonist stabilizing period such as morphine, which will be used in the proposed Phase 3 trial.*

Double-blind comparison of lofexidine and clonidine for opiate withdrawal (detoxification from methadone, UK study): Kahn et al (1997) utilized a double-blind randomized two arm design to examine the relative efficacy and safety of clonidine or lofexidine for opiate detoxification in opiate dependent patients stabilized on methadone in an inpatient setting. A total of 28 individuals were studies with N=14 in the lofexidine group and N=14 in the clonidine group. Subjects were initially stabilized on a relatively low dose of methadone for an eight day period before starting this trial, and medication (lofexidine or clonidine) was given as an adjunct during the last four days of methadone administration. Medication with lofexidine (0.4- 2.4 mg/day) or clonidine was given for at least 16 days but <17 days. Clonidine or lofexidine dose was titrated according to signs and symptoms. Because of the difficulties in obtaining placebo tablets for clonidine, blinding of medication was achieved by encapsulation in identical capsules for the two treatment groups. Encapsulation flaws the rigor of the double-blind design of this trial, but this flaw is in part mitigated by the fact that it was inpatient study. Another psychoactive medication was also administered in the majority of patients – lorazepam (a benzodiazepine). The major outcome measure was a rater-assessed checklist of observable opiate withdrawal symptoms demonstrated by the patient and was similar to the Opiate Withdrawal Scale (Gold version) used in Gold et al. (1981). Overall, the results suggested that lofexidine was equally efficacious as clonidine in the alleviation of opiate withdrawal from methadone, and fewer side effects (hypotension, sedation) were indicated for subjects in the lofexidine <u>versus</u> clonidine group. Clonidine produced significantly greater decreases in systolic blood pressure than lofexidine at doses with comparable efficacy for opiate withdrawal. In this study, reported "symptomatic events" (Table 2, p. 60, Kahn et al., 1997) reveal some differences between lofexidine versus clonidine than upon replication may suggest an improved efficacy of lofexidine on the opiate withdrawal symptom "unwell (including anergy/weak/tired)". A frequent complaint of opiate dependent individuals undergoing detoxification is that they feel "sick". In the Kahn et al. (1997) study, the frequency of patients reporting feeling unwell was 2/14 (14%) in the lofexidine group and 12/14 (86%) in the clonidine group, a highly significant difference (p < 0.001) suggesting the possibility of improved efficacy of lofexidine over clonidine on the "sickness" common during opiate withdrawal. However, other explanations are possible. For example, this may reflect a lower incidence of a particular adverse event associated with lofexidine <u>versus</u> clonidine. Further study of this finding is needed, and in the proposed Phase 3 study a secondary measure (VAS-E) will be used to determine if there is a difference between lofexidine versus placebo in the alleviation of sickness experienced during opiate withdrawal. Postural hypotension did occur in both groups at a relatively high frequency 13/14 (93%) in the clonidine group and 8/14 (57%) in the lofexidine group, as did drowsiness (12/14, 86% for clonidine and 11/14, 79%) for lofexidine. In short, this study provides evidence in a small sample of subjects for the clinical equivalence of lofexidine and clonidine on a major opiate withdrawal scale, and suggests the possible superiority of lofexidine versus clonidine on decreasing the "sickness" associated with opiate withdrawal. The safety of lofexidine in doses up to 2.4 mg/day is also indicated.

Double-blind comparison of lofexidine and clonidine for opiate withdrawal (detoxification from heroin; Taiwan study): Lin et al (1997) compared the relative efficacy and side effects profile of lofexidine <u>versus </u>clonidine in the alleviation of opiate withdrawal signs and symptoms in a randomized two arm double-blind study in 80 heroin addicts evaluated in an inpatient setting

(withdrawal was from heroin). There were 80 hospitalized heroin addicts randomly assigned to treatment with lofexidine or clonidine during in-patient opiate withdrawal. Maximum daily doses were 1.6mg for lofexidine and 0.6mg for clonidine. Encapsulation was used to blind medications, representing a flaw in the rigor of the blind of the design of the study although this is in part mitigated by the inpatient setting where direct observation of patient's taking medication can be assured. Lofexidine and clonidine were equally effective in alleviating the withdrawal syndrome, as measured by an investigator derived 15 item Abstinence Symptoms Rating Scale (ASRS). Better treatment retention rates were seen in the lofexidine group, although no difference was found in the proportion that had reached minimal symptom severity by the time of their discharge. However, there were significantly more problems relating to hypotension with subjects in the clonidine versus lofexidine groups, with twice as many instances of withholding medication due to hypotension in the clonidine (8.8% of doses) versus lofexidine (4.1 % of doses) group. An advantage of this study over all the other previously published studies is that patients were detoxified from heroin, rather than methadone. The former provides a sharper and shorter duration to the expression of opiate withdrawal, and does not have a carry over effect of opiate agonist during the alpha-2 agonist treatment period. The latter represents an inherent confound in other published studies of this type where individuals were first stabilized on methadone. The authors noted that revision of the dosing regimen for lofexidine is called for to optimize this treatment, including the use of a higher initial dose during the early stages of detoxification rather than ramping up the dose to a plateau level over a number of days. Overall, this study provides evidence for the clinical equivalence of lofexidine versus clonidine in decreasing opiate withdrawal symptoms in patients detoxified from heroin. Secondly, this study suggests that the hypotension associated with clonidine resulted in the omission of significantly more doses of clonidine versus lofexidine.

Accelerated lofexidine treatment: In an open study, Bearn et al (1998) compared an accelerated 5-day lofexidine regimen (n=22) with a traditional 10-day lofexidine regimen (n=20), and a methadone regimen (n=19) in the treatment of opiate withdrawal in 61 polysubstance abusing opiate addicts. Both patient and staff were open to the identity of the treatment. The study was an inpatient trial, and subjects were evaluated for a 20 day period including a no medication phase from day 11-20. In the 5-day lofexidine regimen, lofexidine doses were between 1.2 to 2.0 mg (supplemental of 0.4 mg permitted) for five days. In the 10-day lofexidine regimen, lofexidine doses were between 0.6 to 2.0 (supplemental of 0.4 mg permitted) administered for 10 days. The subjects in each group were evaluated for degree of opiate dependence prior to the start of the study, using the conversion formula that 1g of street heroin daily is equivalent to 60 mg methadone daily. The three groups were well equated for initial opiate abuse with no significant group differences between mean estimated dose: 56.0 – 65.5 total opiate dose (mg). On admission, all patients received a 3-day methadone stabilization period as indicated for Bearn et al. (1996) above. A total of 24 patients (39% of the sample) were co-dependent upon benzodiazepines, and these subjects were concurrently detoxified from benzodiazepines during the 20-day study period. Average benzodiazepine dose was 39.0 to 45.0 mg. There were no significant differences in rates of completion of detoxification between the three treatment groups. Both the lofexidine treatment groups had similar effect on blood pressure. It is not possible to comment on the relative effects of lofexidine versus methadone on blood pressure, since vital measures for the methadone group were not provided. However, since the standing systolic and diastolic blood pressures for the patients in the two lofexidine treatment groups did not show significant differences during the medication period and averages remained essentially flat during the medications period (cf. Bearn et al., 1998, Fig 2, p. 231) and it appeared from the study (Bearn et al., 1996) that methadone detoxification was not associated with any

significant perturbations in blood pressure, it may be concluded that on the average the two lofexidine treatments were similar to methadone with respect to an overall lack of effect on postural blood pressure measurements. However, five patients did experience dizziness or postural hypotension necessitating lofexidine dose reductions, all rapidly resolving upon dose reduction. The authors conclude that an accelerated 5-day lofexidine regimen may attenuate opiate withdrawal symptoms more rapidly than conventional 10-day lofexidine or methadone treatment schedules without exacerbating hypotensive side effects. In general, the results of this study provide additional safety information concerning doses of lofexidine up to 2.0 mg/day (with an additional 0.4 mg/day supplement in select cases), and once again suggest the broad equivalence of the safety of lofexidine with methadone with the exception of a few cases of transient positional hypotension in a small subset of lofexidine patients which resolved upon dose reduction. In addition, this study provides preliminary efficacy information that a 5 day lofexidine treatment period (as proposed in the current Phase 3 study) is at least broadly equivalent with a 10-day treatment period of lofexidine or a 10-day methadone detoxification.

Double-Blind Evaluation of Lofexidine versus Clonidine in a Medically Supervised Outpatient Setting, UK Study. Carnwath and Hardman (1998) conducted a randomized double-blind study in the UK, comparing the safety and efficacy of lofexidine (n=26) versus clonidine (n=24) in 50 opiate dependent individuals in an outpatient setting. There was close medical supervision by a nursing staff through home visitations. Doses of medications were 1.6 mg/day for lofexidine and 0.8 mg/day for clonidine with a 10 day duration of treatment. In both cases, medication was titrated up to these final doses. Blinding of medication was done by enclosing tablets of lofexidine or clonidine in capsules, and represents a flaw in the rigor that is needed for double-blind studies considered as pivotal trials by the FDA in the U.S. (The extreme difficulty of obtaining tablet placebos for clonidine underlies the author's choice of encapsulation here). In this study, the opiate dependence of these patients (mixed for methadone and heroin) was on the average the equivalent of 40 mg/day of methadone (*about two-fold below the average level of opiate dependence in the U.S.*). Fifty-eight percent of those starting treatment completed detoxification, and remained opiate free at four weeks. More patients completed the detoxification in the lofexidine than the clonidine group, but the difference was not significant. There were no significant differences between the two treatment groups in the major efficacy major (SOWS, Gossop) (*a bridge measure to the literature to be used as one of the secondary outcome measures in the current Phase 3 study*). Lofexidine was associated with significantly less hypotensive effects then clonidine, and the adverse events of clonidine (especially those related to clinical symptoms of hypotension) required significantly more home visits by nursing staff than lofexidine. Results of this study suggest that efficacy equivalence of lofexidine (1.6 mg/day) versus clonidine in the doses studied, while indicating that at these same doses lofexidine has significantly less hypotensive effects than clonidine. These data also establish the robust tolerability of the 1.6 mg/day lofexidine dose in an outpatient setting. However, the proposed Phase 3 study is being conducted in an inpatient setting, because the tolerability of 3.2 mg/day lofexidine in an outpatient setting is unknown and because both an ad hoc review panel to NIDA and the FDA recommended that the current study be conducted in an inpatient setting to ensure rigorous compliance. Since the dose of lofexidine (3.2 mg/day) planned in the proposed Phase 3 study is twofold greater than the dose used in the Carnwath and Hardman (1998) study, the efficacy to be achieved with the planned dose of lofexidine should be at least equivalent with that obtained by these investigators. Carnwath and Hardman (1998) conclude that lofexidine in the 1.6 mg/day dose can be used successfully in outpatient detoxification, but lofexidine is more economical than clonidine in regard to staff time.

NIDA/Britannia Phase 2 Tolerability/Preliminary Efficacy Studies. As indicated above, alpha-2 adrenergic agonists reduce opiate withdrawal, but a limiting side effect of clonidine is clinically significant hypotension. The suggestions that lofexidine might be as efficacious as clonidine without the same degree of hypotension, encourages interest in the clinical use of this product as an aid for opiate detoxification. As of June of 2000, the experience with lofexidine in the UK is extensive with at least 75,000 detoxifications administered to date. The safety record of this product in the UK is impressive with not a single death and a relatively small number of adverse effects registered with the UK regulatory authorities, the MRC (detailed in Table 1) (cf. Herman et al., 1999, April 7, 1999 unpublished report submitted to the FDA).   However, prior to 1997, the published clinical literature evaluating the efficacy of lofexidine as a treatment for alleviating opiate withdrawal signs and symptoms was limited to four publications using open designs (Gold et al., 1981; Washton et al., 1981, Washton and Resnick, 1982; Washton et al., 1983), although based upon the clinical experience of these investigators there was some evidence that lofexidine might have a better efficacy/side effects profile than clonidine. All of these prior studies examined the efficacy of lofexidine in low dose methadone detoxification.   During this time period, there was also one publication comparing the efficacy of placebo to lofexidine using a double-blind design where the endpoint was efficacy for the alleviation of alcohol withdrawal symptoms in alcohol dependent individuals (Cushman et al., 1985). Recent double-blind controlled investigations published between 1997-1999 referred to above indicate that lofexidine produces significantly less hypotension than clonidine, but displays similar efficacy for the alleviation of opiate withdrawal [e.g., Carnwath and Hardman, 1998 (UK study); Kahn et al., 1997 (UK study); Lin et al., 1997 (Taiwan study)]. With the exception of the Lin et al. (1997) study which used heroin addicts, the majority of patients in the other two double blind studies were detoxified from 40 mg or less of methadone. The average dose of methadone as a treatment for opiate dependence in the U.S. is about 60-80 mg/day, and trending upward. Therefore, higher doses of lofexidine would probably be needed as a treatment for the alleviation of withdrawal symptoms associated with methadone detoxification in U.S. patients. An alternative approach would be initial dose reductions in methadone prior to lofexidine-assisted detoxification, but this approach would be expected to lengthen treatment and cost. Further, since the purity of street heroin appears to be substantially greater in the U.S. than the U.K. (cf. Herman and O'Brien, 1997), it was assessed early on that higher doses of lofexidine would be needed to alleviate the symptoms of opiate withdrawal in U.S. versus U.K. heroin dependent patients (cf. 1996 and 1999 Britannia/NIDA/FDA confidential meetings on lofexidine).

The highest approved dose of lofexidine for this indication in the U.K. (2.4 mg/day) was predicted to be insufficient for heroin detoxifications in the U.S., and MDD (currently DTRD) NIDA in collaboration with both the FDA DACCAD and Britannia Pharmaceuticals, Ltd. determined early on that the first task was to determine the tolerability and preliminary efficacy of these and higher doses in heroin (or morphine) dependent individuals detoxified from known equivalent doses of morphine. The highest tolerable dose of lofexidine for this patient population was unknown, and this was of key interest to both our team and the FDA given the proposed indication and use. The NIDA study summarized below provides the only dose-response data concerning the tolerability and preliminary evidence of efficacy of lofexidine in opiate dependent individuals to date (as of June 2000).   In addition, it was felt that being able to administer a "plateau" dose of lofexidine early on in the withdrawal process would be optimal from a treatment point of view, and that if lofexidine proved to have relatively small hypotensive effects that such a dose regimen would be tolerable.

A series of open Phase 2 dose ranging studies was conducted in a carefully monitored inpatient setting to address this question, at two sites – the Philadelphia VAMC and the Los Angeles VAMC (and subsequently UCLA). Our group has reported on the results of the initial Phase II, 20 day open, two site (Phil, LA), inpatient study assessing the tolerability and preliminary efficacy of lofexidine administered at the following plateau doses (n = number of evaluable): 1.6 mg/day (n=9), 2.4 mg/day (n=9 Phil, n=13 LA), 4.0 (n=3) mg/day) (Herman et al., 1999 a and b; Yu et al., 1999), and results of more recently conducted studies evaluating 3.2mg.day of lofexidine in a 11-14 day design (n=6) (Herman et al., 1999a and b, 2000, in press; Yu et al., 2000) and 3.2 mg/day of lofexidine in an 8 day design (n=6) (Herman et al., 2000, to be presented). This Phase 2 study was the first to include or utilize: a dose-response analysis of lofexidine, lofexidine doses > 2.6 mg/day, a known dose of morphine (100 mg/s.c. /day) for stabilization, and initial plateau lofexidine doses, with three phases in the design: morphine stabilization, detoxification/lofexidine treatment, and no medication. All of the Phase 2 investigations are now complete, including results of the two 3.2 mg/day studies. Data for the first 3.2 mg/day investigation has been summarized descriptively, while that for the second 3.2 mg pilot is in the process of data summarization (as of June 20, 2000). Results of the first study are the most relevant to the proposed investigation since only the first uses a similar morphine-lead in. No unexpected serious adverse events were observed in any subject evaluated to date. One subject displayed syncope at LA (transient at 2.4 mg/day). The subject incidence of dizziness (1 event) during the lofexidine treatment period was: 1.6 mg/day (3/9), 2.4 mg/day (5/9), 3.2 mg/day (4/6), 4.0 mg /day (2/3) in Phil and 2.4 mg (0/13) in LA. Two subjects exhibited vertigo (Phil only) (1.6 mg/day, 2.4 mg/day). Overall, there were no clinically significant quantitative decreases in sitting systolic blood pressure at either 1.6 or 2.4 mg/day at Phil or at 2.4 mg at LA, but such effects were obtained at 3.2 and 4.0 mg/day (for the 1.6, 2.4 and 4.0 mg/day doses, cf. Herman et al., April 7, 1999, unpublished report submitted to FDA, provided as background material). However, there were transient dose-dependent decreases in orthostatic systolic blood pressure (< 85 mmHg), at the Phil site: 1.6mg/day (2/9), 2.4 mg/day (5/9), 3.2 mg/day (4/6), 4.0 mg/day (3/3) mg/day dose (number of affected subjects/evaluable subjects). The small number of subjects evaluated at 4.0 mg/day reflected the view of NIDA at the time of the study and some members of a subsequent external advisory review panel that this was the upper dose limit of lofexidine and that no further subjects should be evaluated at either this or a higher dose (cf. Appendix for summary of June 30, 1998 NIDA review of Lofexidine, this report). **The clinical impression of the principal investigator from Philadelphia who conducted these studies at that site, Elmer Yu, M.D., indicates that for all 12 subjects evaluated at the 3.2 mg/day dose of lofexidine (recent pilot I and II studies) that this dose is clinically more tolerable than 4.0 mg/day in terms of severity of hypotensive effects and rate of recovery from decreases in blood pressure (E. Yu to B.H. Herman, June 20, 2000 for VA/NIDA report).** There were log dose-dependent decreases in objective opiate withdrawal signs on the Modified Himmelsbach Opiate Withdrawal Scale (MHOWS), and results were similar for 3.2 mg/day compared with 4.0 mg/day (see Table 2, this report). Doses > 3.2 mg abolished opiate withdrawal-induced emesis [both in the first (n=6) and the second (n=6) pilots using the 3.2 mg/day dose, and in the 4.0 mg/day dose arm (n=3)], and statistically significant dose-dependent effects demonstrated that the higher the lofexidine dose the fewer numbers of subjects showing opiate withdrawal-induced emesis (cf. Herman et al., 1999a) Table 3). The latter finding is of clinical interest in evaluating the sufficiency of lofexidine as a treatment for the alleviation of opiate withdrawal symptoms, since Himmelsbach (1936) considered opiate withdrawal - induced emesis to be the most severe manifestation of opiate withdrawal and gave it the highest weighting on his efficacy scale (see Table 2, MHOWS scoring, this report). Overall, these results suggest that the optimal tolerable/ maximally efficacious dose of lofexidine for opiate withdrawal is 3.2 mg/day in the

current paradigm utilizing a morphine lead-in where initial stabilization of subjects is documented and the identical primary outcome measure (MHOWS). Therefore, this has lead to the decision to utilize 3.2 mg/day in the proposed Phase 3 efficacy trial, and it is this dose that was presented to the FDA in the April 7, 1999 as the likely predicted dose to be used in this trial.

Brief Update of Further Very Recent Published Research, Retrospective, or Audit Evaluation of Lofexidine Use in Opiate Detoxification. Akhurst (1999) conducted a retrospective evaluation of lofexidine in rapid detoxification from a range of opiates including directly from heroin (N=1074 patients) and reported no major (serious) adverse events in any patient. The sample included patients from drug dependency units in the UK. Overall 60.4% (n=614) of patients successfully completed the lofexidine detoxification. This retrospective study received design input from the FDA. Inpatient: Outpatient detoxification ratio was 403:671. Of patients completing the detoxification, the mean starting dose was 0.8 mg/day (median 0.6 mg/day), titrating to a mean dose of 2.2 mg/day (median 1.6 mg/day) and detoxifying in a mean of 10 days (median = 10 days). The most frequent adverse events were dizziness (8.5%), hypotension (7.5%), sedation (6.6%), dry mouth (5.3%), and bradycardia (3.9%). Therefore, the results of the UK survey in 1,074 opiate dependent individuals provides evidence for the safety of lofexidine in doses up to an average of 2.2 mg/day administered over a 10 day period, providing supportive data to the safety of the proposed Phase 3 trial using a slightly higher dose of lofexidine (3.2 mg/day) over a similar time period. This is especially the case given the absence of any serious and unexpected adverse event in this retrospective study. Given the severity of the opiate withdrawal syndrome, the successful detoxification of 60.4% of patients gives additional preliminary support for the efficacy of lofexidine for the proposed indication related to the alleviation of the signs and symptoms of opiate withdrawal. See also Akhurst (2000).

Sheridan et al. (1999) conducted an audit of the inpatient management of opioid withdrawal in the UK from 214 opioid detoxifications with lofexidine. The authors conclude that induction of lofexidine may proceed more rapidly, and to a higher dosage, than currently recommended, without any apparent widespread problems. Buntwal et al., (2000) reported on the results of a small inpatient study comparing the combination of naltrexone and lofexidine to standard lofexidine treatment. The study found naltrexone/ lofexidine treatment to have a more rapid resolution time of opiate withdrawal syndrome compared to standard lofexidine treatment, without any substantial increases in withdrawal symptoms or hypotensive side effects. The authors emphasize that the results should be interpreted with caution. Strang et al. (1999) has conducted a review of recent randomized and open controlled trials of lofexidine for opiate withdrawal with attention to evidence on efficacy, side effects, and the acceptability of this treatment to the patient population.

Future Indications – Relapse Prevention and Opiate Addiction.
Shaham et al. (1999) have examined the role of NE in reinstatement to heroin seeking in rats. These investigators showed that clonidine (systemic or injections into lateral ventricles) blocked (footshock) stress-induced reinstatement to heroin self-administration. The injection of clonidine into the locus coeruleus (LC) was without effect, suggesting LC is not the site modulating this effect. **These data are the first published report suggesting the potential of an alpha-2 noradrenergic agonist in blocking a process that may be involved in relapse to opiates, implicating an effect for these medications beyond the alleviation of opiate withdrawal symptoms.** Therefore, these results suggest the potential of alpha-2 noradrenergic agonists in the long-term maintenance and management of individuals with opioid dependence, with the potential to decrease relapse. The results with lofexidine are

similar and they have been presented at <u>Society for Neurosciences 1998</u> by Dr. Yavim Shaham. The advantage of lofexidine <u>versus</u> clonidine given the relatively lower incidence of hypotension with lofexidine along with this recently discovered pharmacological effect, suggests that **lofexidine may also have important potential as an anti-relapse agent in opiate addiction**. **Preliminary clinical evaluation of this question is underway at the intramural program of NIDA in a study under the direction of Dr. Kenzie Preston**. In addition, even more recently both clonidine and lofexidine have shown preclinical efficacy in the reduction of (footshock) stress-induced reinstatement to cocaine self-administration (Erb et al., 2000), suggesting the potential of lofexidine as an anti-relapse agent for cocaine dependence in addition to opiate dependence. It is of interest that in these preclinical models, alpha-2 adrenergic agonists showed unique potency in stress-induced reinstatement but not drug-induced or priming-induced reinstatement. Since stress is probably one major factor precipitating relapse to either opiates or cocaine in formerly dependent individuals, it is this type of relapse that may be the most responsive to treatment with alpha-2 adrenergic agonists. Other agents (e.g., CRF antagonists) also appear to show preclinical efficacy in this stress-induced reinstatement model. However, many other factors underlie relapse to either opiates or cocaine in humans, and medications other than/or in addition to alpha-2 adrenergic agonists may prove valuable.

IIIF. Rationale for Pharmacokinetics of Lofexidine in Current Phase 3 Trial.

Pharmacokinetics serves as an integral part of drug development as it provides valuable information of the absorption, distribution, metabolism, and elimination (ADME). One of the objectives of this study is to evaluate the pharmacokinetic (PK) profile of lofexidine hydrochloride in the patient population. Although lofexidine is the most commonly used nonopiate medication for detoxification from opiates in the UK, the available PK information for lofexidine is very limited. Preliminary PK data were obtained from a pilot single dose study in healthy normal volunteers (Confidential and Unpublished Reference, Britannia/Forum Unpublished Pk study, 1999) and an open-label pilot safety study in opiate dependent patients (Confidential and Unpublished Reference, Report to FDA DACCAD, Herman et al., April 7, 1999). The data obtained from the healthy volunteer (n=4) study suggests linear kinetics of lofexidine over the dose range studied (1.2 mg, 2 mg) with a mean half-life of approximately 11 hours and a mean tmax at about 3 hours. In the pilot safety study, the opiate dependent patients were maintained on morphine (50-100 mg/day, subcutaneous (s.c.) injection) for 8 days (100 mg/day morphine on days 3-8) and then withdrawn from morphine on day 9. From day 9 to day 15, the subjects received one of the following lofexidine regimens:

    A. 1.6 mg/day at 0.8 mg BID (n=3)
    B. 2.4 mg/day at 1.2 mg BID (n=4)
    C. 2.4 mg/day at 0.8 mg TID (n=6)

The site physicians were not able to obtain blood by venipuncture in the majority of opiate dependent patients, so the n's in the above PK determinations represent a sub sample of evaluable patients receiving lofexidine. The site physician (Philadelphia) was unable to obtain blood by venipuncture in any of the more recently evaluated patients who received either 4.0 mg/day lofexidine (n=3), or 3.2 mg/day lofexidine (n=6 in Pilot I, and n=6 in Pilot II), underscoring the difficulties of obtaining blood by venipuncture in this patient population. In the samples obtained using doses of lofexidine between 1.6 to 2.4 mg/day, the PK parameters of lofexidine in opiate dependent subjects were comparable to that obtained from healthy normal subjects. The Cmax was reached in approximately 3 to 4 hours.

Although very useful preliminary PK information obtained from the earlier studies, it will not fulfill the PK requirements by FDA. The FDA requires extensive PK studies as a part of NDA, such as single and multiple dose studies, dose proportionality, effect of food, PK in special

population etc. (Unpublished Reports, FDA Guidance, 1987, 1999). Therefore, it is very critical to obtain extensive blood samples from this study and evaluate the pharmacokinetics of lofexidine in the patient population. The data obtained from this study will provide PK estimates (Cmax, AUC, t1/2, trough levels) at steady state in patient population and will be extremely useful to the clinician to optimize therapy as well as to identify PK parameters (Cmax and/or AUC), which may be correlated with drug efficacy or drug toxicity. In addition, the data generated from this study will also help in making rational decisions regarding future PK studies.

IIIG. Conclusion of Introduction: In summary, the existing literature substantiates an effect of alpha-2 adrenergic agonists in the alleviation of opiate withdrawal in both animals and humans. Prior to 1996, the published database for lofexidine was relatively sparse and included only four open studies. Starting with the Bearn et al. (1996) study, there are now a number of published double-blind studies suggesting the efficacy of lofexidine when compared with either methadone (Bearn et al., 1996) or clonidine (Carnwath & Hardman, 1998; Kahn et al., 1997; Lin et al., 1997) in the alleviation of the signs and symptoms of opiate withdrawal. In addition, there have been retrospective surveys in the UK of providing preliminary further evidence of efficacy of lofexidine for this indication (e.g., Akhurst, 1999). Finally, a number of other small open studies comparing lofexidine to clonidine for this indication have been published (e.g., Bearn et al., 1998; Buntwal et al., 2000). However, to date, there has been no double-blind, placebo-controlled investigation of lofexidine for the alleviation of opiate withdrawal signs and symptoms, and certainly no adequately sized trial of this type. Both a NIDA consultant's review panel and the FDA (below) have indicated that such a trial is critical to determine the efficacy of lofexidine for this indication, and to provide the first pivotal efficacy trial for such lofexidine to be approved for such an indication in the U.S. Accordingly, the proposed Phase 3 study represents the first well sized clinical trial to compare lofexidine to placebo using a double-blind design in opiate dependent individuals in the U.S. Further, this will be the only controlled investigation to date, also examining the Pk of lofexidine in plasma, which may provide further insights into dose:efficacy relationships.

IIIH. Summary of Food and Drug Administration Regulatory and Peer Review of Past Phase 2 and Proposed Phase 3 Lofexidine Trial. Both the now completed Phase 2 Tolerability/Preliminary Efficacy and the proposed Phase 2 Pivotal Efficacy trials of lofexidine, have been conducted under **Forum Products, Inc. IND # 47,857 - Lofexidine HCl**. For further details on _**these reviews and approval steps**_, please see **Appendix II**.

IV. METHODS

IVA. Medication and Dose Template for Lofexidine P3 Inpatient Study

	Study Day	Morphine	Group I	Group II
			Study Medication Lofexidine	**Study Medication Placebo**
PHASE I STABILIZATION	1	75 -100 mg/day (s.c.) (25 mg TID or QID)		
	2-3	100 mg/day (s.c.) (25 mg QID)		
PHASE II DETOXIFICATION/ DOUBLE BLIND MEDICATION	4-7		3.2 mg/day (p.o.) (0. 8 mg QID)	Placebo (QID)
	8		1.6 mg/day (p.o.) (0.4 mg QID)	Placebo (QID)
PHASE III POST MEDICATION	9-10		Placebo (QID)	Placebo (QID)

IVB. Subjects

All subjects will be opiate-dependent and seeking detoxification from opiates – i.e., all subjects will be "treatment seeking". The total is N = 96 subjects, with data from 32 subjects to be collected at three sites (University of Pennsylvania/ Philadelphia VAMC (Phil), University of California at Los Angeles/ Long Beach VAMC (LA), New York State Psychiatric Institute/Columbia Presbyterian Medical Center (NY)). The duration and setting of the trial is 11 days in an inpatient unit.

Subjects will be randomly assigned to the two medications conditions: Placebo (P) = 48, Lofexidine (Lofex) = 48 (see Medication section below for blinding details). Therefore, the final total cell assignment per site is as follows: Phil (P = 16, Lofex = 16), LA (P = 16, Lofex = 16), NY (P = 16, Lofex = 16). The projected recruitment time for 32 subjects per site is about 1.60 years.

The primary outcome measure of this study is the Modified Himmelsbach Opiate Withdrawal Scale (MHOWS) collected during the second detoxification day, which has been empirically chosen for its sensitivity in detecting dose differences of lofexidine on an efficacy outcome measure reflecting the severity of physical manifestations of opiate withdrawal (Yu et al., 1998,

1999, 2000; Herman et al., 1999). On the basis of previous preliminary dose-related efficacy data (*ibid*, Fig 1 power curve), the number of subjects chosen (N=96) is that required to give a 90% power ($\beta = 0.10$) to detect a between treatments difference of 8.0 units in total MHOWS scores with $\alpha = 0.05$.

IVB1. Evaluable versus Completer Subject. For the purpose of the efficacy analysis, an *'evaluable subject'* will be defined as one who receives at least one dose of lofexidine or placebo *and* undergoes at least one assessment of all of the MHOWS items on Study Day 4. The focus of the efficacy analysis is on the results of Day 5, with data carried forward for evaluable patients who may drop out before this day. This is assuming that drop outs are $\leq$ 30% of the subject total for a particular medication group, which is almost a certainty. Day 5 corresponds to the second opiate detoxification day, which is the peak opiate withdrawal day and also the day corresponding to a dose-ordering of the efficacy of lofexidine for the reduction of opiate withdrawal symptoms (Herman et al., 1999; Yu et al., 1999).   A completer is defined as a subject who completes up through day 8 and is administered one dose of study medication on day 8 and completes an MHOWS on day 8. The subject number description provided above, refers to the number of "evaluable" individuals. Drop outs will be replaced only if they occur during the initial three day morphine agonist baseline phase.

For safety monitoring, all safety data available from all patients who receive at least one dose of study medication (lofexidine or placebo) will be analyzed.

IVB2. Sample Size and Power Calculations

Refer to Appendix III here including Figures 1-8

IVB3. Factors Relating to Analysis of Primary Efficacy Outcome Variable. The primary efficacy outcome variable is the full MHOWS score, including pupil size measurement on the second day of randomized (lofexidine or placebo) treatment. Subjects dropping out of the study prior to starting randomized treatment will be replaced, while those dropping out after receiving their first dose of randomized medication will not be replaced. Therefore, it is likely that some subjects will drop out of the trial before undergoing their MHOWS assessment on the second day of randomized treatment – probably more in the placebo than in the lofexidine group.

Analysis of this primary outcome variable will be on a basis as close to 'Intention-to-Treat' as is practical in this clinical situation. In the event that a subject drops out prior to the MHOWS assessment on the second day of randomized treatment, their MHOWS score from the first day of randomized treatment will be 'carried forward' to the second day for analysis. Such dropouts would be expected to be because of unacceptably severe opiate withdrawal symptoms, associated with very high MHOWS scores. In the event that one or more of the 14 items of the MHOWS is missing on Study Day 5, the arithmetic mean of the corresponding data on Study Days 4 and 6 will be taken as the Study Day 5 value (or, if Study Day 6 data are not available, the value from Study Day 4 will be 'carried forward to Study Day 5. Accordingly, the only subjects who will be 'non-evaluable' in relation to the primary outcome variable will be those who do not undergo a full MHOWS assessment on the first day of randomized treatment. It is expected that there will be a relatively small number of such subjects who will be "nonevaluable".   Any such "nonevaluable" subjects are more likely to be in the placebo group, so that this small deviation from a true intention-to-

treat analysis will be 'conservative', in the sense that it is likely to result in an under-estimation of the between-groups difference in MHOWS.

A secondary analysis of the MHOWS on the second day of randomized treatment will be undertaken, including only those subjects for whom an actual MHOWS assessment on that day is available (i.e., no 'carrying forward' of results). A greater number of subjects (more in the placebo group than the lofexidine group) are therefore expected to be without data for this analysis. For this reason, to provide information on expected power in this secondary analysis, the power calculations below have been extended to situations with far greater numbers of non-evaluable subjects than are expected for the primary analysis.

IVB4. Basis of Sample Size Estimates and Power Calculations. Sample size estimates and power calculations have been undertaken on the basis of a 2-sample t-test analysis of the primary outcome variable, with an alpha level of 0.05.

Prior pilot studies have provided the following information with respect to the MHOWS on the morning of the second day of lofexidine treatment (cf. Herman et al., 1999, 2000; Yu et al., 1999, 2000; April 7, 1999 report submitted to FDA for **Forum Products, Inc. IND # 47,857 - Lofexidine HCl**, which has been used as a basis for the power calculations and their interpretation:

1.   Data for total MHOWS scores shows a distribution that approximates a normal distribution to satisfy the required assumptions for a 'parametric' analysis.

2.   The greatest standard deviation seen in any pilot study was 11.1 units (seen with lofexidine 1.6 mg/day, N=7), this figure being considerably greater than the standard deviations seen with any of the other lofexidine doses examined in pilot studies. Power calculations are based on the conservative estimate that the pooled standard deviation of lofexidine and placebo groups in the current study will be 11.1 units.

3.   On the basis of the conservative assumption that the lofexidine dose of 1.6 mg/day equates to placebo treatment, the pilot studies lead to expectations of mean MHOWS differences from placebo of 8.3 units with lofexidine 2.4 mg/day, 11.0 units with lofexidine 3.2 mg/day (the dose used in the present study) and 14.6 units with lofexidine 4.0 mg/day. On the basis of limited data from pilot studies in relation to lofexidine 2.2 mg/day (N=6), and also the dose-response relationship seen with lofexidine 1.6 mg/day (N=7), 2.4 mg/day (N=7) and 4.0 mg/day (N=3), it is anticipated that the lofexidine-placebo difference for MHOWS score in this current trial may be of the order of 11 units.

4.   On the basis of the pilot studies, it is considered that a between-group difference in MHOWS of approximately 8 units (i.e. slightly less than the difference seen between 1.6 mg/day and 2.4 mg/day doses of lofexidine in the pilot studies) is the smallest difference that would be regarded as clinically important.

Sample size estimates and power calculations have therefore been undertaken on the basis of an estimated pooled standard deviation of 11.1 units, an alpha level of 0.05 and a minimum clinically important between-groups difference of 8 units, using a 2-sample t-test. The various power analyses are described below and in Appendix I. Power curves [Figures 1-5] for these analyses are presented in Appendix III.

IVB5. Sample Size and Treatment Allocations. On the basis described above (estimated pooled standard deviation 11.1 units, minimum clinically important difference of 8 units), the sample size required to achieve a power of 0.90 (beta = 0.10) with an alpha level of 0.05, assuming an equal numbers of evaluable subjects in the two groups is 82 subjects (41+41) (cf. Figure 5). On the (conservative) assumption of approximately 15% loss of 'evaluable' subjects due to dropout (before completion of MHOWS on the first day of randomized treatment), this equates to approximately 96 subjects (48+48) starting on randomized treatment. This figure of 96 also satisfies the desire for a sample size that is an exact multiple of 6, thereby facilitating a balanced allocation across three sites and two randomized treatment groups.

Consideration has been given, on the basis of ethical and practical issues, to the possibility of allocating more subjects to active treatment than to placebo. However, it has been decided to give equal allocations of subjects to the two treatment groups, in order to maximize power for a given total number of subjects, particularly with reference to the fact that an appreciably greater number of dropouts is anticipated in the placebo group.

IVB6. Conclusions Regarding Study Power. The power calculations (also see Appendix I) indicate that, on the basis of available data and all reasonable expectations of possible dropout rates (equal in both groups or greater in the placebo group), a sample size of 96 subjects (48 allocated to each treatment) should result in more than enough statistical power to detect a difference between groups representing the 'minimum clinically important difference' in the primary outcome variable, and high power to detect the difference between lofexidine and placebo that is anticipated (on the basis of pilot study results).

IVB7. Inclusion Criteria
1. Male or female.
2. Age of subjects: 18 years of age and above.
3. Current dependence on heroin, morphine, or hydromorphone according to DSM-IV criteria
4. Subject-reported use of heroin, morphine, or hydromorphone for at least 21 of the past 30 days.
5. Urine toxicology screen positive for opiates (cf. #4 above) and negative for methadone, levo-alpha-acetylmethadol (LAAM), or buprenorphine at the time of screening.
6. Subject has voluntarily given informed consent and signed the informed consent document.

IVB8. Exclusion Criteria
1. Female subjects who are pregnant or are of childbearing potential and who do not agree to practice complete sexual abstinence or use a medically acceptable method of birth control during the course of the study will be administratively discharged. Acceptable methods include a) oral contraceptives, b) barrier (diaphragm or condom) plus spermicide, c) levonorgestrel implant, d) intrauterine progesterone contraceptive system, or e) medroxyprogesterone acetate contraceptive injection. Serum Beta HCG will be used to assess pregnancy on Day 1 of the protocol.
2. Females nursing an infant are excluded.
3. Self-reported use of methadone, buprenorphine, or levo-alpha-acetylmethadol (LAAM) in the past 14 days.

4. Subjects who have any of the following:
   a. Seizures, or those who have received anticonvulsant therapy during the past 5 years.
   b. Pancreatic disease such as insulin-dependent diabetes.

     c. Liver disease requiring medication or medical treatment, and/or aspartate or alanine aminotransferase levels greater than five times the upper limit of normal.

     d. Gastrointestinal or renal disease which would significantly impair absorption, metabolism or excretion of study drug, or require medication or medical treatment.

     e. Neurological or psychiatric disorders {assessed by clinical interview - the SCID (DSM IV, Axis I)} including psychosis, bipolar disorder, organic brain disease or other disorders which require treatment or which could make study compliance difficult.

     f. Positive tuberculosis (PPD) TB skin test along with a clinical history and chest X-ray indicative of active tuberculosis. (Individuals who have a positive PPD test and have a negative chest X-ray, are not symptomatic for tuberculosis, and do not require antituberculosis therapy will be eligible to participate. Subjects will be asked if they ever tested positive for tuberculosis. If so, they will not be given a PPD and a chest X-ray and clinical history will be used for evaluation purposes. Individuals with a negative chest X-ray who are a symptomatic and do not require antituberculosis therapy will be eligible to participate).

5. An abnormal baseline cardiovascular exam including any of the following:

     a. Clinically significant abnormal ECG (e.g., second or third degree heart block, uncontrolled arrhythmia).

     b. Heart rate less than 45 bpm or symptomatic bradycardia.

     c. Systolic blood pressure less than 90 mmHg or symptomatic hypotension.

     d. Unmedicated blood pressure greater than 160/100.

     (New NIH/NHLB guidelines issued in a May 4, 2000 NIH press release, indicate that the cutoff definition for hypertension should now be standardized to 140/90 mmHg and hypertension may be defined using the systolic index alone (cf. Hypertension, May 2000 issue: Frohlich, E.D. Recognition of systolic hypertension for hypertension. Editorial. Hypertension 35: 1019-1020; Izzo, J.L., Levy, D., and Black, H.R. Importance of systolic blood pressure in older Americans. Hypertension 35: 1021-1024). However, because individuals undergoing withdrawal invariably display very significant elevations in blood pressure, the clinicians in the current study have advised raising this criteria to 160/100 mmHg. Also, the 160/100 mmHg criteria was used in the two site Phase 2 lofexidine study without incident. If the 140/90 mmHg criteria were used in the current study, numerous subjects benefiting from medication assistance who are in severe withdrawal would be inadvertently excluded).

     e. Prior history of significant myocardial infarction.

6. Requirement for any of the following medications: psychotropics (including sedative/hypnotics, antidepressants, neuroleptics), prescription analgesics, anticonvulsants, antihypertensives, antiarrhythmics, antiretroviral medications (current or within the past 4 weeks). (It is anticipated that most individuals admitted to the protocol will be nicotine dependent and may experience nicotine withdrawal symptoms. Subjects who are nicotine dependent will be given nicotine patch therapy for the duration of their participation in the study. Nicotine dependent subjects who refuse nicotine patch medication but who still wish to participate in the opiate detoxification offered by the study, will be included in the study according to the hospital smoking and standard of care regulations at each of the three sites (cf. Appendix IV).

7. Current dependence (by DSM-IV criteria) on any psychoactive substance other than heroin, morphine, or hydromorphone (but not methadone, LAAM, or buprenorphine, cf. #3), cocaine, caffeine, or nicotine that require detoxification will be excluded.

8. Subjects who are symptomatic for HIV and have CD4 counts $\leq$ 200 are not eligible to participate.

9. Blood donation within the past 8 weeks.

10. Participation in an investigational drug study within the past 3 months.

11. Subjects who have such "poor" veins that even single venipuncture needle sticks cannot be obtained in the beginning and end of the protocol (for laboratories reflective of general health status). However, subjects who have veins that are otherwise adequate for single venipuncture needle sticks to assess laboratory chemistries in the beginning and end of the protocol , but whose veins are NOT adequate for venipuncture catheterization for blood Pk lofexidine determination will be included. Each of these statements reflect VA HRC suggested revision of this protocol and Consent as of July 26, 2000.

12. Over sedation from the first dose of morphine on Study Day #1. (Subjects who become overly sedated from the first dose of morphine will not be allowed to continue in the study.

IVC. Medication Lofexidine (Lofex®) and placebo will be provided to the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) in Albuquerque, NM for randomization and distribution in a blind fashion to the research pharmacist at each of the three sites. One half of the subjects at each site will receive placebo and the other half Lofex®. The authenticity of the contents of medication and placebo will be double checked by the CSPCRPCC, prior to medication assignment and distribution.

Britannia Pharmaceuticals, Ltd will provide medication and matching placebo tablets. Lofexidine hydrochloride (HCL) (Britlofex®) is a peach colored tablet containing 0.2 mg of active medication. The subjects, investigators, and site personnel will be blind to medication assignment groups. The study pharmacist at the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) in Albuquerque, NM and the study biostatistician at the Cooperative Studies Program Coordinating Center in Perry Point, MD will not be blind to medication assignment. Study medications will be provided to the site pharmacists by the CSPCRPCC in patient specific kits for days four through ten, which will be labeled with a unique patient randomization number. Each patient kit will contain 7 blister packages with unique package numbers (e.g., 01).

IVD. Design:

IVD1. Table 4 is a flow chart for the entire study, detailing all major medications and screening, primary and secondary outcome measures as a function of study days, number of times these tests are to be administered, and the times that the tests are to be administered on each study day. Also provided in the footnotes is the allowable leeway for acquisition times.

Table 4. **Schedule of Measures and Data Collection for Lofexidine Phase 3**	**Opiate Agonist Phase** **(all Morphine)**			**Detoxification:** **Medication or Placebo Phase** **(randomized to** **Lofexidine or Placebo)**					**Post Med/** **Detox** **Phase** **(Placebo,** **QID)**		**Medical** **Discharge**
Study Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Date											
Day of Week											
Informed Consent, Screening (01), Opiate Screening (02)	1X										
* **Morphine** (0600, 1100, 1630, 2200 h)	�|	▊	▊								
**Lofexidine or Placebo (0800, 1300, 1800, 2300 h)				▊	▊	▊	▊	▊	▊	▊	
Medical History (03)	1X										
Physical Examination (04) (Study Day 1 and Exit Day)	▊										▊
Prior Medications (05)	▊										
Laboratory Assessments: Blood (06,07), Urine (08)	1X										1X
Serum Pregnancy Test (Beta HCG) (09)	1X										
Tuberculosis Skin Test (PPD), RPR, CD4 (10)	1X										
HIV (optional, per separate consent)	Prior to Day 4										
Psychiatric Assessment (SCID, Axis I, DSM IV) (11)	Prior to Day 4										
Addiction Severity Index (ASI) (12)	Prior to Day 4										
Weight (on admission & 0630-0800h ā breakfast) (13)	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X
Primary Outcome Measure:											
*** **Modified Himmelsbach (MHOWS),** obtained at 1000h (13)	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X	
Emesis Tracking (14)	▊	▊	▊	▊	▊	▊	▊	▊	▊	▊	

Form numbers may change (small print)

Table 4, Continued Schedule of Measures and Data Collection for Lofexidine Phase 3											
Study Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Secondary Outcome Measures:											
•**Modified Himmelsbach (MHOWS)** (13) **Peak Effect** Detox/Med Phase											
•**Objective Opiate Withdrawal Scale** (15) (OOWS Handlesman) (1000h)	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X	
•**Short Opiate Withdrawal Scale** (16) (SOWS Gossop) (1000h)	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X	
•**Modified Clinical Global Impressions Scale -** Patient (17) (NIMH MCGI) (1000h)				1X	1X	1X	1X	1X	1X	1X	
•**Modified Clinical Global Impressions Scale -** Rater (18) (NIMH MCGI) (1000h)				1X	1X	1X	1X	1X	1X	1X	
•**Subjective Opiate Withdrawal Scale** (19) (SOWS Handlesman) (1000h)	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X	
•**Visual Analog Scale (VAS-E)** (20)– Efficacy of Medication for Reducing Withdrawal Sickness (1000h)	1X		1X	1X		1X		1X		1X	
Medication Administration/Concomitant Medications (21)	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X
Drop Out Day (cf. End of Study Form (31) **(Reason for Drop Out)**											

Form numbers may change (small print)

Table 4, Continued **Schedule of Measures and Data Collection for Lofexidine Phase 3**											
Study Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Abuse Potential Assessment:											
Addiction Research Center Inventory (22) - (**ARCI-MBG**) (1000h)	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X	
Visual Analog Scale (VAS-High)(23) (1000h)	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X	
Safety Measures:											
(Sitting) Vital Signs (24, 33) (0800, 1000, 1100, 1300, 1800 2300h and at 0800 at day 11)	6X	6X	6X	6X	6X	6X	6X	6X	6X	6X	1X
Orthostatic (Standing) Vital Signs (24,33) (800, 1100, 1300, 1800, 2300 and only at 0800 at day 11)	5X	5X	5X	5X	5X	5X	5X	5X	5X	5X	1X
Electrocardiogram (25) (1300 to 1430h)	1X					1X				1X	
Adverse Events & Abnormal Clinical Signs: (26) (1000h)	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X
Tobacco Withdrawal Scale (27) (**1700**)	1X	1X	1X	1X	1X	1X	1X	1X	1X	1X	
Urine Toxicology (28)	Admission, Monday, Wednesday, Friday, Discharge and As Needed										
Plasma Lofexidine Pk (LCMS) (29) Total of 12 samples (10 ml of plasma each), Day 4: 1X, 0800h; Day 6: 1X, 0800h Day 7: 8X, 0800, 0900, 1000, 1100, 1200, 1300, 1600, 1800h; 2100, 2300; Day 8: 1X:0800; Day 10: 1000h after MHOWS				1 X		1X	8X	1X		1X	

Form numbers may change (small print)

Table 4, Continued
Schedule of Measures and Data Collection for Lofexidine Phase 3

Footnotes to Flow Chart:

Detox = Detoxification

SCID: The Structured Clinical Interview for DSM IV (Axis I)

* Morphine: study day 1 morphine administration times may vary depending upon time of admission.

** Lofexidine: The physician may withhold a dose of study medication if the patient is experiencing symptoms of hypotension (dizziness making it difficult to stand for one minute, or syncope) or if the patient's orthostatic blood pressure is ≤ 80 mmHg systolic immediately before the dose is due to be given. If more than two doses of study medication need to be withheld in a single day, the patient will be terminated from the study and treated for their withdrawal symptoms with standard treatment.

*** MHOWS = Modified Himmelsbach Opiate Withdrawal Scale (Primary Outcome Measure)

time range for collection = 0 to ±30 min for all items

•**Measures, time range and order: These measures should start being collected at 1000, and must be completed by 1200, and shall be collected in the following order: MHOWS, OOWS, SOWS Gossop, MCGI (rater, patient), SOWS (Handelsman), VAS-E, Addiction Research Center Inventory** (**ARCI-MBG**) and **Visual Analog Scale (VAS-High)** for "Drug High".

THERE ARE THREE MAJOR PHASES OF THIS STUDY.

IVD2. (1) Opiate Agonist Stabilization Phase:
Morphine sulfate (100 mg, s.c.) will be used to stabilize subjects on a fixed dose of opiate agonist.

> The total morphine dose during the stabilization period is 75 - 100 mg, s.c. on Study Day 1, and 100 mg, s.c. on Study Day 2-3. The procedure for morphine administration during the opiate agonist stabilization phase is - Day 1, stabilize up to 100 mg, subcutaneous (s.c.) /day of morphine sulfate, Days 2-3, administer 100 mg, s.c. /day morphine sulfate, (25 mg s.c. at 0630h, 1100h, 1630h, 2200h).

IVD3. (2) Detoxification: Medication or Placebo Phase:
Evaluation of the study medication: following abrupt termination of morphine, subjects will receive either Lofex or placebo and the effects of these on the alleviation of opiate withdrawal symptoms will be assessed.

> Days 4-8, no morphine is administered; medicate with Lofex 3.2 mg/day or placebo; study medication will be dosed as 4 tabs of lofexidine 0.2 mg or 4 placebo tabs p.o. at 0800h, 1300h, 1800h and 2300h. On study day 8, medicate with Lofex 1.6 mg/day or placebo [dose with 2 tabs of Lofex and 2 tabs of placebo or 4 tabs of placebo p.o. at 0800h, 1300h, 1800h and 2300h]. Lofex is decreased from 3.2 mg/d to 1.6 mg/d on day 8 for the lofexidine group. The placebo group remains on placebo from day 4 to day 8.

> The physician may withhold a dose of study medication if the patient is experiencing symptoms of hypotension (dizziness making it difficult to stand for one minute, or syncope) or if the patient's orthostatic blood pressure is $\leq$ 80 mmHg systolic immediately before the dose is due to be given. If more than two doses of study medication need to be withheld in a single day, the patient will be terminated from the study drug and treated for their withdrawal symptoms with standard treatment.

IVD4. (3) Post Medication/Detoxification Phase:
 All subjects will receive placebo on study days 9 and 10.

All subjects will be medically discharged on the morning of study day 11, and subjects will receive no placebo or lofexidine on day 11.

IVD5. Rationale and Background of Lead-In Morphine Stabilization Phase: The rationale for initially stabilizing subjects on morphine prior to detoxification is fourfold. First, it would be difficult if not impossible to recruit participants into this study without ensuring their immediate comfort from active opiate withdrawal symptoms upon admission. This is immediately achieved with parenteral morphine. Second, the three day opiate agonist period provides a window of time when the subject is in a stable state to adequately screen and evaluate prior to both detoxification and medication evaluation. Third, it is reasonable to assume that administering a fixed dose of morphine during the lead-in phase, will result in a decrease of variability in the opiate withdrawal signal from the various individuals evaluated. By administering identical doses of morphine for all subjects for an identical period of time, maximal pharmacological stability of the subjects should be achieved.   This should provide a common point for assessing the efficacy of Lofex _versus_ placebo during the

detoxification/medication phase of the study. Fourth and most important, in a prior meeting with the FDA of April 7, 1999 (summarized on April 29, 2000 by the FDA, the FDA approved the primary outcome measure of this study – the MHOWS. The MHOWS is a derivative score requiring the acquisition of initial opiate stabilized baseline information, from which to calculate deviations from or the emergence of opiate withdrawal symptoms (Kolb and Himmelsbach, 1938). As in the FDA's notes from the joint April 1999 meeting, it was agreed that the first inpatient study would be allowed to include a morphine lead-in period, and the lead-in proposed is the minimum time needed to ensure opiate stabilization. It is anticipated that subsequent Phase 3 or 4 studies would not have a morphine lead-in, to more closely parallel actual clinical use of this medication. To achieve the goal of a future no morphine lead-in trial, the current P3 trial will pilot a number of other secondary outcome measures (beyond MHOWS, second detoxification day) that may be useful in future Phase 3 or 4 studies as primary outcome measures.

The 100 mg, s.c. /day morphine plateau dosage in the present study is based on the stabilization in MHOWs scores achieved in opiate dependent individuals by Jasinski, 1977 using morphine sulfate doses between 60 – 120 mg/day, s.c. For this study Jasinski (1977) examined the relative efficacy of three doses of morphine (30, 60, and 120 mg/day, s.c.) to attenuate MHOWS obtained 11 times during the course of each test day. Results indicate that while 30 mg/day produced a return to normal agonist levels that were only about 25% of a stable opiate agonist level, while 60 mg/day returned MHOWS to about 95% of opiate agonist level, and 120 mg/day returned MHOWS to 100% of opiate agonist levels. Therefore, our dose choice of 100 mg/day, s.c. is midway from the 60 – 120 mg/day doses indicated optimal using the MHOWs outcome measure.

In addition, the average methadone maintenance dosage (approximately 80 mg; George Woody, MD; personal communication to Elmer Yu, M.D., March 15, 2000) and average initial dosage (30 mg) of patients at the Philadelphia VAMC. One mg of orally administered methadone is equivalent to 2 mg of parenterally given morphine with respect to suppression of the morphine abstinence syndrome (Isbell et al., 1948; Jasinski et al., 1977). Thus, the dosage of morphine chosen for the present study is equivalent to a methadone dosage intermediate between that used during for treatment initiation and maintenance at the Philadelphia VAMC. Additionally, this morphine dosage has been utilized previously in the assessment of the potential utility of clonidine in managing the opiate-withdrawal syndrome (Cuthill et al., 1990), and in the previous lofexidine Phase 2 open tolerability study conducted at the Philadelphia VAMC and Los Angeles/Long Beach VAMC sites.

IVE. ASSESSMENTS
Measures used to initially characterize subjects include medical history, physical examination, opiate use screening, laboratory assessments of blood and urine (cf. Appendix V for detailing of laboratories), Tuberculosis Skin Test (PPD), body weight, and the Addiction Severity Index (ASI). In addition, females will be administered a serum pregnancy test (beta HCG). Evaluation of seropositivity for HIV by plasma will be optional and per separate consent of each subject (cf. Appendix I, HIV Consent)

IVE1. Primary Outcome Measures
(1)   Modified Himmelsbach Opiate Withdrawal Scale (MHOWS),
         with pupils, second detoxification day

IVE2. Secondary Outcome Measures
(1)   Drop Out Day, day-by-day dropout rate (provided in the End of Study Form that also indicates the Reason for Drop Out)
(2)   Peak Modified Himmelsbach Opiate Withdrawal Scale (MHOWS), peak effect study days 4-8 inclusive
(3)   Objective Opiate Withdrawal Scale (OOWS, Handlesman)

(4)   Short Opiate Withdrawal Scale (SOWS, Gossop)
(5)   Modified Clinical Global Impressions Scale (NIMH, MCGI) (Patient Form)
(6)   Modified Clinical Global Impressions Scale (NIMH, MCGI) (Rater Form)
(7)   Subjective Opiate Withdrawal Scale (SOWS, Handelsman)
(8)   Visual Analog Scale assessing Efficacy of Medication for Decreasing Withdrawal Sickness (VAS-E Measure)
(9)   Number of Concomitant Medications used to treat opiate withdrawal symptoms, study days 4-8 inclusive.

IVE3. Safety Measures:
(1)Sitting Vital Signs: including heart rate, systolic and diastolic blood pressure, oral body temperature, respiratory rate
(2)Standing Vital Signs: including heart rate, systolic and diastolic blood pressure
(3)Clinical Assessment on Electrocardiograms (ECG),
Evaluation of quantitative ECG parameters
(4) Physical Examination (any abnormal clinical signs)
(5) Laboratory Chemistries (abnormal values, in some cases beyond those expected to be elevated for opiate dependent individuals – e.g., liver enzymes as 5XUNL, cf. Appendix V)
(6) Urine Toxicology (for drugs of abuse)
(7) Adverse Events
(8) Abnormal Vitals Resolution and Termination Event Log

IVE4. Abuse Liability Measure List
(1) Addiction Research Center Inventory (ARCI) - euphoria (MBG) subscale, (2) VAS-H for "Drug High" - potential abuse related liability of lofexidine

IVE5. Other Measures:
(1) **Plasma Pk.** See pharmacokinetic measures for further details (below). A total of 14 samples (10 ml each) of blood will be obtained on study days 4-10 as follows. On study day 4, a single sample will be obtained at 0800h (prior to any dose of lofexidine). On study day 6, a single sample will be obtained at 0800h (this is after two full days of 3.2 mg/day lofexidine, and prior to the dosing of lofexidine for study day 6 (third day of lofexidine)). On study day 7 (4th day of 3.2 mg/day lofexidine administration), ten samples will be obtained at the following times of day: 0800h, 0900h, 1000h, 1100h, 1200h, 1300h, 1600h, and 1800h, 2100h, 2300h. On study day 8 (5th day of lofexidine administration), a single sample will be obtained at 0800h (prior to the dose for 1.6 mg/day). On study day 10, a single sample will be obtained at 1000, immediately after the MHOWS. The purpose of obtaining these plasma samples will be to estimate the Steady State and Cmax of lofexidine in plasma.

(2) **Laboratory Assessments**: Additional assessments included CBC, PT, PTT, panel 7, panel 9, TSH, T_4, RPR, Hepatitis B screen, Hepatitis C antibody, HIV (optional and per consent), Serum Beta HCG, urinalysis (cf. Appendix V for complete laboratory detailing).

(3) **Tobacco Withdrawal Assessments**. **This will be obtained one time per day at the end of the day on each day of the study for all smokers, whether they are allowed to smoke during the study or are using a nicotine patch instead of smoking (at 1730h). Details of this measure and its rationale are below.**

IVE6. Description and Rationale of Outcome Measures:

Description and Rationale of Primary Outcome Measures:

Modified Himmelsbach Opiate Withdrawal Scale (MHOWS) (Jasinski, 1977): This is an assessment of objective signs of opiate withdrawal performed by a rater, according to a quantitative continuous scale with weighted values for specific signs. The original form was developed by Himmelsbach (Kolb and Himmelsbach, 1938), to quantify the severity of observable symptoms of opiate withdrawal in humans. The original description of the Himmelsbach Opiate Withdrawal Scale (HOWS), along with the raw scores for patients exposed to varying doses of morphine is found in Kolb and Himmelsbach (1938). As a result of increased research on the effects of a variety of opiate interventions and improved technology for measuring various items (e.g., pupil diameter) in humans undergoing opiate withdrawal, Jasinski developed a modified version of the MHOWS. This newer version is here referred to as the Modified Himmelsbach Opiate Withdrawal Scale (MHOWS) (Jaskinski, 1977). Use of the MHOWS in a double-blind, study of morphine versus clonidine in morphine withdrawal was used in a study by Jasinski et al. (1985).

The rationale for using the MHOWS as the primary outcome measure in the current Phase 3 trial is that results of our initial dose-response Phase 2 tolerability/preliminary efficacy studies suggested efficacy of this measure reflecting a dose ordering on the second detoxification day (e.g., Yu et al., 1999; Herman et al., 1999). Further, the Food and Drug Administration (FDA), approved this as our primary outcome measure based upon a meeting on April 7, 1999, based upon the objectivity of this measure and its use in the literature for nearly 60 years in the quantitative assessment of the efficacy of opiate and nonopiate medications in the alleviation of opiate withdrawal symptoms.

Table 5. Scoring Method for the Modified Himmelsbach Opiate Withdrawal Scale (MHOWS)

I. DISCONTINUOUS SIGNS
The following discontinuous signs of abstinence, will be recorded once daily throughout the entire period of the study:

Yawning	Lacrimation	Rhinorrhea	Perspiration
Tremor Goose-flesh	Restlessness	Appetite	

The frequency for these signs will be the sum of one daily observation (10 min in duration), obtained 2h after medication or placebo administered (first dosing of the day). The points awarded for these discontinuous signs of abstinence are:

Yawning	1 point if observed on the day
Lacrimation	1 point if observed on the day
Rhinorrhea	1 point if observed on the day
Perspiration	1 point if observed on the day

Tremor	3 points if observed on the day
Goose-flesh	3 points if observed on the day
Anorexia	3 points if appetite is coded as "poor" or "none" for any meal that day
Restlessness	5 points if observed on the day.
Emesis	0 points if the number of emesis is 0 or missing for the day
	5 points if the number of emesis is 1 for the day
	10 points if the number of emesis is 2 for the day
	15 points if the number of emesis is ≥ 3 for the day

Emesis: The number of episodes of emesis will be recorded for each day, from 0000 to 2400.

II. CONTINUOUS SIGNS

Pupil dilation, temperature, respiration, systolic blood pressure and weight will be measured 1X per day in conjunction with the MHOWS in the AM (2h after the first dose of medication or placebo). The overall daily measurement for pupil dilation, temperature, respiratory rate, systolic BP and weight will be the AM 2h following medication measurements. Morphine agonist baseline evaluations for pupil dilation, temperature, respiratory rate, and systolic blood pressure will be the average of study day 1 & 2. The baseline for weight will be study day 2. These baseline values will be compared to study day 3 (the final morphine agonist baseline day) and each of the five abstinence daily AM values for pupil, temperature, respiration, systolic BP and weight with the following point assignment. Similar comparisons will be made for the two post detoxification/medication days.

Pupil dilation	1 point for each 0.1 mm increase in pupil size.
Temperature	1 point for each 0.1 degree C. rise.
Respiration	1 point for each respiration per minute increase.
Systolic BP	1 point for each 2 mm Hg. rise (up to 30 mm).
Weight	1 point for each pound loss.

The score for any day is the sum of these points.

Table 5 details the 14 items of the MHOWS to be used in the present study, and the weighting of each item. The MHOWS score for any day is the sum of the 14 items that make up this scale. The rating of the MHOWS will include one observation period, 10 min in duration, conducted 2h following the first dose of medication/placebo administered per day. Over half of the items on the MHOWS are discontinuous measures and include yawning, lacrimation, rhinorrhea, perspiration, tremor, goose flesh, anorexia, restlessness, and emesis. With the exception of anorexia and emesis, each of these items will be screened during the MHOWS observation period. One point is assigned if the patient exhibits at least one occurrence of any of the following signs during the day: yawning, lacrimation, rhinorrhea, and perspiration. The maximum daily sum of these single point items is four. Operational definitions for each of these are provided in the Operations Manual to assure uniformity of collection across the study sites. If observed in the day, three points is assigned to tremor and to goose flesh. Each of the three meals are rated separately for "anorexia", and the subject is given 3 points if "appetite" is coded as "poor" or "none" for any meal of the day. Restlessness is scored 5 points if observed on the study day. The discontinuous item with the highest point loading is "emesis" which can vary from 0 to a maximum of 15 points (if ≥ 3 emesis episodes are observed in one day). Himmelsbach gave emesis the highest point loading, since he recognized this symptom occurring only with very severe opiate withdrawal in a frequency correlated with withdrawal severity. Emesis will be recorded once per day,

based upon emesis episodes occurring during the past 24h period. Continuous signs of the scale include: pupil dilation, temperature, respiration rate, sitting systolic blood pressure, and body weight. Each of these continuous measures are derivative measures obtained as a comparative increase or decrease (as indicated) from a stable morphine opiate agonist baseline. The point assignment for each of these five continuous measures is detailed in Table 5. In this study, the morphine agonist baseline for these continuous measures will be the average of values obtained on study day two and three. Therefore, at the end of the study a single MHOWS for the study day 3 morphine agonist values will be provided, along with each of the succeeding medication or placebo days during the detoxification period and the post detoxification period.

Description and Rationale of Secondary Outcome Measures:
This section includes descriptions of six of the nine secondary outcome measures. The remaining three secondary outcome measures are self-explanatory from the title of the measure and/or are described in further detail in the statistical sections of this protocol.

1. Objective Opiate Withdrawal Scale (OOWS) (Handelsman et al., 1987). In the OOWS, a rater determines the presence or absence of 13 physical signs of opiate withdrawal in about a 10 min observation period. In its original form, the OOWS observation is performed while the subject is filling out the SOWS, Handelsman (below). However, to optimize study efficiency, the OOWS observation will take place simultaneously with the MHOWS observation (above), although it will be scored on a dedicated CRFs using all of the original OOWS scale language. The single exception is the timing of collection of an emesis measure which will be scored for the same time period as that for this factor on the MHOWS (above), rather than being confined to the brief observation period. The minimum score is zero and the maximum is 13. For future studies, a possible advantage of the OOWS over the MHOWS is that the OOWS does not require an initial stable opiate agonist period for its computation. If the current Phase 3 study with an opiate lead-in confirms the efficacy of lofexidine over placebo, then it is likely that future studies will not include an opiate lead-in to better simulate the clinical use of lofexidine. If the latter does occur, then the OOWS would be more suitable than the MHOWS. A drawback of the OOWS over the MHOWS in the current study is its relative lack of sensitivity (even severe withdrawal appears to have a low ceiling of 1 or 2), and the relatively fewer published studies standardizing the OOWS versus the MHOWS on the effects of morphine and withdrawal from morphine.

2. Short Opiate Withdrawal Scale (SOWS, Gossop) (Gossop, 1990). The SOWS, Gossop is an opiate withdrawal scale consisting of 10 items which the patient rates him/ herself on a 4 point scale of 0 =none, 1= mild, 2= moderate, to 3= severe. It consists of both objective and subjective symptoms of opiate withdrawal. The minimum score is 0 and the maximum score is 30. The ten SOWS, Gossop items are nausea, stomach cramps, muscle spasms, feelings of coldness, heart pounding, muscular tension, aches and pains, yawning, runny eyes, and problems sleeping. The rationale for including the SOWS, Gossop is to provide a "bridge" measure of opiate withdrawal used in recent published double-blind and open studies conducted in the United Kingdom comparing lofexidine to methadone detoxification (e.g., Bearn et al., 1996; Bearn et al., 1998) and lofexidine to clonidine detoxification (e.g., Carnwath and Hardman, 1998). Accordingly, in the present PIII study, by collecting SOWS, Gossop data for both lofexidine (3.2 mg/d) and placebo, a direct comparison of the results of this study with these previous studies will be possible.

3 & 4. Modified Clinical Global Impressions Scale (NIMH, MCGI, both Rater and Patient Completed) (adapted from Psychopharmacology Bulletin 21: 839-943, 1985 by Herman, B.H. 091499). The Clinical Global Impressions rating scale (1985) was developed by NIMH and has been used in thousands of investigations evaluating the efficacy index (ratio of therapeutic effect relative to side effects) of hundreds of medications for the treatment of psychiatric disorders in children, adolescents and adults. Accordingly, obtaining gestalt global efficacy information from such a scale is of interest especially when such results can be compared to such a large data base of both medications and psychiatric illnesses that may be co-morbid with opiate dependence (e.g., depression, attention deficit disorder). In its original format, there are four questions in the scale. The first question has been modified to tailor this scale to define "ill" as "severity of opiate withdrawal symptoms" as appropriate for the current study. Question #1 refers to the "severity of illness" and asks the rater to evaluate the patient based upon clinical experience according to a gradation of severity from 0 (not assessed), 1 (normal, not at all ill) to 7 (among the most extremely ill patients). This question has been modified by our group in language in the patient version, to make both the question and answers more appropriate to a patient group. Question #2 refers to "global improvement" and has been omitted from this study since there is no untreated expression of opiate withdrawal symptoms observed from which to judge an improvement (all patients accepted into the study are immediately treated with morphine – i.e., there is no untreated baseline withdrawal). In its original format, Question #3 is the "efficacy index", and a rater's responses are recorded on a factorial grid – side effects on one side and therapeutic effects on the other side. The subpart of this question pertaining to "side effects relative to the therapeutic effects" is answered in a graded fashion as "none", "side effects do not significantly interfere with patient's functioning", "side effects significantly interfere with patient's functioning", "side effects outweigh therapeutic effect". The subpart of this question pertaining to "therapeutic effect" cannot be assessed since the definition is based upon the rater observing the patient in their untreated opiate withdrawal state (i.e., from an untreated baseline). The original factorial grid has been eliminated because of unacceptably high complexity for our raters. Simple modifications have been made to the MCGI to tailor this for the patient's own self-rating of the same events described above and the rater's assessment of side effects of the medication on the patient. Thus, these modified global impressions rating scales provide a gestalt view of the efficacy of lofexidine versus placebo in alleviating the various levels of illness associated with opiate withdrawal (question #1), along with the side effects of this medication (question #2). The scale in this form should take rater and patient between 5-10 min to complete. In future clinical trials with lofexidine, the MCGI can be used in its entirety since there will not be an initial morphine agonist period, and the clinicians will have the opportunity to observe the patients as they come into clinic for treatment of opiate withdrawal symptoms. In conjunction with the VAS-S scale, the MCGI should provide a good gestalt tool for assessing both the global efficacy and side effects of lofexidine relative to placebo from the perspective of both the clinician and patient. Since there are no published studies examining the relative power and reliability of visual analogue versus adjective rating scales for this type of outcome, inclusion of both at this phase as secondary outcomes with potential interest as future primary outcomes is indicated.

5. Subjective Opiate Withdrawal Scale (SOWS, Handelsman) (Handelsman et al., 1987).
This scale contains 16 symptoms, and the subject rates him/herself according to the intensity of the symptoms as 0 (not at all) to 4 (extremely). The minimum score is 0 and the maximum score is 64. Items are a mixture of "physical" and "subjective" symptoms and signs of opiate distress and withdrawal. The rationale for inclusion of this scale as a secondary outcome measure is to begin to estimate the efficacy of lofexidine in the alleviation of "subjective" symptoms of opiate withdrawal beyond the "objective" ones suggested in the MHOWS

above. In addition to the total score, items of particular interest include "feel like shooting up", and those indicative of the "anxiety" and "nausea" associated with the distress of opiate withdrawal. The composite SOWS scores in our previous Phase II study, failed to suggest a dose-dependent ordering of four doses of lofexidine (1.6, 2.4, 3.2, and 4.0 mg) although such a dose ordering was suggested for a few individual items. Previous research by Jasinski et al. (1985) suggested that the alpha-2-noradrenergic agonist, clonidine, was not efficacious in treating the "objective" but not the "subjective" symptoms of opiate withdrawal when compared with morphine. Data from Kahn et al. (1998) suggest that this may not be the case for lofexidine where some efficacy for the alleviation of opiate withdrawal sickness has been suggested when compared with clonidine. The inclusion of a placebo group in the current study, will clarify the sensitivity of the SOWS in assessing the efficacy of lofexidine on opiate withdrawal.

6. Visual Analog Scale Assessing Efficacy of Medication in Decreasing Withdrawal Sickness (Visual Analog Scale – Withdrawal Sickness Alleviation, VAS-E). The VAS-E measure is suggested by the results of the double-blind study of Kahn et al. (1997) comparing the efficacy of lofexidine (n=14) versus clonidine (n=14) in the alleviation of withdrawal symptoms from abrupt cessation of methadone. Although the overall efficacy of lofexidine and clonidine was similar in that study, one exception was that lofexidine treated individuals reported feeling "unwell (including anergy, weak, tired)" significantly less than clonidine-treated subjects (p<0.001) (in Kahn et al., 1997, see Table 2). This result suggests that lofexidine may have efficacy in alleviating "withdrawal sickness". This is a surprising result since typically clinicians do not describe clonidine (compared with methadone) as alleviating the generalized/overall "sick" feeling associated with opiate withdrawal (NIDA Consultants Review, June 30, 1998). Two limitation of the Kahn et al. (1997) study were the relatively small number of subjects and the lack of a placebo group. Therefore, the current Phase 3 study will provide additional and more definitive evaluation of the efficacy of lofexidine in alleviating "withdrawal sickness" using a larger sized trial and one with a placebo group.

The method for capturing this information includes a 100 mm visual analog scale, whereby the patient places a mark corresponding most closely to the degree of efficacy of the medication or placebo during the detoxification period in alleviating "withdrawal sickness" from a range of "not effective" to 'completely eliminates withdrawal sickness'.

Description and Rationale of Tertiary or "Other" Measures:

1. Tobacco Withdrawal Symptoms Daily Diary (Hughes and Hatsukami, 1986). It is expected that subjects will be matched for any tobacco withdrawal symptoms that they may have, so that this factor should not affect the assessment of the efficacy of lofexidine versus placebo in the alleviation of opiate withdrawal. At the same time, it is recognized that although all subjects are asked to abstain from smoking while inpatients at the three sites, only site (Philadelphia) will be able to guarantee that no subject will smoke either on the ward or outside of the hospital per the policy of the associated institution. It is anticipated that the great majority of patients in this study will be smokers (approximately, between 98-99%), since opiate dependent individuals ALMOST always smoke. As emphasized by the VA HRC (July 24, 2000 meeting), SOME opiate dependent individuals do NOT smoke. All subjects with tobacco dependence will be offered nicotine patch replacement therapy as stated elsewhere. The nicotine patch therapy should eliminate nicotine withdrawal symptoms in opiate dependent patients while in hospital (cf Appendix). However, some patients at both the New York and LA/LB sites who are smokers will not chose the nicotine patch option, and it is possible that these subjects may experience a small degree of nicotine withdrawal. (They will be permitted supervised smoking outside of the hospital). In order to systematically track the possible

influence of this variable that is beyond our capacity to control other than indicated in this protocol and the appendix, ALL smokers (whether they are allowed to smoke during the study or not) will be require to fill out a Tobacco Withdrawal Symptoms Daily Diary one time a day (1730h). This is a self-report scale consisting of 6 items and takes about 10 min for the patient to complete. The scale is published (Hughes and Hatsukami, 1986) and used extensively in tobacco research, and it is the one recommended by a tobacco research expert from the University of Pennsylvania, Peter Gariti, Ph.D. Analyses of subjects on this measure will be viewed as tertiary, and provide an index of the degree of nicotine withdrawal experienced by smokers in the lofexidine and placebo groups.

IVE7. Pharmacokinetic measurements:

A total of 14 samples (10 ml each) of plasma will be obtained on study days 4-10 as follows (summarized below). The purpose of obtaining these plasma samples will be to estimate the Steady State and Cmax of lofexidine in plasma. The blood samples will be collected at the following time points (expressed as hours post lofexidine dosing) for pharmacokinetic assessments of lofexidine:

Day 4 (first day of lofexidine administration):	0 hr (prior to 1st dose)
Day 6 (third day of lofexidine administration):	0 hr (prior to 9th dose)
Day 7 (fourth day of lofexidine administration):	0 (prior to 13th dose), 1, 2, 3, 4 hr
	5 hr (prior to 14th dose), 8 hr
	10 hr (prior to 15th dose), 13 hr,
	15 hr (Prior to 16th dose)
Day 8 (fifth day of lofexidine administration):	0 hr (prior to 17th dose – 1.6 mg/day)
Day 10 (right after 10AM MHOWS):	After 1000 MHOWS

A total of 14 samples of blood (10 ml each) will be collected in 10cc heparinized glass tubes, for a total of 140 ml (about 10 tablespoons) of blood for Pk assays. Each of these 10 ml blood samples will provide quadruplicate aliquots of plasma for Pk lofexidine/placebo determinations. The total amount of plasma needed for the lofexidine assay is about 1ml, and at a minimum these need to be analyzed in duplicate. From 10 ml of blood per sample, there will be about 5 ml of plasma. This in turn yields about 4 aliquots of plasma each about 1.2 ml in volume. Plasma duplicates for each time point will be shipped to PPD Pharmaco for assay. The other plasma duplicates will be held at each site's freezer in case any of these samples are lost in shipment or fail in the assay or require independent corroboration for concentration of lofexidine. At the END of the study, after ALL samples are analyzed and the results are assessed as appropriate, the residual duplicate blood samples stored in the freezer will be disposed.

A total of 14 samples (10 ml each) of plasma will be obtained on study days 4-10 as follows (summarized above). On study day 4, a single sample will be obtained at 0800h (prior to any dose of lofexidine). On study day 6, a single sample will be obtained at 0800h (this is after two full days of 3.2 mg/day lofexidine, and prior to the dosing of lofexidine for study day 6 (third day of lofexidine)). On study day 7 (4th day of 3.2 mg/day lofexidine administration), ten samples will be obtained at the following times of day: 0800h, 0900h, 1000h, 1100h, 1200h, 1300h, 1600h, 1800h, 2100h, and 2300h. On study day 8 (5th day of lofexidine administration), a single sample will be obtained at 0800h (prior to the dose for 1.6 mg/day). The last blood sample will be obtained on study day 10 (2nd day of post detoxification phase) at 1000h (right

after MHOWS). **All Pk blood samples will be obtained within –15 min to 0 min relative to the time collection hour (i.e., at this interval prior to lofexidine or placebo administration for any overlapping time points).**

There will not be any change in the sampling scheme even if a dose of lofexidine or placebo will be held due to the tolerability issue (Section IVD3 of the protocol). However, the data obtained from the reduce dosing group will be analyzed separately.

 The blood samples shall be immediately centrifuged at 3000 rpm in a refrigerator centrifuge (+ 4°C) for 15 min to separate plasma. The plasma (about 2.5 ml) shall be collected in a plastic vial and shall be immediately stored frozen at –70° C in an upright position. The vial shall be labeled with the study code, subject number, and date and time of blood collection. The vial shall be kept frozen until shipment. The time from draw to centrifuge must be no more than 15-30 minutes, and the time from centrifuge to freezer must be no more than 15 minutes; thus, no more than 30-45 minutes shall elapse from draw to freezing a specimen.

The blood samples will be drawn by venipuncture with venipuncture catheterization (heparin lock). ***The catheter will be inserted into the participant's vein on study day 4 and will remain in their vein through study day 8 (a total of 5 days). If the catheter falls out during this period, a new catheter will be placed back into the participant's vein.*** It is recognized that many opioid dependent individuals who use opiates frequently and in high doses as required for this protocol, do not have "good" veins. Consequently, per the **VA HRC (July 26, 2000)** subjects will be permitted to participate in this protocol even in the event that their veins are not adequate for venipuncture catheterization. In short, blood for lofexidine/placebo determinations will NOT be collected if there is difficulty in venipuncture catheterization. [However, as also suggested by the VA HRC (July 26, 2000), and as indicated elsewhere in this protocol and in the Consent, subjects will be excluded from this protocol if they have such "poor" veins that even single venipuncture needle sticks cannot be obtained in the beginning and end of the protocol (for laboratories reflective of general health status)].

Storage and shipment of blood samples:

Plasma samples shall be kept frozen at –70° C until shipment. For shipment to PPD Pharmaco, Inc., all samples shall be packed in insulated containers with enough dry ice to keep the samples frozen for up to 3 days and shipped to PPD Pharmaco Inc. via overnight mail service.

Analytical method:

Plasma samples will be analyzed by LC/MS/MS method. This method is the newest technology in the Mass Spectrometry field. LC/MS refers to Liquid Chromatography / Mass Spectrometry. LC/MS/MS does not have a comparable spelled out origin. In simple mass spectrometry, a sample passes through the ion source and quadropole and gets fragmented and the mass is detected. In MS/MS, compound passes through a multiple of quadrupoles (2-3) and this will ultimately enhance the sensitivity as well as selectivity of the detectors. By using the LC/MS/MS technique, compounds can be easily detected at pg levels.   The assay has been developed and validated by PPD Pharmaco Inc. with the limit of quantification (LOQ) of 50 pg/ml. **NOTE: THE PARTICULARS OF THE ASSAY METHOD ARE HIGHLY CONFIDENTIAL AND THE ASSAY METHOD IS OWNED BY BRITANNIA/FORUM, WHO REQUESTS THAT NO FURTHER INFORMATION THEN INDICATED ABOVE IS REVEALED.**

Timed Acquisition and Number of Times Each Outcome or Safety Measure is Obtained. See Flow Chart, Table 4.

IVF. Behavioral Management. On all study days patients will be invited to participate in the behavioral and psychiatric therapies provided by their inpatient facility. Additionally, they will be invited to join a variety of therapeutic groups designed to prevent relapse to opiates once they are released from this inpatient study. From a clinical point of view, it is likely that such therapeutic interventions will be of limited usefulness to subjects actively undergoing detoxification in an inpatient unit. However, these nonmedication interventions will be offered to all subjects. Random urine screens (beyond those obtained during screening, every Monday, Wednesday and Friday, and at discharge) will be performed to ensure that patients have remained free of illicit drugs during the trial. Random urine screens will be chosen centrally at the VACSP by the study biostatistician.

Subjects that request to be dropped out of the study will be rescued using standard pharmacotherapy and/or supportive therapy.

Subjects will be reimbursed for their participation and effort at the rate of $20 per day. They will be reimbursed for each day they are enrolled in the study regardless of whether they complete the entire study. In addition, patients will receive $5 per day for not smoking, if they did not smoke at all while they were a study patient. Reimbursement will be given in two divided payments; one-half will be given on the day AFTER discharge and the other half one week later.

IVG. Concomitant Medications Permitted Subjects may receive concomitant medications that are not exclusionary to their participation.

IVG1. Approved Concomitant Medication List
The following medications are allowable; other medications must be cleared with the medical monitor of this study:

1. Multivitamins
2. Guaifenesin (for cough)
3. Alumina, Magnesia and Simethicone (for dyspepsia, minor efficacy for nausea)
4. Dioctyl sodium sulfosuccinate (for constipation)
5. Psyllium hydrocolloid suspension (for constipation)
6. Bismuth sulfate (Pepto-Bismol) (for diarrhea)
7. Acetaminophen (for headache, muscle aches, or other discomfort)
8. Zolpidem (for insomnia)
9. Nicotine patch (for nicotine withdrawal symptoms)

Note: For intolerable nausea and emesis, if a subject requires any medication (including a prescription opiate or nonopiate or an over-the-counter opiate or nonopiate) other than the slight anti-nauseant effects of #3 above {alumina, magnesia, simethicone}), the subject will be dropped from the study and given appropriate treatment according to the standard of care.

IVG2. Dosing and Criteria for Administration of Concomitant Medications

1. Multivitamin, one tablet p.o., administered daily at 9 AM

2. Guaifenesin, two tsp, p.o., administered every 2 hrs, PRN, for cough

3. Alumina, Magnesia and Simethicone, 30 cc, p.o., administered every 4hrs, PRN, for dyspepsia and nausea

4. Dioctyl sodium sulfosuccinate, 100 mg, p.o., administered every 8 hrs, PRN, constipation

5. Psyllium hydrocolloid suspension, one tablespoon, p.o., administered every 12 hrs, PRN, constipation

6. Bismuth sulfate (Pepto-Bismol) (for diarrhea) 30 c.c., p.o., PRN after loose bowel movements up to 6 doses in 24 hours

7. "Acetaminophen 650 mg p.o. every 6 hrs PRN for headache, muscle aches, or other discomfort. To be administered up to four doses every 24 hours."

8. Zolpidem 10 mg, p.o., PRN, for insomnia, may repeat one time if administered prior to 5:00 AM (i.e, 3h) prior to the first morning dose of lofexidine or placebo. Zolpidem must not be administered prior to 11:00 PM (which is the time of the last daily dose of lofexidine or placebo). The criteria for nightly administration of Zolpidem will be more liberal that that for the administration of other concomitant medications, as there is published data and clinical experience suggesting that neither clonidine or lofexidine is effective in alleviating insomnia associated with opiate withdrawal.

9. Nicotine patch (Nicoderm CQ), topically applied, 21 mg/daily in patients smoking $\geq$ 1 pack per day. The patch dose of nicotine will be reduced to 14 mg/day for nicotine dependent patients smoking one half of a pack to less than one pack (10 – 19 cigarettes) per day. The patch dose of nicotine will be reduced to 7 mg/day for nicotine dependent patients smoking less than one half of a pack (1 – 9 cigarettes) per day. This reduced dosage form of nicotine is likely to be required in a very small minority of nicotine dependent patients in the subject population of opiate dependent individuals (Garity, 2000, in preparation). Medication for nicotine dependence will be determined in a manner consistent with DSM IV criteria. An additional incentive to be patched includes $5.00 a day, with the total amount to be paid in an all or none fashion at the end of the study. Only patients who comply with the nicotine patch procedure and the strictly enforced no smoking policy will receive $55 at the end of the study.

Please see **Appendix IV** for further details on rationale underlying nicotine patch administration for cigarette smokers (nicotine dependent patients).

IVH. Medical Termination Criteria from Continued Protocol Participation
The following events would preclude a participant from continuing to receive study medication once enrolled. The abnormal vitals events that might trigger a medical termination are carefully tracked for occurrence and timed resolution on a separate case report form: "Abnormal Vitals Resolution and Termination Event Log ", which will be carefully analyzed in conjunction with the cardiovascular safety analysis of this study.

1. Cardiac events.
    a. Clinically significant abnormal ECG (e.g., second or third degree heart block or uncontrolled arrhythmia).

b. Persistent Symptomatic Hypotension. Hypotension not responding to bed rest, which leads to missing more than two doses of study medication in a day.

c. Single Occurrence of Symptomatic Bradycardia. A single occurrence of heart rate less than 60 beats per minute (regardless of blood pressure) associated with chest pain, shortness of breath, or decreased level of consciousness.

d. Persistent Hypertension. Blood pressure greater than 185/110 mmHg recorded on three separate occasions taken at least five minutes apart AND within a one hour time period. All three readings must be greater than or equal to 185/100 – either systolic $\geq$ 185 mmHg or diastolic $\geq$ 110 mmHg – to require study termination. (Note: If BP is $\geq$ 185/110 - either systolic $\geq$ 185 mmHg or diastolic $\geq$ 110 mmHg - BP must be taken twice more within the hour, at least 5 minutes apart.)

e. Medical Intervention for Cardiac Event. Any medical intervention (Nonmedication or Medication Inclusive) used for the treatment of any cardiac event, with the exception of a positional intervention in subjects displaying hypotension.

f. Any other clinically significant cardiac sign or symptom that would place the subject at inappropriate risk.

2. Serious medical problem thought to be related or unrelated to the study medications.

3. Intercurrent illness or medical complications precluding safe administration of study medications.

4. Exclusionary criteria noted after the subject has been entered into the protocol.
a. Evidence of illicit drug use while participating in the study.
b. Alcohol or other sedative/hypnotic withdrawal signs and symptoms developing following enrollment into the study.
c. Oversedation from initial morphine dose.

5. Lack of compliance with protocol and/or unit procedures.

6. Subject request.

Subjects who have begun receiving morphine, placebo or lofexidine and are precluded from continuing on study medication (as described above) will not be discharged from the protocol until they have been medically stabilized. This stabilization may include medically supervised opiate withdrawal (involving behavioral therapy and/or non-opiate pharmacotherapy) or transfer to an appropriate methadone or levo-alpha-acetylmethadol (LAAM) therapy program. Nonveteran subjects who are terminated from this protocol will be referred to the appropriate intake units at the three sites to ensure medical stabilization prior to discharge.

V. Statistical Methods

VA. Outline of Study Design. This is a double blind, randomized, placebo-controlled parallel-group study, to be performed at three sites, to evaluate the efficacy and clinical

safety/tolerability of lofexidine 3.2 mg/day in the treatment of opiate detoxification. Subjects will first undergo stabilization on morphine during an "opiate agonist period" of three days' duration (Study Days 1-3). Morphine will then be stopped abruptly and trial medication given for a detoxification treatment period of 5 days (Study Days 4-8), followed by assessment during two further days (Study Days 9-10) up to the morning of Study Day 11. Randomization will take place after the 'opiate agonist period' and immediately before the first dose of lofexidine/ placebo is due to be administered on study day 4. Assessment of efficacy will be primarily by means of various 'opiate withdrawal scales', together with clinical and laboratory assessments of safety/tolerability and potential abuse liability.

VB. Outcome Variables.

VB1. Primary Efficacy Endpoint. The primary outcome measure will be the Modified Himmelsbach Opiate Withdrawal Scale, including pupil size measurements ('MHOWS'), as assessed on Study Day 5 (second day of lofexidine/ placebo). For those MHOWS items scored as 'changes from baseline', that baseline will be taken as the arithmetic mean of measurements taken on Study Days 2 and 3 (in opiate agonist phase).

In view of the 'quasi-intention-to-treat' method of analysis (see below), the only patients who are 'non-evaluable' in relation to this primary efficacy endpoint will be any who fail to undergo a full MHOWS assessment on the first day of trial medication (Study Day 4).

VB2. Secondary Efficacy Endpoints

The secondary outcome measures are:

1.   Drop Out Day/Day-by-day dropout rate
2.   Peak MHOWS score observed during Study Days 4-8 inclusive
3.   Objective Opiate Withdrawal Scale ('OOWS'), Handlesman
4.   Short Opiate Withdrawal Scale ('SOWS', Gossop)
5.   Modified Clinical Global Impressions ('MCGI') Rating Scale (Patient)
6.   Modified Clinical Global Impressions ('MCGI') Rating Scale (Rater)
7.   Subjective Opiate Withdrawal Scale ('SOWS', Handelsman)
8.   Visual Analog Scale: Efficacy of Medication for the Alleviation of   Withdrawal Sickness (VAS-E)
9.   Number of Concomitant Medications Related to Opiate Withdrawal, Study Days 4-8 Inclusive

The first two of these secondary outcomes are considered to be of the greatest clinical importance, the others being 'supportive' and/or exploratory. For those quantitative outcome variables assessed on a daily basis, the following derived indices of the scores will be analyzed:

1.   Score on Study Day 5 (second day of lofexidine/placebo) - in the case of MHOWS this is the primary endpoint described above.
2.   Peak score observed, regardless of day on which it occurs.

VB3. Other Observations Relating to Efficacy
The relationship between the rate and timing of subject drop out from the study, treatment and opiate withdrawal scale scores will be examined and explored descriptively.

VB4. Safety Monitoring Variables

Safety monitoring variables will consist of:

1.   Measurements of vital signs (sitting)
        (blood pressure and heart rate; respiration rate, oral body temperature)
2.   Measurement of vital signs (standing)
        (blood pressure and heart rate)
3.   Effects on the electrocardiograms (ECG)
4.   Any abnormal clinical signs detected on physical examination
5.   Effects on Laboratory Chemistries (blood chemistry and   hematology) investigations
        (cf. Appendix V, for abnormalities)
6.   Urine toxicology for drugs of abuse
7.   Symptomatic adverse events reported by subjects

VB5. Abuse Liability Assessments
1. Addiction Research Center Inventory (ARCI) euphoria (MBG) subscale
2. VAS-H for "Drug High" – potential abuse related liability of lofexidine

VC. Statistical Analysis of Efficacy Outcome Variables

General Considerations. The various opiate withdrawal rating scales utilized in this study are known to usually result in data which is suitable for 'parametric' summary and analysis, and the analytical proposals assume that will prove to be the case with data from the proposed study. However, the data will first be examined for suitability for such analyses (after appropriate transformation, if necessary) and if that fails to be the case then appropriate alternative distribution-independent approaches to summary and analysis of the data will be utilized. It is, however, considered unlikely that this situation will arise.

Even though the trial is placebo-controlled, all hypothesis tests will be two-tailed, and the threshold for rejection of null hypotheses will be $p = 0.05$. Confidence intervals where cited will be two-sided 95% ones.

Full summary statistics for all outcome variables will be presented, including confidence intervals of estimated effect sizes where indicated, supplemented by graphical presentations of the summary data where appropriate. Full listings of all assessed variables will be made available.

Inclusion of Subjects in Analyses. For the purpose of efficacy analysis, an *'evaluable subject'* will be defined as one who receives at least one dose of lofexidine or placebo *and* undergoes at least one assessment of all of the MHOWS items on Study Day 4. For safety monitoring (clinical, laboratory, symptomatic adverse events), all data available from all patients who receive at least one dose of study medication (lofexidine or placebo) will be analyzed.

VC1. Primary Efficacy Outcome Variable. MHOWS scores on Study Day 5 for the two treatment groups will be compared by means of a mixed effects model analysis of variance (ANOVA) (including site as a random factor), the null hypothesis being of no difference in these scores between treatment groups. If a significant overall treatment effect is observed, treatment effects within each of the sites will also be examined.

The primary analysis will be as close to an "intention-to-treat" basis as is possible in the clinical situation. Should a subject drop out of the study prior to MHOWS assessment on the second detoxification treatment day (Study Day 5), then the score from the previous day (Study Day 4) will be 'carried forward' and, for analytical purposes, will be regarded as the score for Study Day 5 (*the second detoxification treatment day*). This carry forward procedure will be used only if there are no more than 30% of such dropouts (14 patients) in either one of the treatment groups. Hence the only patients omitted from this analysis will be any who do not undergo an MHOWS assessment on the first day of randomized study medication (Study Day 4).

If MHOWS assessment on the second detoxification treatment day was undertaken, but some of the scored items are missing, then, if data for these item(s) for both Study Day 4 and Study Day 6 are available, the arithmetic mean of those two figures will be taken as the value for Study Day 5 to permit a 'second detoxification treatment day MHOWS total' to be calculated. If data are not available for Study Day 6, then the figure from Study Day 4 will be 'carried forward' as the Study Day 5 value.

Two confirmatory analyses of the primary outcome will be undertaken - first a corresponding analysis undertaken only on those patients who have actual (and not 'partially averaged' or carried forward') MHOWS scores for Study Day 5 and, second, a repeat of the primary analysis including age, duration of addiction and baseline MHOWS score (Study Day 3) as covariates.

VC2. Secondary Efficacy Analyses. Particularly in view of the large number of secondary outcome variables, analysis of these will be primarily exploratory and descriptive in nature, with the main emphasis on estimation. While inferential analyses will be undertaken, the results will be interpreted in the light of the exploratory nature of these analyses. For all inferential analyses, the null hypothesis will be that there is zero difference between treatment groups for the variable in question.

For all of the assessments performed on a daily basis, analysis will be undertaken on the following derived indices:

1.   The score on Study Day 5 (second day of lofexidine/placebo), handling of missing data in the fashion described for the primary outcome variable, above. In the case of MHOWS scores, this index will be the primary outcome variable.

2.   The peak observed score for the scale concerned (regardless of the day on which it occurred). It is not anticipated that there will be any appreciable amount of 'missing data' for these analyses.   The latter situation could only arise if a subject had no data at all, from any detoxification treatment day, for the scale concerned. Any such subjects will be excluded from the analysis in question, and it is expected that the omission of such a small anticipated number of such subjects would not lead to appreciable bias.

Analysis of all quantitative secondary outcome variables whose data satisfies the required assumptions (distributional etc.) will be analyzed in the manner described for the primary outcome variable, utilizing a mixed effects model analysis of variance (ANOVA) (including site as a factor). Where appropriate, further confirmatory analyses will be performed including age, duration of opiate addiction and baseline (Study Day 3) MHOWS scores as covariates. If particular sets of data do not satisfy (after transformation if necessary) the

required assumptions of such techniques, appropriate corresponding distribution-independent methods will be utilized.

Dropout of patients from the two groups will be compared using survival analysis, the null hypothesis of no difference between groups being tested with a log-rank test, stratified by site. Confirmatory analyses including factors such as age, duration of opiate addiction and baseline MHOWS scores will be explored using a Cox proportional hazards model.

Parts of the MCGI not suitable for quantitative analysis will be analyzed using appropriate distribution-independent methods.

The relationship between dropout from the trial and assessed levels of opiate withdrawal symptoms will be explored by comparing, at various timepoints, MHOWS scores of subjects who did, and did not dropout from the trial.

VC3. Abuse Potential Analyses. There are two secondary outcome measures that provide an important assessment of the potential abuse liability of lofexidine: (1) Addiction Research Center Inventory (ARCI) - euphoria (MBG) subscale, and (2) one visual analogue scale (VAS) for "Drug High" that assesses potential abuse related liability aspects of lofexidine. Analysis of these quantitative secondary outcome variables whose data satisfies the required assumptions (distributional etc.) will be analyzed in the manner described for the primary outcome variable, utilizing a mixed effects model analysis of variance (ANOVA) (including site as a factor).   Other analyses may be performed as indicated in the above for secondary measures.

VC4. Safety Monitoring Analyses. The outcome variables related to safety - symptomatic and objective (clinically observed or laboratory measurements) will be dealt with in an essentially descriptive fashion. Should appreciable numbers of subjects, in one or both treatment groups, exhibit the same abnormality or suffer the same adverse event, then the proportions in the two treatment groups so affected will be compared using Chi-Squared or Fisher's Exact tests.

For the purpose of summary and analysis, all of the quantitative measures (vital signs – blood pressure and heart rate **-** sitting and standing, respiration rate – sitting, oral body temperature - sitting, quantitative EKG indices, blood chemistry and hematology), results will be classified as 'normal' or 'abnormal' on the basis of established clinical criteria or, where appropriate, the laboratory's normal reference ranges (cf. Appendix V). However, the descriptive treatment of all quantitative safety data will focus mainly on descriptive handling of individual subjects' measurements, with particular reference to the magnitude of changes and whether or not there were any clinical correlates (symptoms or other signs) of abnormal measurements.

Although the main emphasis will be on changes/abnormalities of safety variables within individuals, heart rate and blood pressure (both sitting and standing), respiration rate (sitting), and oral body temperature will be analyzed quantitatively. Analytic techniques as applied to efficacy data will be employed, with tests of the null hypotheses of no difference between groups, both over the period of Study Days 4-8 inclusive and also on a day-by-day basis. Baseline (Study Day 3) values of the corresponding variable will be used as an additional covariate for analyses, as appropriate.

Symptomatic adverse events (AEs) (including those related to blood pressure and/or or heart rate changes) will be dealt with essentially descriptively, with a classification into degrees of clinical severity. The occurrence of AEs will be assessed daily an AE case report form (CRF) will be completed (see below for further details on Adverse Events Reporting and Serious Adverse Events. If appropriate, the incidence and/or severity of particular adverse events in the two groups will be compared using Chi-Squared or other appropriate hypothesis tests.

Quantitative indices derived from ECGs will be analyzed as for heart rate and blood pressure. Qualitative aspects of the ECGs will be assessed by cardiologist(s); abnormalities and changes will be summarized and, where appropriate, compared between groups using appropriate statistical tests.

VI. Data Management Plan and Case Report Forms (CRF)

Data management activities and statistical analytical support will be coordinated through the Department of Veterans Affairs Cooperative Studies Program Coordinating Center in Perry Point, MD (CSPCC). Data will be collected at the study sites on Case Report Forms (CRFs), which will be supplied by CSPCC. Completed forms will be submitted on a regular basis to CSPCC. Draft copies of the CRFs are in Appendix VI.

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

The CSPCC will also prepare summary reports of the data so that progress of the study can be monitored. Various reports will be prepared for NIDA, Britannia Pharmaceutical Limited and the Data Safety Monitoring Board (DSMB), and others, as appropriate. These reports, as well as the final analyses, will be prepared in cooperation with the coordinating center in Perry Point.

VII. PUBLICATIONS AND PRESENTATIONS

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

VIII. STUDY MANAGEMENT AND MONITORING

1. Study Management

The daily activities of the study will be conducted by the local investigators and study coordinators at the participating medical centers. The study chairmen's office, NIDA, the Cooperative Studies Program Coordinating Center (CSPCC) at the Perry Point, MD, VA

Medical Center and the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) in Albuquerque, NM, will provide leadership and guidance to the local centers as well as performing their assigned tasks.

The study chairmen's office (Chairman, Charles P. O'Brien, M.D., Ph.D.) will provide medical leadership for the study. All questions and concerns of a medical nature will be answered or dealt with here. This office will also be in routine contact with the participating centers to ensure that the study is performed in accordance with the protocol and to encourage the local study teams to remain on schedule. The study chairmen will chair all meetings of study participants and will represent the study along with the study biostatistician at all meetings of outside review committees.

The CSPCC will provide administrative, data processing and statistical support for the study. All data forms will be submitted to the CSPCC for processing. The CSPCC will edit the data and create the study database. CSPCC staff will provide guidance on forms completion. All reports during the ongoing phase of the study and the final statistical analyses will be the responsibility of the CSPCC. Administrative guidance such as budgetary and local R&D approvals will be provided by CSPCC staff. CSPCC staff will also monitor study progress to ensure that the study is proceeding as scheduled. A study team dedicated to this study has been established. This team will be headed by the study biostatistician and will include a project manager, a statistical programmer, a database programmer and two computer assistants.

The CSPCRPCC will be responsible for all drug aspects of the study. This includes all regulatory aspects of drug use, procuring the drug, packaging and distributing the drug, working with the local pharmacies, and accounting for and disposal of the drug at the end of the study. CSPCRPCC staff will answer all drug-related questions and will provide 24-hour coverage should drug unblinding be necessary. The study pharmacist for the study will head the CSPCRPCC study team.

The participating investigators at each of the participating medical centers will be responsible for all aspects of the study at his/her site. This includes patient recruitment and follow-up, obtaining initial and yearly R&D Committee (and IRB) approvals, ensuring coverage for the study in his/her absence or the absence of other study staff, and ensuring the integrity of the study protocol and data from his/her site. A study coordinator will be provided for each site and the investigators will be responsible for supervising this person. The investigator may also add additional staff on his own such as a co-investigator to help him/her with the conduct of the study, but the primary participating investigator will be responsible for training and overseeing the work of any additional staff.

2. Monitoring

A number of groups will be charged with monitoring the various aspects of the study. These groups include the Study Group, the Executive Committee, the Data Monitoring Board, the CSPCC Human Rights Committee, the VA/NIDA Review Committee and a Contract Research Organization MQS, Inc. With the exception of the VA/NIDA, each of these committees will meet at the beginning of patient intake, six to nine months later, and yearly thereafter. In addition, a special monitoring unit will also site visit each of the participating

centers. This study monitoring will not preclude the yearly monitoring that the local IRB/R&D Committee must do.

The <u>Study Group</u> consists of all participating investigators and meets annually to discuss the progress of the study and any problems encountered during the conduct of the trial. No interim endpoint data is presented to this group.

The <u>Executive Committee</u> is the management and decision-making body for the operational aspects of the study.   The committee consists of the study chairmen, the study biostatistician, the study pharmacist, two to three participating investigators and the heads of the central laboratories. This committee monitors the performance of participating medical centers and quality of data collected.   The Executive Committee formulates plans for publications and oversees the publication and presentation of all data from the study. Permission from this committee must be granted before any study data may be used for presentation on publication. This group also does not receive interim endpoint data.

The <u>Data Safety Monitoring Board</u> (DSMB) is a group of outside experts in the area of clinical trials and biostatistics that reviews the progress of the study and monitors patient intake, outcomes, adverse events, and other issues related to patient safety. The DSMB makes recommendations to the Chief of the Cooperative Studies Program about whether the study should continue or be stopped.   The DSMB can consider patient safety or other circumstances as grounds for early termination, including either compelling internal or external evidence of treatment differences or infeasibility of addressing the study hypotheses (e.g., poor patient intake, poor adherence to protocol). Interim analyses will be provided to the DSMB by the study biostatistician at intervals specified by the board. The reports of the DSMB on adverse events will be sent to the PIs for transmittal to their respective IRB as per NIH policy on adverse event reporting in multicenter trials.

The <u>Human Rights Committee</u> (HRC) at the CSPCC reviews the study annually to ensure that patient's rights and safety are being properly protected. The HRC will be presented with a report from the study biostatistician about the progress of the study and ethical issues relevant to the HRC. In the interim, the HRC may be asked to convene if there is any serious event requiring its attention. The HRC will usually meet at the same time as the DSMB so that they have the expertise of the DSMB available to them if needed.

The Contract Research Organization (MQS Inc.) makes prestudy, interim and final close out study visits to each site. They will also follow the direction of VACSP in the handling and correction of clinical study data.

3. **Sponsor Clinical Monitoring Plan**

Participating investigators agree to routine data audits by the staff of the VACSP monitoring unit, as well as by NIDA or Britannia Pharmaceutical Limited. The Primary group to provide clinical monitoring is appointed by the Sponsor Britannia Pharmaceutical Limited. The Contract Research Organization appointed to provide this service is MQS, Inc. 29 East Railroad Ave., Jamesburg, N.J. 08551

To assure compliance with Good Clinical Practices written procedures will be established and followed by MQS. These procedures will include clinical monitoring instructions, monitoring trip report forms, and issue/resolution forms. These procedures and forms will establish a working relationship between the clinical monitoring group MQS, the VACSPCC for Data Management, and the VACSP Good Clinical Practices Monitoring Group. In addition the MQS clinical monitors will receive training in the relevant clinical issues that relate to this clinical trial and the protocol.

The monitor designated as the representative of the Sponsor is assigned to oversee the conduct and progress of the study. The monitor will submit original, signed monitoring reports and telephone communication reports to the GCPMG. After GCMPG conducts a review of the reports, they will send copies to the sponsor, NIDA and the CSPCC. The monitor's responsibilities include (but are not limited to): periodic on-site inspection of clinical sites and records, and assuring that sites comply with Good Clinical Practices. The monitor will perform several types of site visits during the course of the trial.

Prestudy Visit
During the Pre-Investigation visit, the proposed investigational site will be evaluated to ensure an adequate patient base as well as sufficient staff and experience. Each potential Investigator will be made fully aware of the responsibilities and requirements of participating in this study, including IRB approval, enrollment rate, patient selection, informed consent and clinical data and investigational drug record keeping methods. In addition, the facility will be evaluated to ensure that it contains the adequate equipment and certifications to conduct the study.

Study Intiation Visit
Before the study begins, the monitor will visit the investigational site. The purpose of this visit is to review with the Investigator and staff the provisions and proper conduct of the clinical investigation. This includes a detailed review of the protocol, CRFs and study procedure manual. Requirements for timely and accurate reporting of clinical data and unanticipated adverse events will be established as well as ensuring safe and secure storage of the investigational drug. The monitor will confirm that the informed consent form to be used is the one approved by the IRB, verify that all necessary documents are on file at the site and confirm that there are methods to maintain all documents and records throughout the study as required by Good Clinical Practices.

ADVERSE EVENTS REPORTING. In accordance with FDA reporting requirements, all adverse events (AEs) occurring during the course of the clinical trial and 30 days after a subject's participation in this clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the specific instructions detailed in this section of the protocol, and as indicated above and below. The occurrence of AEs will be assessed daily and an AE case report form (CRF) will be completed.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, <u>whether or not the event is considered medication-related</u> or clinically significant. For this study, AEs will include events reported by the subject, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and <u>do not worsen</u>

are not considered AEs. All AEs must be recorded on the AE Form. The AE Form is also used to record follow-up information for unresolved events reported on previous visits.

Each day, a study investigator must review the AE Form completed for the previous day for any events that were reported as continuing. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study investigators for satisfactory resolution. AEs may be reported up to 30 days following completion of, or termination from the study.

SERIOUS ADVSERSE EVENTS. Each AE will be classified by a study investigator as serious or non-serious and appropriate reporting procedures followed.

Serious adverse events (SAEs) are defined as **any**:
>> fatal event,
>> immediately life-threatening event,
>> permanent or substantially disabling event,
>> event that requires or prolongs inpatient hospitalization, or
>> any congenital anomaly.

This category also includes any event that a study investigator or the medical monitor judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution. An unexpected event is one that is not described with respect to nature, severity, or frequency in the current Investigator's Brochure.

Any SAE (including death) due to any cause, which occurs during the course of this investigation, whether or not related to the investigational medication, must be reported within **24-hours** by telephone to: the Study Medical Monitor (To Be Named by Forum Products, sister company of Britannia Pharmaceuticals, Ltd.). Forum will also inform Dr. Ivan Montoya, NIDA within **24-hours** of any SAE.

The telephone report is to be followed by submission of a completed SAE Form with demographic information and a narrative explanation of the event. Attached to the SAE Form should be photocopies of the AE Form, the Concomitant Therapy Forms, and the Medical History Form from the subject's CRFs.

Unexpected serious medical events are also to be reported immediately to the responsible institutional review board according to local regulatory requirements. All participating investigators will be notified of any serious and unexpected AE requiring submission to the FDA in an IND safety report from the sponsor.

Forum Products (sister company of Britannia Pharmaceuticals, Ltd.) will inform NIDA (Dr. Ivan Montoya) of all SAEs which occur during the study. Forum Products, as IND holder, is required by FDA regulations to report these to the FDA in a timely fashion. All AEs that are both serious and unexpected must be reported to the FDA, in writing, within **fifteen (15) calendar days** of notification of the sponsor of the SAE. If the SAE is fatal or life threatening, there is an additional obligation of Forum to notify FDA by telephone within **seven (7) calendar days**, with a follow-up written report **within an additional eight (8) calendar days**.

There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA regulations governing the reporting of SAEs to FDA. The study investigators in this study have the responsibility of promptly reporting all SAEs to Forum, so that Forum can comply with these regulations. Forum will subsequently inform NIDA within 24h.

In the event that a study subject either withdraws from the study or an investigator decides to discontinue the subject from the study due to a SAE, the subject must have appropriate follow-up medical monitoring. If the subject is hospitalized, medical monitoring will consist of not less than daily evaluation by physical examination, vital signs, laboratory evaluations, and if applicable, ECG monitoring for significant treatment-emergent abnormalities. Monitoring will continue until the problem prompting hospitalization has resolved or stabilized with no further change expected or is discovered to be clearly unrelated to study medication or progresses to death.

Periodic Monitoring Visits. The study monitor will maintain personal contact with the Investigator and staff throughout the study by telephone, mail and on-site visits. On-site monitoring will begin after the first patient is enrolled and will continue until the study is complete. The purpose of these monitoring visits is to ensure ongoing protocol compliance, and adequacy of the Investigator and the facility to carry out the study. During these visits, the monitor will verify adequate patient enrollment, appropriate informed consent procedures, accurate data reporting (including a comparison of the CRFs with source documents), continued IRB approval of the study, and proper administration of the investigational drug. The monitor will evaluate and summarize the results of each visit in a written report as well as correspondence with the site, identifying any ongoing data problems and specifying recommendations for resolution.

Final Monitoring Visit. At the completion of the study, the monitor will conduct a final on-site visit to ensure that all study data has been submitted to the CSPCC, confirm that the Investigators files are accurate and complete, review the record retention requirements of the Investigator, ensure the return or disposal of remaining investigational drug to CSPCRPCC, review drug accountability records and assure that all applicable requirements for closure of the study are met.

The following areas will be monitored:

CONDUCT OF THE STUDY:
Adherence to the clinical protocol
CRF completion
Signed and dated consent forms
IRB communication and continuing approval
Clinical laboratory and normal ranges
Source document review

STUDY SITE:
1. The investigator has adequate time to allocate to the study
2. Patient recruitment is adequate
3. There is adequate staff and facilities
4. All research staff are qualified to perform their duties

5. Unanticipated adverse events are reported as required
6. Progress reports are submitted when required

PHARMACY:
1) There is secure and adequate storage
2) Area is restricted to authorized personnel only
3) Drug accountability records are kept and can be reconciled to a pill count and are traceable to each patient.
4) Records of investigational drug receipts are in order.
5) PI instructions to the pharmacy are consistent with the protocol.

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