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# PHASE 1, PILOT STUDY TO EXAMINE THE CARDIOVASCULAR EFFECTS OF SMOKED MARIJUANA, INTERACTIONS WITH ORAL DRONABINOL, AND EFFECTS OF DRONABINOL ON WITHDRAWAL IN MARIJUANA DEPENDENT VOLUNTEERS


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# 1 LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| AIDS | Acquired Immunodeficiency Syndrome |
| AUC | area under the plasma concentration curve |
| BP | blood pressure |
| CRF | Case Report Form |
| $C_{max}$ | maximum plasma concentration |
| CNS | central nervous system |
| DSMB | Data and Safety Monitoring Board |
| DPMC | Division of Pharmacological and Medical Consequences |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition |
| ECG | electrocardiogram |
| EEG | electroencephalogram |
| FDA | Food and Drug Administration |
| GC-MS | gas chromatograph-mass spectroscopy |
| HBsAg | hepatitis B surface antigen |
| HIV | human immunodeficiency virus |
| HR | heart rate |
| IRB | Institutional Review Board |
| NIDA | National Institute on Drug Abuse |
| MedDRA | Medical Dictionary of Regulatory Affairs |
| MJ | marijuana |
| MWSC | Marijuana Withdrawal Symptom Checklist |
| PK | pharmacokinetic(s) |
| SAE | serious adverse event |
| SAMHSA | Substance Abuse and Mental Health Services Administration |
| SCID | structured clinical interview for DSM-IV |
| SD | standard deviation |
| THC | Δ-9-tetrahydrocannabinol |
| THCV | Δ-9-tetrahydrocannabivarin |
| THC-COOH | 11-nor-Δ-9-tetrahydrocannabinol-9-carboxylic acid |
| THCV-COOH | 11-nor-Δ-9-tetrahydrocannabivarin-9-carboxylic acid |
| $T_{max}$ | time to maximum plasma concentration |
| VAS | visual analog scale |
| WDS | withdrawal discomfort score |

## 2 STUDY SCHEMA

**FIGURE 1. OVERALL STUDY SCHEMA**

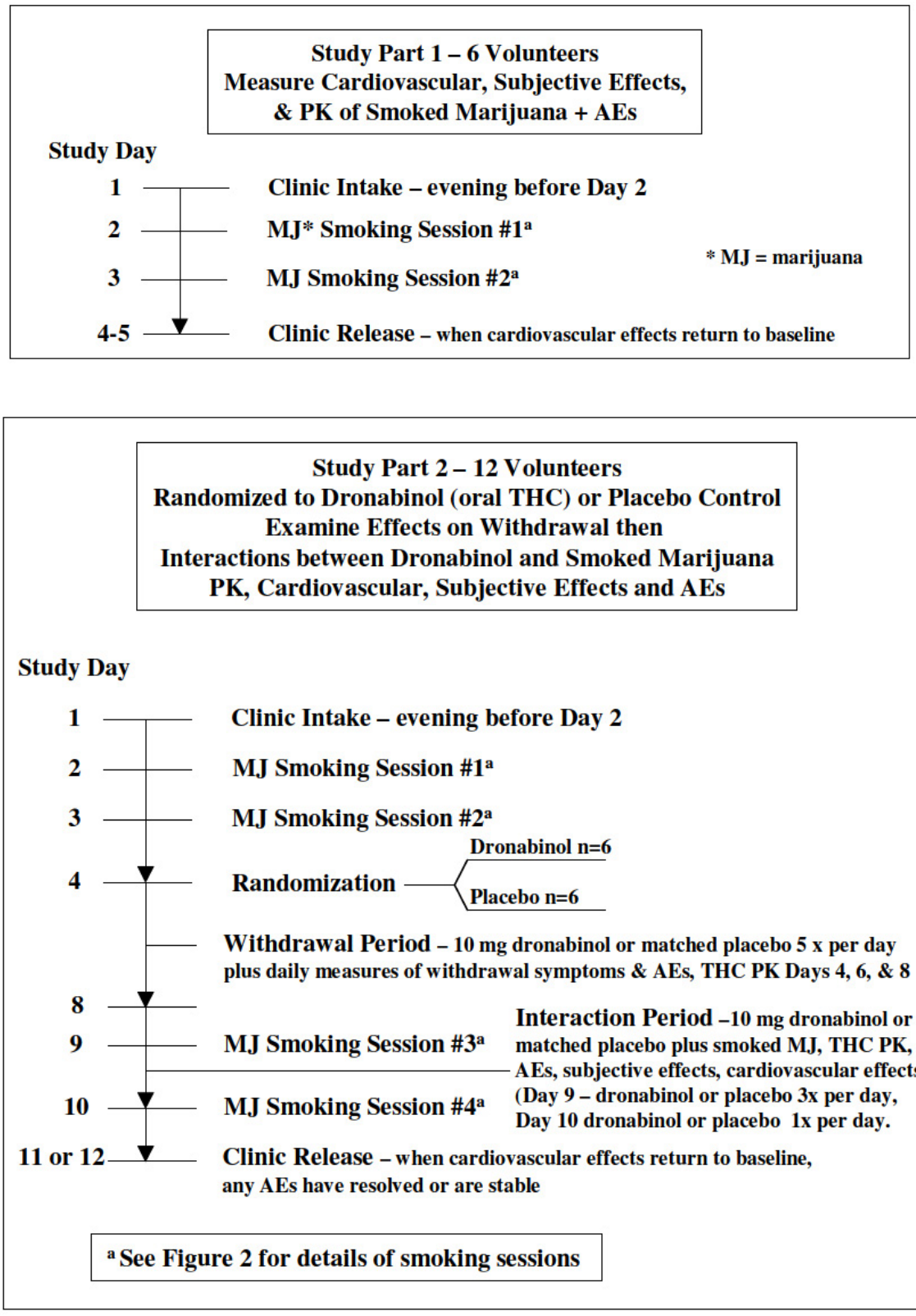
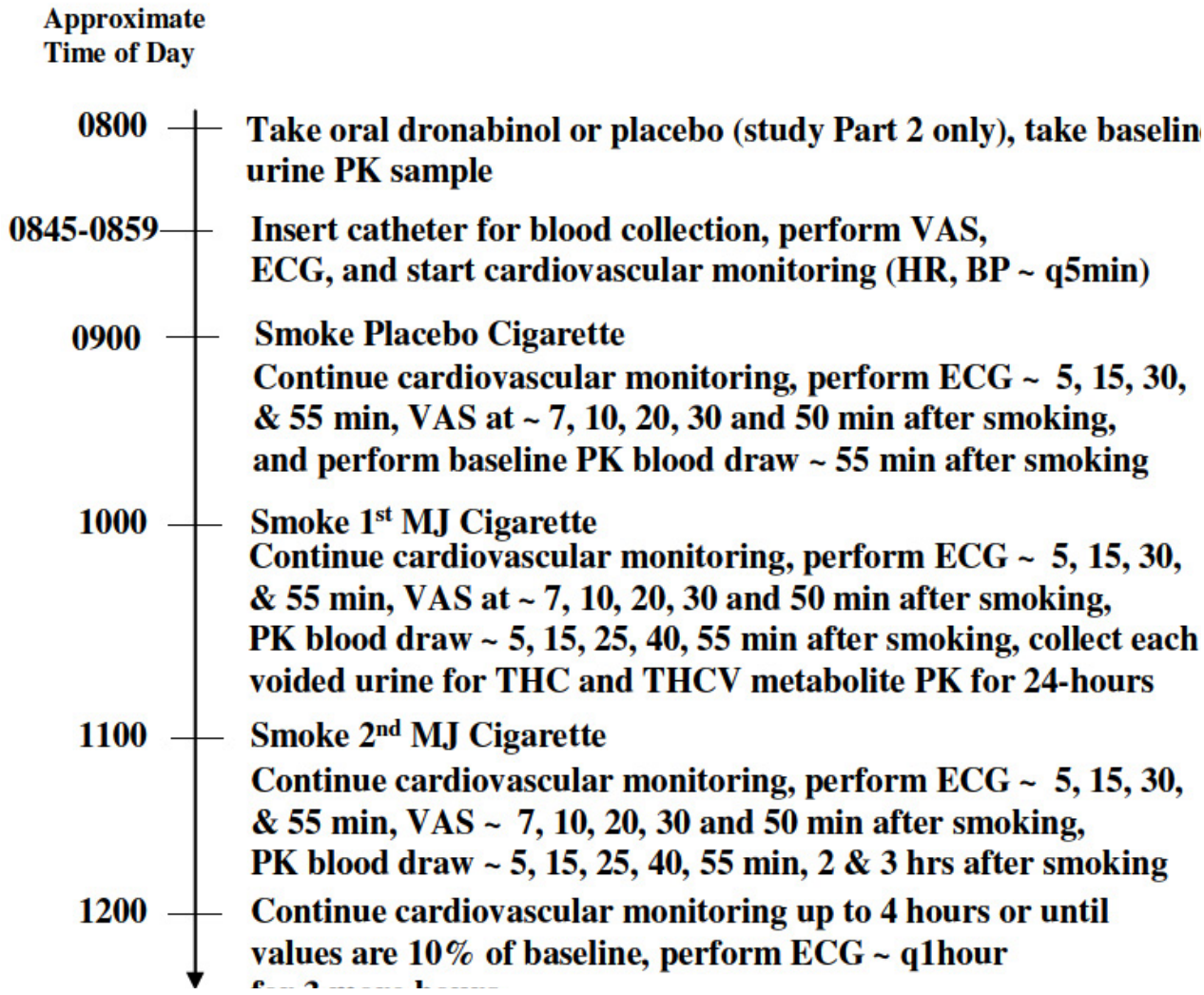


**FIGURE 2. SMOKING SESSIONS**



## 3 ABSTRACT

**STUDY OBJECTIVES:** The objectives of this Phase 1 study are: 1) to determine if dronabinol [the oral medication dosage form of THC (Δ-9-tetrahydrocannabinol), the primary psychoactive component of marijuana], when given during smoking of a marijuana cigarette changes the cardiovascular effects of smoked marijuana or has any other combination side effects, 2) to characterize the cardiovascular effects and the subjective effects of smoked marijuana in marijuana dependent volunteers, 3) to characterize the pharmacokinetics (PK) of smoked marijuana in the presence and absence of dronabinol, and 4) to determine the effect of dronabinol on marijuana withdrawal symptoms compared to placebo.

**STUDY DESIGN:** This in-patient study will be conducted in two parts as shown in **Figure 1**. Study Part 1 is intended as a pilot study to characterize the cardiovascular effects/safety, subjective effects, and PK of smoked marijuana and to familiarize study staff with the conduct of controlled smoking sessions. Study Part 2 is intended to examine the effects of dronabinol on withdrawal symptoms and to evaluate the safety, PK, and cardiovascular and subjective effects of the combination of oral dronabinol and smoked marijuana to determine if there are potential significant drug interactions before conducting outpatient studies. A maximum 28-day screening period will precede enrollment of volunteers into each part of the study. Subjects who complete Study Part 1 can be enrolled in Study Part 2; however, they must undergo all screening assessments to reconfirm eligibility. In Study Part 1, six (6) marijuana dependent volunteers will be enrolled and undergo controlled marijuana smoking sessions for two sequential days during which three repeated smoking sessions, one-hour apart, will be conducted each day along with measurements of cardiovascular effects, subjective effects, and THC PK. The first session each day will be with a placebo marijuana cigarette and each of the two following sessions will be with active marijuana cigarettes. After Part 1 is completed and safety is evaluated by the investigators and Medical Monitor, Part 2 will be a placebo-controlled, parallel group design study in which 12 marijuana dependent volunteers will be randomized to treatment with either dronabinol or placebo. This part of the study will be single-blind with respect to marijuana and placebo cigarette identity and double-blind with respect to dronabinol and placebo capsule identity. In Study Part 2, all volunteers will undergo the same two in-patient days of smoking sessions described above for the Study Part 1 volunteers, after which they will be randomized in a 1:1 ratio (6 per group) to one of two treatment groups: 1) dronabinol (10 mg 5 times-per-day on non-smoking session days and 10 mg 1 or 3 times-per-day on smoking sessions days) or 2) matched placebo capsules. Study Day 2 and 3 smoking sessions are intended to collect baseline measure as well as to allow a two-day period for all subjects to be exposed to a controlled amount of smoked marijuana. On the day of randomization, the 5-day withdrawal period of the study will begin by not allowing the subjects to smoke any marijuana cigarettes during this time. Withdrawal symptoms, subjective effects, and peak and trough plasma levels of THC and its major metabolite, 11-nor-Δ-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH), will be assessed during this part of the study. After completing the withdrawal period, the interaction period of part 2 of the study will begin. During the interaction period, two sequential days of smoking sessions will be conducted in the same manner as prior sessions.

**STUDY POPULATION:** Twelve (12) to eighteen (18) healthy male and female volunteers between the ages of 18 and 45 with Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for marijuana dependence determined by structured clinical interview (SCID) and who have a one-year history of marijuana use, provide one THC positive urine specimen which is negative for cocaine, amphetamines, opiates, and benzodiazepines during a maximum 28-day screening period and meet all other eligibility criteria will be enrolled in the study.

**TREATMENTS:** Two days of smoking sessions will be conducted during Study Part 1 and 4 days of smoking sessions will be conducted during Study Part 2 as shown in Figure 1. Each day's smoking session will consist of smoking a placebo cigarette followed by two-marijuana cigarettes spaced one hour apart. The subject will not be told the order in which they will receive the active marijuana and placebo marijuana cigarettes; however, study staff will know the identity and thus the study is considered to be single-blind with respect to this investigational agent. The active marijuana cigarettes contain approximately 3 % THC by weight (approximately 20 mg of THC). The placebo cigarettes are nearly identical in appearance and smell, except that cannabinoids are removed by solvent extraction. Smoking is conducted in a cued manner of 3 puffs with 40 seconds between puffs that is sufficient to pyrolize an entire cigarette. Each puff is timed for 5 seconds of inhalation and 10 seconds of holding in the lungs before exhaling. Subjects participating in study Part 2 will be randomized to double-blind treatment with dronabinol or matched placebo capsules on Study Days 4 - 10. Dronabinol, 10 mg, or placebo capsules will be taken 5 times per day at approximately 0800, 1100, 1400, 1700, and 2000 hours except on smoking session days when the 1100, and 1400 hour time points will be skipped because the subject will be smoking a marijuana cigarette and undergoing cardiovascular assessments during these time periods. In addition, dronabinol will not be taken after the completion of the last smoking session on Study Day 10.

**SAFETY ASSESSMENTS:** All candidates for study enrollment will have a medical and drug use history taken, SCID, physical examination, vital signs, blood chemistries, hematology, urinalysis, and infectious disease screen, and a baseline 12-lead ECG completed during screening. Medication use and a qualitative urine drug screen for THC, cocaine, amphetamines, opiates, and benzodiazepines will be assessed during screening and on the day of admission. Urine will be collected daily and sent to a central laboratory for quantitative 11-nor-Δ-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH) analysis. All women must have a negative pregnancy test within two days of clinic intake to be eligible. Vital signs will be assessed daily while in clinic with continuous cardiac monitoring of heart rate (HR) and blood pressure (BP) being conducted during smoking sessions and recorded every five minutes (q5min). ECG monitoring will be conducted 5 minutes prior to and at 5, 15, 30 and 55 minutes after the beginning of each smoking session, then hourly after the completion of the smoking sessions for approximately another 3 hours. Adverse Events (AEs) will be assessed daily during the inpatient period.

**PHARMACOKINETIC (PK) MEASURES:** THC PK will be assessed during Study Parts 1 and 2. On study days 2 and 3 (Study Part 1) and 2, 3, 9 and 10 (Study Part 2), blood will be collected 5 minutes prior to the start of the active marijuana cigarette smoking sessions and at 5, 15, 25, 40 and 55 minutes after the completion of the smoking of each active marijuana cigarette

and at and 2 and 3 hours after smoking the last active marijuana cigarette. In addition, urine at each time of voiding will be collected right before the start of the active marijuana cigarette smoking sessions and up to 24 hours following the start of the smoking session and will be tested for the two major metabolites of the forms of THC found in marijuana cigarettes including 11-nor-Δ-9-tetrahydrocannabivarin-9-carboxylic acid (THCV-COOH) and THC-COOH. In addition, in Study Part 2, plasma will be collected at peak and trough times (based on dronabinol $T_{max}$) on Study Days 4, 6, and 8, during the withdrawal period, when no marijuana cigarettes will be smoked to determine each individual's PK parameters throughout this period. THC and THC-COOH blood PK measures to be determined during smoking sessions include $C_{max}$, $T_{max}$, and $AUC_{0\text{-}55min}$ after the smoking of each marijuana cigarette with $AUC_{0\text{-}4\ hr}$ and $AUC_{0\text{-}\infty}$ also being calculated starting from the time of the first marijuana cigarette of the day.

**PSYCHOLOGICAL ASSESSMENTS:** The subjective effects of marijuana during smoking sessions and while taking dronabinol during the withdrawal period will be assessed using a 3-item visual analog scale (VAS). Marijuana withdrawal symptoms will be assessed daily using a 10-item Marijuana Withdrawal Symptom Checklist (MWSC).

**ANALYSIS:** The primary safety outcome measures, HR and BP, collected during each of the two active marijuana cigarette smoking periods per day will be compared separately between the group treated with dronabinol and the group treated with placebo capsules using repeated measures analysis of variance (ANOVA). These same comparisons will be performed for the secondary outcomes measures, VAS scores. Scores of individual items and total withdrawal discomfort score (WDS) generated from the MWSC will be plotted over time to examine trends in the severity of withdrawal symptoms. Mean scores in the groups treated with dronabinol or placebo capsules will be compared on individual days using a t-test or appropriate non-parametric test. No adjustments for multiple comparisons will be made.

Mean HR and BP over time will be plotted for each of the three sequential smoking periods per day for smoking sessions 1 and 2 for all 12 to 18 subjects in Study Parts 1 and 2. Each daily session's data will be examined separately. Time to peak change and peak changes in HR and BP may be compared between the first and second active marijuana cigarettes smoked during one day, if it appears that the effects do not parallel one another during each of these two smoking periods.

Changes in ECG readings during placebo marijuana smoking sessions and active marijuana smoking sessions will be reported for each of the three groups of six subjects (the first 6 subjects enrolled during Study Part 1 and the 6 subjects in each of the placebo capsule and dronabinol capsule groups in Study Part 2) as summary statistics. Likewise, the severity and frequency of AEs for these three groups will also be presented as summary statistics.

The mean and 90% confidence intervals for THC and THC-COOH blood PK parameters during each of the following study periods will be summarized:

1. The 55-minute period that blood was collected after each separate active marijuana cigarette was smoked ($AUC_{0\text{-}55min}$, $C_{max}$, and $T_{max}$) and $AUC_{0\text{-}4hr}$ and $AUC_{0\text{-}\infty}$ (where time 0 is the smoking start time for the first marijuana cigarette of the day).

2. Peak and trough levels of THC on study days 3, 5, and 7.|

Plasma THC concentrations over time will be plotted for all samples collected on smoking days. In addition, urinary kinetics for THCV-COOH and THC-COOH including excretion rate constant and half-life during active smoking sessions will also be determined and presented as summary statistics.

All statistical comparisons will be two-sided and a $p<0.05$ will be considered significant.

# 4 INTRODUCTION

## 4.1 Marijuana Dependence

### *4.1.1 Incidence and Prevalence*

Marijuana is the most commonly used illegal substance in the United States. In a recent survey reported by Substance Abuse and Mental Health Services Administration (SAMHSA), there were an estimated 2.6 million new marijuana users in 2001.[1] In 2002, over 14 million Americans age 12 and older used marijuana at least once in the month prior to being surveyed, and 12.2 percent of past year marijuana users used marijuana on 300 or more days in the past 12 months. This translates into 3.1 million people using marijuana on a daily or almost daily basis over a 12- month period. The latest treatment data indicate that, in 2004, marijuana was the primary drug of abuse in about 16 percent (298,317) of all admissions to treatment facilities in the United States. Marijuana admissions were primarily male (74 percent), white (54 percent), and young (44 percent under 20 years old). Those in treatment for primary marijuana use had begun use at an early age; 56 percent had used it by age 14 and 92 percent had used it by age 18.[2]

### *4.1.2 DSM Definition of Marijuana Abuse and Dependence*

The DSM defines marijuana abuse as repeated instances of use under hazardous conditions; repeated, clinically meaningful impairment in social/occupational/educational functioning; or legal problems related to marijuana use. Marijuana dependence is defined as increased tolerance, compulsive use, impaired control, and continued use despite physical and psychological problems caused or exacerbated by use.

### *4.1.3 Acute and Chronic Medical Conditions Associated with Marijuana Use*

The short-term effects of marijuana can include problems with memory and learning; distorted perception; difficulty in thinking and problem solving; loss of coordination; increased appetite, and tachycardia.[3,4,5] Use can cause burning and stinging of the mouth and throat, often accompanied by a heavy cough. Mittlemen *et al*.[6] reported that marijuana use is associated with a 4.8-fold increased risk of myocardial infarction within one hour of smoking, presumably due to marijuana's effect on hemodynamic consequences, including a dose-dependent increase in heart rate, supine hypertension, and postural hypotension.

Long term use is associated with cognitive deficits leading to behavior changes, altered social relationships, educational underachievement, reduced workplace productivity, motor vehicle

accidents, general health problems, epithelial damage to the lungs, possible increased risk of infection, and increased risk of use of other substances.[7]

In a randomized controlled trial assessing two types of psychosocial interventions for marijuana dependence, 60 subjects seeking treatment for marijuana dependence with no other alcohol or drug dependence diagnosis other than nicotine had a mean Beck's Depression Inventory (BDI) score of 15.8 (SD = 10) reflecting a moderate depressive symptomatology in this population.[8] In addition, although the eligibility criteria for this study excluded subjects with any active psychosis or other severe psychiatric disorder as determined by SCID, the average t score on the global symptom index of the Brief Symptom Inventory (BSI) was 66.8 (SD = 11). Scores above 62 indicate clinically significant psychiatric symptoms compared to a non-psychiatric population.[9] Budney *et al*.[10] compared sociodemographics, substance use, psychosocial functioning, psychiatric symptoms, and medical status in 62 individuals seeking treatment for marijuana dependence to 70 treatment-seeking, cocaine-dependent individuals. They reported that substantial psychosocial and psychiatric problems were observed in both groups. In general, the marijuana group reported substance-use histories and a range of impairment comparable with the cocaine group; however, they showed less severe dependence. Other studies have also reported a relationship between depression,[11] anxiety,[12,13] and personality disturbances[14] with marijuana use. Marijuana's adverse impact on memory and learning can last for days or weeks after the acute effects of the drug wears off.[15,16]

Students who smoke marijuana get lower grades and are less likely to graduate from high school, compared with their non-smoking peers.[17-20] A study of 129 college students found that, for heavy users of marijuana (those who smoked the drug at least 27 of the preceding 30 days), critical skills related to attention, memory, and learning were significantly impaired even after they had not used the drug for at least 24 hours.[16] The heavy marijuana users in the study had more trouble sustaining and shifting their attention and in registering, organizing, and using information than did the study subjects who had used marijuana no more than 3 of the previous 30 days. More recently, the same researchers showed that the ability of a group of long-term heavy marijuana users to recall words from a list remained impaired for a week after quitting, but returned to normal within 4 weeks.[21] Thus, it is possible that some cognitive abilities may be restored in individuals who quit smoking marijuana, even after long-term heavy use. One study suggested that early age of onset of marijuana use may be associated with long term cognitive deficits, particularly verbal intelligence quotient.[22]

Several studies associate workers' marijuana smoking with increased absences, tardiness, accidents, workers' compensation claims, and job turnover. A study of municipal workers found that those who used marijuana on or off the job reported more withdrawal behaviors such as leaving work without permission, daydreaming, spending work time on personal matters, and shirking tasks that adversely affect productivity and morale.[23] In another study, marijuana users reported that use of the drug impaired several important measures of life achievement including cognitive abilities, career status, social life, and physical and mental health.[4]

A study of 450 individuals found that people who smoke marijuana frequently but do not smoke tobacco have more health problems and miss more days of work than nonsmokers primarily due to respiratory illnesses.[24] Someone who smokes marijuana regularly may have many of the same

respiratory problems that tobacco smokers do, such as daily cough and phlegm production, more frequent acute chest illness, a heightened risk of lung infections, and a greater tendency to obstructed airways.[25] Smoking marijuana has been reported to increase the likelihood of developing cancer of the head or neck, and the more marijuana smoked the greater the increase.[26] A study comparing 173 cancer patients and 176 healthy individuals produced strong evidence that marijuana smoking doubled or tripled the risk of these cancers. Marijuana use also has the potential to promote cancer of the lungs and other parts of the respiratory tract because it contains irritants and carcinogens.[27] In fact, marijuana smoke contains 50 to 70 percent more carcinogenic hydrocarbons than does tobacco smoke.[28] It also produces high levels of an enzyme that converts certain hydrocarbons into their carcinogenic form at levels that may accelerate the changes that ultimately produce malignant cells.[3] Marijuana users usually inhale more deeply and hold their breath longer than tobacco smokers do, which increases the lungs' exposure to carcinogenic smoke.

Research has shown that babies born to women who used marijuana during their pregnancies display altered responses to visual stimuli, increased tremulousness, and a high-pitched cry, which may indicate neurological problems in development.[29] During infancy and preschool years, marijuana-exposed children have been observed to have more behavioral problems than unexposed children and poorer performance on tasks of visual perception, language comprehension, sustained attention, and memory.[30,31] In school, these children are more likely to exhibit deficits in decision-making skills, memory, and the ability to remain attentive.[30-32]

### *4.1.4 Marijuana Withdrawal Syndrome*

A distinctive marijuana withdrawal syndrome has been identified, but it is mild and short-lived.[33] Symptoms first appear in habitual users within 24 hours and are the most noticeable during the first 10 days, but withdrawal symptoms may last as long as 28 days. The syndrome includes restlessness, irritability, anxiety, insomnia, sleep EEG disturbance, nausea, anorexia, stomach pain, anger, depressed mood, headaches, strange dreams, and cravings for marijuana.[34] During withdrawal, some patients display increased aggression on psychological tests, peaking approximately one-week after the last use of the drug.[34] Budney *et al*. [33] have developed and validated a Marijuana Withdrawal Symptom Checklist (MWSC) comprised of the most commonly reported symptoms of withdrawal experienced by marijuana smokers seeking treatment for dependence. This symptom checklist was reported to have a reliability $\alpha = 0.89$ supporting its use as a withdrawal severity scale. In addition, the items included on this scale have been used by others investigating marijuana withdrawal in the in-patient clinical setting.[13,34-38]

### *4.1.5 Marijuana Abuse, Medical Use, and Mechanism of Action*

Marijuana is a dried, shredded green/brown mix of flowers, stems, seeds, and leaves of the hemp plant Cannabis sativa that is usually smoked as a cigarette or in a pipe. It is also smoked in blunts, which are cigars that have been emptied of tobacco and refilled with marijuana, often in combination with another drug. Use also might include mixing marijuana in food or brewing it as a tea. As a more concentrated, resinous form it is called hashish and, as a sticky black liquid, hash oil. The main active chemical in marijuana is Δ-9-tetrahydrocannabinol (THC). The THC in

smoked marijuana rapidly passes from the lungs into the bloodstream, which carries it throughout the body, including the brain. In the brain, THC binds to cannabinoid receptors many of which are found in the parts of the brain that influence pleasure, memory, thought, concentration, sensory and time perception, and coordinated movement.[39] Autoradiography of cannabinoid receptors in brain sections from several mammalian species, including human, reveals a unique and conserved distribution; binding is most dense in outflow nuclei of the basal ganglia, the substantia nigra pars reticulata and globus pallidus, and in the hippocampus and cerebellum.[39] Generally, high densities in forebrain and cerebellum implicate roles for cannabinoids in cognition and movement. Sparse densities in lower brainstem areas controlling cardiovascular and respiratory functions may explain why high doses of THC are not lethal. Smoked cannabis produces a dreamy state of consciousness in which ideas seem disconnected, unanticipated, and free-flowing. Time, color, and spatial perceptions may be altered. In general, a feeling of well-being and relaxation (a "high") results. These effects last 2 to 3 hours after inhalation.

THC has been approved by the FDA under the trade name of MARINOL® (common name dronabinol) for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional treatments and of appetite loss associated with weight loss in people with acquired immunodeficiency syndrome (AIDS). In addition, it has been recommended in a recent report by the Institute of Medicine as a treatment for pain due to its analgesic effects. Evidence for the addictive properties of marijuana has been shown in animals. In a study in Sprague-Dawley rats, the effects of THC and heroin on *in vivo* dopamine transmission in the nucleus accumbens were compared by brain microdialysis.[40] THC and heroin increased extracellular dopamine concentrations selectively in the shell of the nucleus accumbens; these effects were mimicked by the synthetic cannabinoid agonist WIN55212-2. SR141716A, an antagonist of central cannabinoid receptors, prevented the effects of THC but not those of heroin. Naloxone, a generic opioid antagonist, administered systemically, or naloxonazine, an antagonist of mu1 opioid receptors, infused into the ventral tegmentum, prevented the action of cannabinoids and heroin on dopamine transmission. Thus, THC and heroin exert similar effects on mesolimbic dopamine transmission through a common mu1 opioid receptor mechanism located in the ventral mesencephalic tegmentum.

### *4.1.6 Pharmacology of THC and THCV*

The information on the pharmacology of THC is mainly from studies of the orally administered FDA licensed form of the drug, dronabinol. Dronabinol is highly protein bound and may displace other protein-bound drugs. THC is readily absorbed from the gastrointestinal tract. The systemic availability, following oral administration, is 10 to 20% relative to an intravenous dose indicating extensive first pass metabolism. Maximum plasma concentrations appear approximately 2 to 3 hours after oral dosing. THC has a long half-life (approximately 60 hours) due to sequestration in body tissues and to enterohepatic recirculation.

THC is metabolized chiefly in the liver where it is converted to THC-COOH and more than 20 other metabolites. The 11-hydroxy-metabolite is psychoactive and appears in the plasma in roughly the same quantities as the parent drug. It has a terminal half-life of approximately 15 to 18 hours. Biliary excretion is the major route of elimination. Within 72 hours following oral

administration, approximately 50% of the dose is recovered in the feces; another 10 to 15% appears in the urine either unchanged or as a metabolite. After exposure to THC, additive hypertension might occur with amphetamines, cocaine, and other sympathomimetic agents; additive tachycardia with atropine, antihistamines and other anticholinergic agents; additive drowsiness and CNS depression with benzodiazepines, barbiturates, antihistamines, muscle relaxants and other CNS depressants.

Heustis *et al*. (1992) examined the kinetics of drug effect and the PK of THC after controlled smoking of two different concentrations of marijuana cigarettes (1.75% or 3.55% THC) in 6 male volunteers.[41] Rapid blood sampling with a continuous withdrawal pump allowed simultaneous collection with concurrent physiologic and behavioral measures. Mean plasma levels of 7.0 and 18.1 ng/ml THC were observed after the first inhalation of a 1.75% and 3.55% THC cigarettes, respectively. Blood levels increased rapidly and peaked at 9 minutes, before initiation of the last puff sequence at 9.8 minutes. Three of six subjects reported increases in drug "liking" scores after the first puff, and all subjects responded by the second puff of a high dose cigarette. Significant increases in heart rate and diastolic blood pressure occurred shortly after peak blood levels. This study showed that behavioral and physiologic effects appear concurrently or within minutes after the rapid appearance of THC in blood during marijuana smoking.

THCV is the C3 homologue of THC and a natural component of most cannabis products but it does not exist in dronabinol.[42] THCV is metabolized by human hepatocytes to THCV-COOH; therefore, the presence of the latter in a urine specimen would indicate that the donor must have used marijuana or a related product (with or without dronabinol). Therefore, the rate of excretion of THCV-COOH in urine after active smoking sessions can be assessed even in individuals who have taken drabinol.

### *4.1.7 Cardiovascular Effects of Smoked Marijuana*

Heustis et al. (2001) examined the effects of smoked marijuana in marijuana experienced volunteers on heart rate.[43] In this study, healthy volunteers smoked an active marijuana cigarette containing 2.64% THC divided into 8 puffs at 60-second intervals. Heart rate was significantly increased by a mean of 30 beats per minute with the peak occurring 15 minutes after smoking. At 60 minutes after smoking, the mean heart rate had decreased but was still 15 beats per minute above placebo smoking controls.

Receptor-mediated and probably nonneuronal sites of action account for cannabinoid effects on the cardiovascular system. The biological effects of cannabinoids are mediated by specific receptors. Two cannabinoid receptors have been identified so far: CB1-receptors are expressed by different cells of the brain and in peripheral tissues, while CB2-receptors were found almost exclusively in immune cells. Through the use of a selective CB1 receptor antagonist and CB1 receptor-knockout mice, the hypotensive and bradycardic effects of cannabinoids in rodents was attributed to activation of peripheral CB1 receptors.[44,45] In hemodynamic studies using the radioactive microsphere technique in anesthetized rats, cannabinoids were found to be potent CB1-receptor dependent vasodilators in the coronary and cerebrovascular beds. These findings implicate the endogenous cannabinoid system in the pathologic mechanism of hemorrhagic, endotoxic and cardiogenic shock. Finally, there is evidence that the extreme mesenteric

vasodilation, portal hypertension and systemic hypotension present in advanced liver cirrhosis are also mediated by the endocannabinoid system.

### *4.1.8 Current Treatment Practices for Marijuana Dependence*

Most interventions for marijuana dependence are based on adaptations of alcohol interventions and include individual or group therapy focused on education regarding the deleterious effects of marijuana use and changing behavior patterns such as triggers and situations that allow for marijuana use.[46] Some clinics offer anti-anxiety prescriptions and vitamin supplements in addition to counseling. Marijuana Anonymous is a 12-step program in the US that follows the fellowship movements of Alcoholics and Narcotics Anonymous. No medications are currently available for treating marijuana dependence. While 16% of admissions to treatment facilities indicate that marijuana is the primary drug of abuse [Treatment Episode Data Set (TEDS), 1994 – 2004][2], there have been very few systemic clinical research studies to evaluate the efficacy of different treatment modalities.

### *4.1.9 Medication Studies*

Several small Phase 1 clinical trials have been conducted by Haney *et al*.[13,36-38,47] to examine the effects of medications on marijuana withdrawal symptoms or on the blockade of the subjective and cardiovascular effects of marijuana. The effects of nefazodone, which is an antidepressant with sedative properties, was studied on the withdrawal symptoms of marijuana.13 This placebo-controlled study evaluated 7 research volunteers (1 female and 6 male) for a 52-day study period with inpatient and outpatient days. Marijuana was smoked 5 times per inpatient day. On inpatient days 5-8, only active marijuana was smoked, while on days 9-16, only placebo marijuana was smoked. Patients were maintained on two doses of nefazodone (450 mg/day). Mood, psychomotor task performance, food intake and sleep were measured daily. The result of the study showed that nefazodone maintenance did not alter the acute effects of active marijuana as compared to placebo. However, during marijuana withdrawal, nefazodone decreased ratings “anxious”, and “muscle pain”, while having no effect on the marked increase in ratings of “irritable”, “miserable” or decreased sleep quality. In the conclusion, nefazodone decreased certain marijuana withdrawal symptoms, but subjects still reported substantial discomfort. These data provide further evidence of marijuana withdrawal, and highlight the need for more marijuana treatment options.

Two other studies were completed on effects of oral THC (designated Study #1) and divalproex, a mood stabilizer (designated Study #2), on marijuana withdrawal symptoms.[38] The focus of these two studies was to determine if either a cannabinoid agonist, oral THC, or a mood stabilizer, divalproex, would attenuate a broader range of marijuana withdrawal symptoms than the antidepressants. The rationale for using a cannabinoid agonist such as THC to treat marijuana dependence is similar to the rationale for using the opioid agonist, methadone, to treat opioid dependence. There are a number of important similarities between methadone and oral THC: both have a slow onset and a long duration of action compared to heroin or smoked marijuana. As a slow-acting agonist, oral THC is predicted to decrease craving and symptoms of marijuana withdrawal at doses that produce minimal intoxication. The rationale for testing divalproex was that it has been used to treat irritability, mood lability, and temper outbursts, which are similar to symptoms of marijuana withdrawal. These two studies demonstrated that: 1) oral THC

administration decreased a subset of marijuana withdrawal symptoms compared to placebo administration in Study #1; and 2) maintenance on divalproex prior to and during marijuana abstinence markedly worsened mood, as well as performance on a range of cognitive tasks in Study #2. Therefore, these data suggested that oral THC attenuated symptoms of withdrawal at doses that produce no apparent subjective effects. Unlike the agonist approach to treating marijuana withdrawal used in Study #1, Study #2 showed that divalproex worsened mood ratings of irritability, edginess, anxiety, and sleepiness during abstinence from marijuana, and decreased the amount of time subjects chose to spend in a social setting.

Given the successful use of sustained-release bupropion in treating nicotine dependence, Haney *et al*. (2001) investigated how maintenance on bupropion influenced symptoms of marijuana withdrawal compared to maintenance on placebo.36 In this study, marijuana smokers (n=10) were maintained outpatient on active (300 mg/day) or placebo (0 mg/day) bupropion for 11 days, and were then maintained inpatient on the same bupropion dose for 17 days. For the first 4-inpatient days, subjects smoked active marijuana (2.8% THC) 5 times/day. For the remaining inpatient days, subjects smoked placebo marijuana (0.0% THC) 5 times/day. Subjects were then maintained outpatient on the alternate dose of bupropion for 11 days, followed by a second inpatient residential stay, paralleling the first. Bupropion had few behavioral effects when subjects smoked active marijuana, however, during placebo marijuana smoking, i.e., active marijuana withdrawal, ratings of irritability, restlessness, depression, and trouble sleeping were increased by bupropion compared to placebo maintenance. Thus, bupropion does not show promise as a potential treatment medication for marijuana dependence.

## 4.2 Dronabinol

Dronabinol (trade name MARINOL®) is a cannabinoid designated chemically as (*6aR-trans*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[*b,d*] pyran-1-ol. Dronabinol, the active ingredient in MARINOL® capsules, is synthetic THC. THC is also a naturally occurring component of Cannabis sativa (marijuana).

### *4.2.1 Rationale for Studying Dronabinol*

Specific neurotransmitter receptor agonists such as methadone are successful in treating substance abuse and dependence by minimizing the early withdrawal effects after cessation of use. As a slow-acting agonist, oral THC is predicted to decrease craving and symptoms of marijuana withdrawal at doses that produce minimal intoxication and has been shown in a small Phase 1 study to attenuate several of the withdrawal symptoms associated with marijuana cessation, specifically ratings of anxious, irritable, trouble sleeping, chills, craving, and large decreases in food intake. Because oral THC in combination with smoked THC has the potential to result in increased cardiovascular effects, it is important to more fully characterize the cardiovascular effects of smoked THC and determine if there are significant safety concerns when combining smoked and oral dosage forms before conducting a larger outpatient study.

### *4.2.2 Pharmacology of Dronabinol*

Dronabinol is an orally active cannabinoid, which, like other cannabinoids, has complex effects on the central nervous system (CNS), including central sympathomimetic activity. Cannabinoid

receptors have been discovered in neural tissues. These receptors may play a role in mediating the effects of dronabinol and other cannabinoids. Dronabinol-induced sympathomimetic activity may result in tachycardia and/or conjunctival injection. Its effects on blood pressure are inconsistent, but occasional subjects have experienced orthostatic hypotension and/or syncope upon abrupt standing. Dronabinol also demonstrates reversible effects on appetite, mood, cognition, memory, and perception. These phenomena appear to be dose-related, increasing in frequency with higher dosages, and subject to great interpatient variability. After oral administration, dronabinol has an onset of action of approximately 0.5 to 1 hours and peak effect at 2 to 4 hours. Duration of action for psychoactive effects is 4 to 6 hours, but the appetite stimulant effect of dronabinol may continue for 24 hours or longer after administration. Tachyphylaxis and tolerance develop to some of the pharmacologic effects of dronabinol and other cannabinoids with chronic use, suggesting an indirect effect on sympathetic neurons. In a study of the pharmacodynamics of chronic dronabinol exposure, healthy male volunteers (N=12) received 210 mg/day dronabinol, administered orally in divided doses, for 16 days (dronabinol Package Insert). An initial tachycardia induced by dronabinol was replaced successively by normal sinus rhythm and then bradycardia. A decrease in supine blood pressure, made worse by standing, was also observed initially. These volunteers developed tolerance to the cardiovascular and subjective adverse CNS effects of dronabinol within 12 days of treatment initiation. Tachyphylaxis and tolerance do not, however, appear to develop to the appetite stimulant effect of dronabinol capsules. In studies involving patients with AIDS, the appetite stimulant effect of dronabinol capsules has been sustained for up to five months in clinical trials, at dosages ranging from 2.5 mg/day to 20 mg/day.

***Absorption and Distribution:*** Dronabinol is almost completely absorbed (90 to 95%) after single oral doses. Due to the combined effects of first pass hepatic metabolism and high lipid solubility, only 10 to 20% of the administered dose reaches the systemic circulation. Dronabinol has a large apparent volume of distribution, approximately 10 L/kg, because of its lipid solubility. The plasma protein binding of dronabinol and its metabolites is approximately 97%. The elimination phase of dronabinol can be described using a two compartment model with an initial (alpha) half-life of about 4 hours and a terminal (beta) half-life of 25 to 36 hours. Because of its large volume of distribution, dronabinol and its metabolites may be excreted at low levels for prolonged periods of time.

***Metabolism:*** Dronabinol undergoes extensive first-pass hepatic metabolism, primarily by microsomal hydroxylation, yielding both active and inactive metabolites. Dronabinol and its principal active metabolite, THC-COOH, are present in approximately equal concentrations in plasma. Concentrations of both parent drug and metabolite peak at approximately 2 to 4 hours after oral dosing and decline over several days. Values for clearance average about 0.2 L/kg-hr, but are highly variable due to the complexity of cannabinoid distribution.

***Elimination:*** Dronabinol and its biotransformation products are excreted in both feces and urine. Biliary excretion is the major route of elimination with about half of a radiolabeled oral dose being recovered from the feces within 72 hours as contrasted with 10 to 15% recovered from urine. Less than 5% of an oral dose is recovered unchanged in the feces. Following single dose administration, low levels of dronabinol metabolites have been detected for more than 5 weeks in the urine and feces.

### *4.2.3 Safety of Dronabinol*

Adverse experiences information was derived from well-controlled clinical trials conducted in the US and US territories involving 474 patients exposed to dronabinol (dronabinol Package Insert). Studies of AIDS-related weight loss included 157 patients receiving dronabinol at a dose of 2.5 mg twice daily and 67 receiving placebo. Studies of different durations were combined by considering the first occurrence of events during the first 28 days. Studies of nausea and vomiting related to cancer chemotherapy included 317 patients receiving dronabinol and 68 receiving placebo. A cannabinoid dose-related "high"(easy laughing, elation and heightened awareness) has been reported by patients receiving dronabinol capsules in both the antiemetic (24%) and the lower dose appetite stimulant clinical trials (8%). The most frequently reported adverse experiences in patients with AIDS during placebo-controlled clinical trials involved the CNS and were reported by 33% of patients receiving dronabinol capsules. About 25% of patients reported a minor CNS adverse event during the first 2 weeks and about 4% reported such an event each week for the next 6 weeks thereafter. Rates derived from clinical trials in AIDS- related anorexia (N=157) and chemotherapy-related nausea (N=317). The probably causally related incidence of AEs occurring 3% to 10% were the following: asthenia, palpitations, tachycardia, vasodilation/ facial flush, abdominal pain, nausea, vomiting, amnesia, anxiety/nervousness, ataxia, confusion, depersonalization, dizziness, euphoria, hallucinations, paranoid reaction, somnolence, and abnormal thinking.

### *4.2.4 Other Safety, Drug Abuse and Dependence Concerns*

Dronabinol is considered abusable and is controlled [Schedule III (CIII)] under the Controlled Substances Act. Both psychological and physiological dependence have been noted in healthy individuals receiving dronabinol, but addiction is uncommon and has only been seen after prolonged high dose administration. Chronic abuse of cannabis has been associated with decrements in motivation, cognition, judgment, and perception. The etiology of these impairments is unknown, but may be associated with the complex process of addiction rather than an isolated effect of the drug. No such decrements in psychological, social or neurological status have been associated with the administration of dronabinol capsules for therapeutic purposes. In an open-label study in patients with AIDS who received dronabinol Capsules for up to five months, no abuse, diversion or systematic change in personality or social functioning were observed despite the inclusion of a substantial number of patients with a past history of drug abuse. An abstinence syndrome has been reported after the abrupt discontinuation of dronabinol in volunteers receiving dosages of 210 mg/day for 12 to 16 consecutive days. Within 12 hours after discontinuation, these volunteers manifested symptoms such as irritability, insomnia, and restlessness. By approximately 24 hours post-dronabinol discontinuation, withdrawal symptoms intensified to include "hot flashes", sweating, rhinorrhea, loose stools, hiccoughs and anorexia. These withdrawal symptoms gradually dissipated over the next 48 hours. Electroencephalographic (EEG) changes consistent with the effects of drug withdrawal (hyperexcitation) were recorded in patients after abrupt dechallenge. Patients also complained of disturbed sleep for several weeks after discontinuing therapy with high doses.

## 5 STUDY OBJECTIVES

The main objectives of this pilot/Phase 1 study are:

1. to determine if dronabinol when given during smoking of a marijuana cigarette changes the cardiovascular effects of smoked marijuana or has any other combination side effects,
2. to characterize the cardiovascular effects and the subjective effects of smoked marijuana in marijuana dependent volunteers,
3. to characterize the PK of smoked marijuana in the presence and absence of dronabinol, and
4. to determine the effect of dronabinol on marijuana withdrawal symptoms compared to a placebo group.

## 6 STUDY SPONSOR

NIDA will be the Investigational New Drug (IND) application holder and study sponsor.

## 7 STUDY SITE

This study will be conducted in the Clinical Pharmacology Unit of the Uniformed Services University of Health Sciences in Bethesda, Maryland.

## 8 STUDY DESIGN

This in-patient study will be conducted in two parts as shown in **Figure 1**. Study Part 1 is intended as a pilot study to characterize the cardiovascular effects, subjective effects, and PK of smoked marijuana and to familiarize study staff with the conduct of controlled smoking sessions. Study Part 2 is intended to examine the effects of dronabinol on withdrawal symptoms and to evaluate the safety, PK, and cardiovascular effects of the combination of oral dronabinol and smoked marijuana to determine if there are potential significant drug interactions before conducting outpatient studies.

A maximum 28-day screening period will precede enrollment of volunteers into either part of the study. During this screening period, candidates must have a rapid urine drug screen positive for THC and negative for cocaine, amphetamines, opiates, and benzodiazepines. Candidates must also have a one-year history of marijuana use and a diagnosis of dependence; however, it is expected that a combination of light to fairly heavy (heavy use is defined as 3-6 marijuana cigarettes per day 6-7 days per week) users will be enrolled. In Study Part 1, six (6) marijuana dependent volunteers will be enrolled and undergo controlled marijuana smoking sessions for two sequential days during which three repeated smoking sessions, one-hour apart, will be conducted each day along with measurements of cardiovascular effects, subjective effects, and THC and THC-COOH PK. The first session each day will be with a placebo marijuana cigarette and each of the two following sessions will be with active marijuana cigarettes. Before starting Study Part 2, all safety data will be evaluated by the Principal Investigator, NIDA Investigators and the NIDA Medical Monitor. As the extent of cardiovascular effects of smoked marijuana have not been systematically studied with this dose of marijuana, it will be important to examine the magnitude of the effects before starting Study Part 2.

After Study Part 1 is completed, the second part of the study will be a placebo-controlled, parallel group design study in which 12 marijuana dependent volunteers will be randomized to treatment with either dronabinol or placebo. This part of the study will be single-blind with respect to marijuana and placebo cigarette identity and double-blind with respect to dronabinol and placebo capsule identity. Subjects who complete Study Part 1 can be enrolled in Study Part 2; however, they must undergo all screening assessments to reconfirm eligibility. In Study Part 2, all volunteers will undergo the same two in-patient days of smoking sessions described above for the Study Part 1 volunteers. These smoking sessions will provide baseline data on the cardiovascular and subjective effects as well as THC and THC-COOH PK parameters before the withdrawal period. On Study Day 4, subjects will be randomized equally to receive either dronabinol or placebo. Six subjects will receive dronabinol 10 mg 5 times per day on non-smoking session days and three times per day on smoking session days. Six subjects will receive matched placebo on the same schedule. On the last smoking session day, Day 10, only the first (8 am) dose of dronabinol/placebo will be administered. On the day of randomization, the 5-day withdrawal period of the study will begin by not allowing the subjects to smoke any marijuana cigarettes during this time. Withdrawal symptoms, subjective effects, and peak and trough plasma levels of THC and THC-COOH will be assessed during this period. After completing the withdrawal period, the interaction period of the study will begin. During the interaction period two sequential days of smoking sessions will be conducted in the same manner as prior sessions.

## 9 SUBJECT SELECTION

Twelve (12) to eighteen (18) healthy males and females between 18 and 45 years-of-age with a diagnosis of marijuana dependence according to DSM-IV criteria will be enrolled in the study. As dronabinol has not been examined in pediatric or elderly populations and the population should not have cardiovascular conditions, the ages have been restricted to 18 though 45 years, inclusive. To confirm the diagnosis of marijuana dependence and lack of abuse or dependence on other drugs of abuse, each candidate must have a positive urine drug screen for marijuana (THC > 50 ng/mL using an FDA approved rapid test device) that is also negative for cocaine, amphetamines, opiates, and benzodiazepines.

### 9.1 Inclusion Criteria

Potential subjects **must:**

1. Be men and women between 18 and 45 years-of-age.
2. Have a DSM-IV diagnosis of current marijuana dependence as determined by SCID.
3. Be able to provide written informed consent.
4. Be willing and able to comply with study procedures including being able to participate in an in-patient study lasting 3-4 days (study Part 1) or 12 days (study Part 2).
5. Report regular marijuana use for the past year.
6. Provide 1 marijuana positive urine specimen (> 50 ng/mL) within the 28-day screening period.
7. Be in general good health as determined by medical and psychiatric history, physical exam, vital signs, blood chemistries, hematology, medical urinalysis, infectious disease screen, current medication use, and ECG.

8. If female, have a negative pregnancy test and agree to use of one of the following methods of birth control or be surgically sterile:

    a. oral contraceptives
    b. patch
    c. barrier (diaphragm or condom) with spermicide or condom only
    d. intrauterine progesterone or non-hormonal contraceptive system
    e. levonorgestrel implant
    f. medroxyprogesterone acetate contraceptive injection
    g. complete abstinence from sexual intercourse
    h. hormonal vaginal contraceptive ring
    i. contraceptive sponge

### 9.2 Exclusion Criteria

Potential subjects **must not:**

1. Be using any prescription medication to treat a chronic medical condition.
2. Have a lifetime history of psychosis or current major psychiatric disorder requiring treatment, or current schizophrenia or bipolar disorders.
3. Have cardiovascular problems such as tachyarrythmias, angina pectoris, or hypertension.
4. Be pregnant or lactating (THC is secreted in breast milk).
5. Have participated in any experimental study within 8 weeks (the nature of excluded studies may be discussed with NIDA investigators).
6. Have donated blood (>200 cc) in the past 4-weeks prior to clinic intake.
7. Have current physical dependence on any substance (including alcohol) other than nicotine or caffeine.
8. Have a positive urine drug screen or report using drugs during the 28-day screening period for the following drugs: cocaine, amphetamines, opiates, and benzodiazepines.
9. Have a history of seizure disorders of any etiology.
10. Have clinically significant laboratory values (outside of normal limits), in the judgment of the investigator.
11. Have a positive test for hepatitis B surface antigen (HBsAg), or positive serology for hepatitis C virus or human immunodeficiency virus-1 (HIV-1).
12. Have sensitivity to marijuana, other cannabinoids, or sesame oil.
13. Have received a medication that could interact adversely with study drug, with the time of administration of study drug and other medications based on the longest time interval of A, B, or C, below:

    A) Five half lives of other medication or active metabolite(s), whichever is longer
    B) Two weeks
    C) Interval recommended by other medication's product labeling

Medications that fall into this category include: drugs that are tightly protein bound.

**Notes on inclusion/exclusion criterion:** If any clinical findings and tests are positive or clinically significant, the subject will be notified of the test results and counseled to consult with his/her physician for evaluation and treatment.

## 10 INVESTIGATIONAL AGENTS

**Dronabinol and Placebo Capsules:** Dronabinol is manufactured by Banner Pharmacaps Inc. for Unimed Pharmaceuticals Inc., a Solvay Pharmaceuticals Inc., Company. Ten (10) mg dronabinol solution in sesame oil in soft gelatin capsules (NDC 0051-0023-21) are orange, identified by UM or RL. Drabinol will be purchased from a licensed source. Drabinol will be over encapsulated for blinding purposes. The placebo capsule will be identically matched to the capsule used to over encapsulate drabinol but will have an inert filler. Capsules will be prepared by the local site pharmacy.

**Marijuana Cigarettes and Placebo Marijuana Cigarettes:** Marijuana and placebo marijuana cigarettes will be supplied by NIDA. The active marijuana cigarettes contain approximately 3 % THC by weight (approximately 20 mg of THC). The placebo cigarettes are nearly identical in appearance and smell, except that cannabinoids are removed by solvent extraction.

### 10.1 Randomization to Treatment

The data management center will supply the research pharmacist with 12 envelopes each containing the treatment assignment to dronabinol or placebo capsule for subjects enrolled in Part 2 of the study. Each envelope will contain a randomization number for the subject that will be used to track the treatment assignment. Only the research pharmacist will have access to the treatment assignment, unless the treatment is to be unblinded. A block randomization scheme will be prepared by the data management center.

### 10.2 Dispensing Investigational Agents

Dronabinol or placebo capsules will be dispensed directly to the subject by a study nurse each time they are scheduled to receive a capsule. Dronabinol, 10 mg, or placebo capsules will be taken 5 times per day at approximately 0800, 1100, 1400, 1700, and 2000 hours except on smoking session days when the 1100, and 1400 hour time points will be skipped because the subject will be smoking a marijuana cigarette and undergoing cardiovascular assessments during these time periods. On the last day that the subject is scheduled to receive dronabinol, Study Day 10, capsules will only be taken at 0800 and will not be resumed after the end of the smoking sessions. A record of the time each capsule is dispensed will be made on an Investigational Agent Dispensing CRF. Marijuana and placebo cigarettes will be provided to the subject immediately prior to each scheduled smoking session. The end of each cigarette will be tightly rolled and smoked through a plastic cigarette holder to obscure the contents of the cigarette (the placebo cigarettes are not quite as green in appearance as the active marijuana cigarettes).

### 10.3 Blinding Plan

Dronabinol and placebo capsules will be double-blinded. The identity of the active and placebo cigarettes will be known to study staff but blinded to the subject (single-blinded). Subjects will

not be told the order in which they will receive active or placebo marijuana cigarettes to maintain the blind. In addition, the end of the cigarette will be twisted closed to obscure the contents, as the extracted marijuana has a slightly different color than the active marijuana.

### 10.4 Labeling

Capsules will be packaged in high-density polyethylene bottles with sufficient capsules for the subject for the entire treatment period. The label on the bottle will include the subject's randomization code number, the protocol number, number of tablets, directions for use the words "Caution: New Drug – Limited by federal law to investigational use; expiration date and lot number" (the same expiry date and lot number will be used for placebo capsules as that of the actual drug).

### 10.5 Storage

**Dronabinol Capsules** should be packaged in a well-closed container and stored in a cool environment between 8° and 15°C (46° and 59°F) and alternatively could be stored in a refrigerator. Protect from freezing.

**Marijuana and placebo cigarettes** should be stored frozen in an airtight container and humidified at room temperature for 24 hours prior to use.

### 10.6 Used/Unused Supplies

At the end of the study, all unused investigational agents must be inventoried. If any investigational agent is lost or damaged, its disposition should be documented. Unused investigational agents will be retained at the clinic site pending instructions for disposition by the Sponsor at the end of the study.

### 10.7 Instructions for Subjects on Use of Investigational Agents

Dronabinol must be swallowed whole to work effectively. Instruct the subject to not crush or chew the capsules.

### 10.8 Conduct of Smoking Sessions

Smoking sessions will be conducted using controlled timing of events that has been shown to produce reliable increases in heart rate and plasma levels of THC.[38,48] A study staff member will use a timer to track the timing of events and will state the following actions to the subject to signal the beginning of the activity period: 1) light the cigarette – wait 30 seconds, 2) get ready – wait 5 seconds, 3) inhale – wait 5 seconds, 4) hold smoke in lungs – wait 10 seconds, and 5) exhale. A maximum of 5 puffs will be smoked in this manner with a 5 second delay between puffs. If the entire cigarette is pyrolized before the fifth puff, no further inhalations will be performed.

## 11 STUDY PROCEDURES

Tables 1 and 2 show the schedule of Time and Events for Study Parts 1 and 2, respectively.

**Table 1. Time and Events for Part 1 of the Study**

| Study Period | Screening | In-Clinic | | | Clinic Release |
|---|---|---|---|---|---|
| **Study Day** | **- 28 to-1** | **1** | **2** | **3** | **4-5** |
| **Screening Assessments** | | | | | |
| Informed Consent | X | | | | |
| SCID/Psych Evaluation | X | | | | |
| Demographics | X | | | | |
| Medical History | X | | | | |
| Marijuana Use History | X | | | | |
| Prior medications | X | | | | |
| Physical exam | X | | | | |
| Blood Chemistry | X | | | | |
| Hematology | X | | | | |
| Urinalysis | X | | | | |
| Infectious Disease Screen | X | | | | |
| Urine pregnancy test[a] | X | X | | | |
| 12-lead ECG | X | | X | X | |
| Urine drug screen | X | X | | | |
| **Safety Assessments** | | | | | |
| Vital signs[b] | X | X | X | X | X |
| Continuous cardiac monitoring | | | X | X | |
| ECG repeated monitoring | | | X | X | |
| Adverse events | | X | X | X | X |
| Con. Medications | | X | X | X | X |
| **Psychological Assessments** | | | | | |
| MWSC[c] | | X | X | X | |
| VAS – Drug Effects[d] | | X | X | X | |
| **Pharmacokinetics** | | | | | |
| Blood draw for THC and THC-COOH PK[e] | | | 13X | 13X | |
| Urine collection for THC-COOH and THCV-COOH PK[f] | | | X | X | |
| **Study Activities** | | | | | |
| Clinic Intake | | X | | | |
| Smoking Sessions | | | X | X | |
| Clinic Release | | | | | X |

**Notes for Table 1:**

[a] If the pregnancy test is completed within two days of clinic intake, it does not have to be repeated on the day of clinic intake.

[b] Vital signs are taken any time of the day during screening, in the evening on Study Days 1 to 3, and any time before clinic release on Day 4-5.

[c] The MWSC is performed approximately the same time each day (1430 hours).

[d] The VAS assessments are performed after the MWSC except on smoking session days when it is taken prior to and approximately 7, 10, 20, 30, and 50 minutes after each of the 3 smoking periods on these days.

[e] The total volume of blood collected during the part of the study for PK measurements is 130 mL (5 mL x 26 collections) with approximately 24 mL collected for clinical laboratory assessments at screening.

[f] Urine will be collected before the start of the smoking session, and every time the subject voids for 24 hours after the start of the smoking session.

**Table 2. Time and Events for Part 2 of the Study**

| Study Period | Screening | Baseline | | | Withdrawal Period | | | | | Interaction Period | | Clinic release |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **- 28 to -1** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11-12** |
| **Screening Assessments** | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | |
| SCID/Psych Evaluation | X | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | |
| Marijuana Use History | X | | | | | | | | | | | |
| Prior medications | X | | | | | | | | | | | |
| Physical exam | X | | | | | | | | | | | |
| Blood Chemistry | X | | | | | | | | | | | X |
| Hematology | X | | | | | | | | | | | X |
| Urinalysis | X | | | | | | | | | | | |
| Infectious Disease Screen | X | | | | | | | | | | | |
| Urine pregnancy test[a] | X | X | | | | | | | | | | |
| 12-lead ECG | X | | X | X | | | | | | X | X | |
| **Safety Assessments** | | | | | | | | | | | | |
| Urine drug screen | X | X | | | | | | | | | | |
| Nicotine use – self report | X | X | X | X | X | X | X | X | X | X | X | |
| Vital signs[b] | X | X | X | X | X | X | X | X | X | X | X | X |
| Continuous cardiac monitoring | | | X | X | | | | | | X | X | |
| ECG repeated monitoring | | | X | X | | | | | | X | X | |
| Adverse events | | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medications | | X | X | X | X | X | X | X | X | X | X | X |
| **Psychological Assessments** | | | | | | | | | | | | |
| MWSC[c] | | X | X | X | X | X | X | X | X | X | X | |
| VAS – Drug Effects[d] | | X | X | X | X | X | X | X | X | X | X | |
| **Pharmacokinetics** | | | | | | | | | | | | |
| Blood draw for THC and THC-COOH PK[e] | | | 13x | 13x | 2x | | 2x | | 2x | 13 x | 13 x | |
| Urine collection for THC-COOH and THCV-COOH PK[f] | | | X | X | | | | | | X | X | |
| Urine collection for Quantitative THC-COOH[g] | | | X | X | X | X | X | X | X | X | X | |
| **Study Activities** | | | | | | | | | | | | |
| Clinic Intake | | X | | | | | | | | | | |
| Smoking Sessions | | | X | X | | | | | | X | X | |
| Randomization | | | | X | | | | | | | | |
| Dronabinol/placebo Treatment | | | | | X | X | X | X | X | X[h] | X[h] | |
| Clinic Release | | | | | | | | | | | | X |

**Notes for Table 2:**

[a] If the pregnancy test is completed within two days of clinic intake, it does not have to be repeated on the day of clinic intake.

[b] Vital signs are taken any time of the day during screening, in the evening on Study Days 1 to 10, and any time before clinic release on Days 11-12.

[c] The MWSC is performed approximately the same time each day (1430 hours) – during the withdrawal period, this is approximately 30 minutes after the 1400-hour dose of dronabinol/ placebo.

[d] The VAS assessments are performed after the MWSC except on smoking session days when it is taken prior to and approximately 7, 10, 20, 30, and 50 minutes after each of the 3 smoking periods on these days.

[e] The total volume of blood collected during this part of the study for PK measurements is 290 mL (5 mL x 58 collections). An additional approximately 40 mL will be collected for clinical laboratory assays.

[f] Urine will be collected before the start of the smoking session, and every time the subject voids for 24 hours after the start of the smoking session.

[g] Urine is collected daily, starting Day 2, for quantitative THC-COOH levels.

[h] The 0800, 1700, and 2000 hour doses are given on study Day 9 and only the 0800 hour dose is given on study Day 10.

### 11.1 Subject Recruitment

Interested candidates who are marijuana users but not seeking treatment and are available to stay in the clinic for up to 5 days (study Part 1) or 12 days (study Part 2) will meet with the investigator or a designated investigational staff member and receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the informed consent form. Recruitment strategies may include flyers, newspaper advertisements, or radio advertisements. The responsible IRB and NIDA will approve all advertising materials used for subject recruitment.

### 11.2 Screening and Baseline Assessments

Screening and baseline assessments will be conducted as shown in **Tables 1 and 2**. Screening must be completed within 28-days of signing consent. After consent has been signed, demographic information and a medical and psychiatric history will be obtained. A drug use history will be collected focusing on marijuana use including age-at-onset, and quantity and frequency of use in the past 30 days (timeline follow back methods will be used to assist in the collection of this data). The candidate will have a SCID for substance dependence and other Axis I disorders and will be given a urine drug screen for marijuana, cocaine, amphetamines, opiates, and benzodiazepines. Once a marijuana positive urine specimen has been obtained, a physical exam and a baseline ECG will be performed. Vital signs will be checked and medication use in the past 30 days will be recorded. Blood will be collected for chemistries, hematology, and infectious disease screening. A urine specimen will be collected for medical urinalysis. All women regardless of their child bearing potential will have a urine pregnancy test. Once preliminary eligibility has been established, candidates will be scheduled for clinic intake in the late afternoon or early evening on Study Day 1. Once at the clinic, all women will have a pregnancy test unless the first test was conducted within two days of clinic intake. Each candidate will be assessed for

continued general good health and a review of current medication use. A urine drug screen will also be performed to make sure the candidate has not used other drugs of abuse. If the subject is still eligible, they will complete the clinic intake procedures and be considered enrolled in the study. After intake, the first baseline VAS and MWSC assessments will be completed. The screening and intake procedures will be identical for Study Parts 1 and 2.

### 11.3 Study Part 1 Procedures

In the morning after the day of clinic intake (study Day 2), subjects will have breakfast at approximately 0700 hours and will be taken to the clinic area where smoking sessions will occur. Smoking sessions will be performed according to the schema shown in **Figure 2 and Table 3** with the exception of taking dronabinol or placebo capsules. Note that the times in the schedule are optimal times for study procedures to be conducted, but are considered approximate as it may not be possible to perform all of the assessments at the exact time shown in the table. Baseline VAS assessments and 12-lead ECG will be performed. Continuous cardiac monitoring [HR and BP, with data recorded every 5 minutes will be started approximately 15 minutes before smoking the first cigarette of the day]. The first cigarette will be a placebo marijuana cigarette, the second and third cigarettes will be active marijuana cigarettes. All three cigarettes will be smoked one- hour apart. Continuous cardiac monitoring will be performed through the one-hour period following the smoking of the third cigarette of the day and up to 4 hours longer if parameters have not returned to within 10% of baseline. A 12-lead ECG will be repeated at 5, 15, 30 and 55 minutes after the start of each smoking session, then hourly after the end of the third smoking session for approximately 3 more hours. Blood for PK measurements will be taken approximately 5 minutes before the start of the first active marijuana cigarette, at 5, 15, 25, 40 and 55 minutes after the start of smoking of each active marijuana cigarette, and at 2 and 3 hours after the start of the last active marijuana cigarette of the day. No food will be consumed until 55 minutes after the third cigarette of the day has been smoked to not introduce this variable into the cardiac responses. Tobacco-smoking subjects may not smoke from 1-hour prior to session initiation until 90 minutes after the completion of smoking the last marijuana cigarette of the day. The activities performed on Study Day 3 are identical to those on Day 2. AEs, medication use, and a urine drug screen will be assessed daily while in the clinic. The MWSC will be completed each in-clinic day, even though the subject is not likely to be experiencing withdrawal, to collect data on the variability of this measure. On Study Day 4, if the subject is not experiencing any AEs that need longer-term follow-up, they will be discharged from the clinic.

**Table 3. Timeline of Activities During Smoking Sessions**

| Approximate Time of the Day | Approximate Time Relative to the Start of the Smoking Sessions | Activity |
|---|---|---|
| 0700 to 0859 | -120 min to –1 min | Collect a voided urine specimen for THC-COOH and THCV-COOH PK |
| 0700 | -120 min | Eat breakfast |
| 0800 | -60 min | Take drabinol or placebo capsule |
| 0800 - 0845 | -60 to –15 min | Move to treatment room and prepare for sessions |
| 0845 -0859 | -15 to –1 min | Insert catheter for blood collection (could already be in place from prior day's session), perform VAS, ECG, start BP and HR continuous monitoring (record data q5min) |
| **0900** | | **Smoke placebo cigarette (repeat same schedule for marijuana cigarettes:**<br>**Light up – 30 sec**<br>**Get ready – 5 sec**<br>**Inhale – 5 sec**<br>**Hold – 10 sec**<br>**Exhale and wait –5 sec**<br>**Repeat from get ready up to 5 more times** |
| 0900 onward for 24 hours | | Collect every voided urine specimen for THC-COOH and THCV-COOH PK |
| 0905 | 5 min | ECG, HR, BP |
| 0907 | 7 min | VAS |
| 0910 | 10 min | VAS, HR, BP |
| 0915 | 15 min | ECG, HR, BP |
| 0920 | 20 min | VAS, HR, BP |
| 0925 | 25 min | HR, BP |
| 0930 | 30 min | ECG, HR, BP, VAS |
| 0935 | 35 min | HR, BP |
| 0940 | 40 min | HR, BP |
| 0945 | 45 min | HR, BP |
| 0950 | 50 min | VAS, HR, BP |
| 0955 | 55 min | Draw blood for baseline PK (5 mL), ECG, HR, BP |
| **1000** | **0** | **Smoke marijuana cigarette** |
| 1005 | 5 min | PK blood, ECG, HR, BP |
| 1007 | 7 min | VAS |
| 1010 | 10 min | VAS, HR, BP |
| 1015 | 15 min | PK blood, ECG, HR, BP |
| 1020 | 20 min | VAS, HR, BP |
| 1025 | 25 min | PK blood , HR, BP |
| 1030 | 30 min | ECG, HR, BP, VAS |
| 1035 | 35 min | HR, BP |
| 1040 | 40 min | PK blood, HR, BP |

| Approximate Time of the Day | Approximate Time Relative to the Start of the Smoking Sessions | Activity |
|---|---|---|
| 1045 | 45 min | HR, BP |
| 1050 | 50 min | VAS, HR, BP |
| 1055 | 55 min | PK blood, ECG, HR, BP |
| **1100** | **0** | **Smoke marijuana cigarette** |
| 1105 | 5 min | PK blood, ECG, HR, BP |
| 1107 | 7 min | VAS |
| 1110 | 10 min | VAS, HR, BP |
| 1115 | 15 min | PK blood, ECG, HR, BP |
| 1120 | 20 min | VAS, HR, BP |
| 1125 | 25 min | PK blood , HR, BP |
| 1130 | 30 min | ECG, HR, BP, VAS |
| 1135 | 35 min | HR, BP |
| 1140 | 40 min | PK blood, HR, BP |
| 1145 | 45 min | HR, BP |
| 1150 | 50 min | VAS, HR, BP |
| 1155 | 55 min | PK blood, ECG, HR, BP |
| 1200 | 60 min | Continue HR + BP q15min until back to baseline or normal limits |
| 1200 - 1300 | | Return to main clinic and have lunch |
| 1300 | 2 hrs | ECG, PK blood |
| 1400 | 3 hrs | ECG, PK blood |
| 1500 | 4 hrs | ECG |
| 1700 | 6 hrs | Take drabinol or placebo capsule |
| 2000 | 9 hrs | Take drabinol or placebo capsule |

### 11.4 Study Part 2 Procedures

Study Part 2 procedures are identical to those described for Study Part 1, until Study Day 4.

***Randomization and Start of the Withdrawal Period:*** On Study Day 4, Part 2 subjects will be randomized to treatment with either dronabinol or placebo and start taking their capsules at 0800 hours. A staff member will submit a randomization request form to the study pharmacist and receive the subject's blind coded capsules for the duration of the study. Capsules will be taken 5 times per day at 0800, 1100, 1400, 1700, and 2000 hours from Study Days 4 through 8. Vital signs will be monitored each evening during this period. The MWSC should be assessed approximately the same time each day (1430 hours) during the withdrawal period. This is approximately 30 minutes after the 1400-hour dose of dronabinol/placebo. The VAS assessments should follow the MWSC assessment. Peak and trough THC levels will be determined on Study Days 4, 6, and 8 by collecting a blood sample at just prior to the 0800 capsule dose and another at 1600 hours (2 hours after the 1400 hours capsule dose).

**Interaction Period:** During the interaction period, the two days of smoking sessions conducted on Study Days 2 and 3 will be repeated on Study Days 9 and 10. A detailed timeline of activities during these smoking sessions is shown in Table 3. On Study Day 9, dronabinol or placebo capsules will be taken at 0800, 1700, and 2000 hours. On Study Day 10 dronabinol or placebo capsules will only be taken at 0800 hours. Vital signs, VAS, and the MWSC will be performed in the same manner as during smoking sessions #1 and #2. AEs, medication use, and the urine drug screen will be assessed daily while in the clinic. The MWSC will be completed each in-clinic day even thought the subject is not likely to be experiencing withdrawal. On Study Day 11 or 12, if the subject is not experiencing any AEs that need longer-term follow-up, they will be discharged from the clinic.

### 11.5 Stopping Criteria for Additional Marijuana Cigarette

If at any time during the first active marijuana cigarette of the day, BP or HR exceed any of the following:

- Systolic BP > 165 mm;
- Diastolic BP > 100 mm;
- HR > 130 bpm;

the second marijuana cigarette of the day will not be given and the subject will be suspended from further study participation.

### 11.6 Safety Monitoring Plan

In order to perform an interim safety analysis after completion of Part 1 of the study, a Safety Committee comprised of the Principal Investigator, NIDA Investigators, and NIDA Medical Monitor will meet as soon as possible and evaluate the safety data collected on the 6 volunteers enrolled in study Part 1. This data will include cardiovascular measurements and adverse events summaries prepared by the Data Management Center. In the event that this group decides that a significant change is needed in the protocol, a revised protocol will be prepared and submitted to the IRB for review and approval before proceeding with Study Part 2. This revised version of the protocol will also be submitted to FDA for comment. If the protocol only requires administrative changes, these revisions will also be submitted to the IRB and FDA as administrative changes for expedited review by the IRB.

### 11.7 Maintaining and Breaking Study Blind

The decision to break the study blind for an individual subject lies with the site principal investigator (PI) and the NIDA Project Manger and/or with the NIDA medical monitor or NIDA designee, but should be resorted to only in cases of life-threatening emergency when knowledge of the treatment arm investigational drug will influence clinical management.

### 11.8 Reimbursement

Subjects will be reimbursed for travel expenses, for study participation, and for time contributed to this research study in the form of vouchers or retail script.

### 11.9 Study Termination

#### *11.9.1 Subject Withdrawal/Suspension*

An investigator may suspend a subject from receipt of investigational agents and further study procedures if s/he deems it clinically appropriate or for significant side effects from the investigational agents.

An investigator may suspend a subject from further study participation for any of the following reasons:

1. Serious or unexpected AEs, which would make further study participation not in the subject's best interests.
2. Failure to comply with the study protocol
3. Serious or chronic protocol violations.
4. Serious intercurrent illness.
5. Administrative reasons, such as presenting a danger to staff or other subjects.

A subject may voluntarily withdraw from the study anytime s/he wishes. Study participants withdrawn from the protocol secondary to a medical or psychiatric concern will be referred for appropriate treatment. Subjects will be asked to sign a general consent for the release of information to the referred health care. Study staff may request transportation for emergency treatment of a subject if medically appropriate (e.g., for acutely psychotic or suicidal subjects).

#### *11.9.2 Trial Discontinuation*

The study sponsor has the right to discontinue the investigation at any time.

### 11.10 Concomitant Medications

Any medications (including prescription, over-the-counter, herbal supplements and health store products) to be taken during the study must be approved by the investigator.

## 12 CLINICAL AND LABORATORY ASSESSMENT METHODS

Study assessments should be completed according to the schedule shown in **Table 1** for Study Part 1 and in accordance with the **Table 2** for Study Part 2.

### 12.1 Adverse Events

An investigative staff nurse or physician will assess AEs at least once daily and more frequently during all smoking sessions. If an AE is reported that requires medical attention, it should be reported to a study physician immediately. The study physician will meet with the study staff at least once a week to review AEs recorded by the nurse on all subjects, and the study physician may then meet any subjects for whom additional follow-up or AE assessment is indicated. The study physician will also assess the subjects for any medical or psychiatric adverse event. AEs will be assessed by asking the subject open-ended questions like "How have you been feeling since I last saw you?" Cardiovascular AEs will be monitored by examining vital signs and ECG

tracings. The type of AE, severity of the AE and the relationship of the AE to the study treatments will be recorded on an AE CRF, according to the procedures described in Section 13.6 and Appendix I.

### 12.2 Blood Chemistries

Blood chemistries will be performed during screening to establish eligibility and at the end of the treatment for Part 2 subjects. Quantitative analysis will be performed for the following analytes: alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyltranspeptidase (GGT), total bilirubin, alkaline phosphatase (ALP), sodium, potassium, chloride, magnesium and bicarbonate. The laboratory performing these assessments should be either directly regulated by the College of American Pathologist (CAP) or the Clinical Laboratory Improvement Act of 1988 (CLIA) or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

### 12.3 Demographics

Age, gender, ethnicity, years of education, usual employment pattern in the past 30 days, and marital status data will be collected. A Demographics CRF will be completed for all subjects who sign a consent form.

### 12.4 Eligibility Checklist

An eligibility checklist will be used to determine if the candidate meets all inclusion and exclusion criteria during screening. The checklist will be transcribed on a CRF and collected for all candidates who were screened to monitor the reason for screening failure.

### 12.5 Hematology

Blood will be collected in anticoagulant containing evacuated venous blood collection tubes (e.g., Vacutainer™) for hematologic assessments during screening to establish eligibility and at the end of the treatment for Part 2 subjects. Complete blood counts (CBC) with differentials and platelet count will be performed. Quantitative analyses for hemoglobin, hematocrit, red blood cells, platelets, total white blood cells, and percentage of neutrophils, lymphocytes, monocytes, eosinophils, and basophils will be performed. The laboratory performing these assessments should be either directly regulated by the College of American Pathologist (CAP) or the Clinical Laboratory Improvement Act of 1988 (CLIA) or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

### 12.6 Infectious Disease Panel

Blood will be collected in a serum separation evacuated venous blood collection tube (e.g., Vacutainer™) and serum separated according to standard procedures. Qualitative analysis reporting positive/negative results will be performed for the following analytes: HbsAg, hepatitis C virus antibody, and HIV-1 antibody. The laboratory performing these assessments should be either directly regulated by the College of American Pathologist (CAP) or the Clinical

Laboratory Improvement Act of 1988 (CLIA) or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

### 12.7 Marijuana Withdrawal Symptom Checklist (MWSC)

The MWSC is a 10-item self-administered questionnaire developed by Budney *et al*. (1999).[33] Each of the 10 items is a withdrawal symptom that is rated on a 4-point scale as follows: 0 = not at all; 1 = mild; 2 = moderate; 3 = severe. The 10 withdrawal symptoms include: 1) craving, 2) irritability, 3) nervousness, 4) depression, 5) anger, 6) restlessness, 7) sleep problems, 8) decreased appetite, 9) strange dreams, and 10) headaches. Symptoms will be evaluated individually and by computing a total withdrawal discomfort score (WDS) that is the sum of the individual item scores. These symptoms were selected by Budney *et al*. (1999) from a larger list of 22-items as the subset of items that ≥ 40% of adults seeking treatment for marijuana dependence indicated as a withdrawal symptom that they had experienced. They reported the reliability of this scale to be $\alpha = 0.89$. The MWSC is performed approximately the same time each day (1430 hours) – during the withdrawal period, this is approximately 30 minutes after the 1400-hour dose of dronabinol/placebo.

### 12.8 Marijuana and Other Drug History

A drug use history will be collected focusing on marijuana use including age-at-onset, years of use, and quantity and frequency of use in the past 30 days (timeline follow back methods will be used to assist in the collection of this data). The history of other drug use will also be collected including any drug use, years of use, and current use.

### 12.9 Medical History

To establish subject eligibility, a relevant medical history will be obtained to assure medical fitness.

### 12.10 Medical Urinalysis

Urine will be collected and analyzed for specific gravity, pH, blood, protein, glucose, ketones, leukocytes, and nitrites at the local site's clinical laboratory.

### 12.11 Nicotine Use – Self Report

Tobacco smoking is permitted during the study but not from 1-hour prior to session initiation until 90 minutes after the completion of smoking the last marijuana cigarette of the day. Subjects will report the daily number of tobacco cigarettes smoked per day.

### 12.12 Physical Examination

A physical examination of the oral cavity, head, eyes, ears nose and throat, cardiovascular system, lungs, abdomen (liver/spleen), extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system and general appearance will be performed during screening. Height and weight will be recorded.

### 12.13 Pregnancy Test

An FDA approved urine pregnancy test designed to measure human chorionic gonodotropin will be performed on screening and admission. However, if the pregnancy test is completed within two days of clinic admission, it does not have to be repeated. All female subjects will be tested regardless of their childbearing capacity.

### 12.14 Prior and Concomitant Medications

All medications taken by the subject 28 days prior to the start of screening and during the inpatient time period will be recorded on a medications CRF. Any medications during the in-clinic phase of the study must be pre-approved by the study physician whenever possible to avoid interactions with study agent.

### 12.15 Structured Clinical Interview (SCID)

A DSM-IV SCID will be conducted during screening to assess the candidate's marijuana-dependence, dependence or abuse of other drugs and other Axis-I disorders and to rule out any major psychiatric disorders (e.g., affective disorders, schizophrenia).

### 12.16 Treatment Compliance

Compliance with investigational agents will be recorded every time a capsule is dispensed to a subject or a marijuana or placebo cigarette is smoked by a subject.

### 12.17 Urine Drug Screen

Urine will be collected and tested for substances of abuse using an FDA approved Onsite Testing Device for cannabinoids/marijuana (THC), cocaine, amphetamines, opiates, and benzodiazepines during screening and on the day of admission. The test device will use the cut-offs for a positive test as follows:

| Drug of Abuse | Cut Off Limit for a Positive Test |
|---|---|
| Amphetamines | 500 ng/mL |
| Benzodiazepines | 300 ng/mL |
| Cannabinoids/Marijuana | 50 ng/mL |
| Cocaine | 300 ng/mL |
| Opiates | 300 ng/mL |

### 12.18 Urine Collections for THC-COOH and THCV-COOH

THC Metabolite Analysis. Urine will be collected at screening (cut-off at 50 ng/mL) and quantitative analysis for THC-COOH every inpatient morning starting with Day 2. On smoking session days, the first morning urine specimen will also be part of the urine samples collected for analysis and treated as described below.

***PK for Metabolites of THC and THCV.*** On smoking session days, urine samples will be collected as separate volumes as they are voided, measured and the volume recorded. The last specimen will be collected at approximately 24 hours after the first cigarette was smoked. The urine samples will be screened for the presence of THC-COOH at a cutoff of 50 ng/mL. Quantitative assay for THC-COOH and THCV-COOH will also be performed.

***Sample Preparation and Shipment to a Central Lab.*** Two 20 mL aliquots of all urine samples will be frozen. One will be sent to a central lab for analysis of THC-COOH and THCV-COOH content by gas chromatography-mass spectroscopy (GC-MS).[42] The other sample will be retained as a back-up sample at the site.

### 12.19 Vital Signs and Continuous Cardiac Monitoring

**Daily routine vital signs** to be assessed include oral temperature, sitting blood pressure, pulse rate and respiratory rate.

**Continuous Cardiac Monitoring.** Before and after each smoking session, the subjects' physiologic responses will be closely monitored using repeated HR, BP, and ECG readings. Prior to the start of each day's smoking sessions, a 12-lead ECG will be done, and baseline HR and BP will be recorded. Monitoring will continue with HR and BP being recorded approximately every 5 minutes following the baseline assessment throughout all three smoking sessions. At the end of the third cigarette of the day, BP and HR monitoring will continue every 15 minutes until back to within 10% of baseline or within normal limits. ECG will be monitored at 5, 15, 30 and 55 minutes after the start of each smoking session, then every hour for another 3 hours (approximately until 1500 hours).

### 12.20 THC and THC-COOH PK

During study Part 2, blood will be collected on study days 4, 6, and 8 for peak and trough THC levels. Five (5) mL blood samples in heparinized tubes will be collected. Blood for trough levels will be collected just prior to the first capsule of the day at 0800 hours and blood for peak levels will be collected at approximately 1600 hours (two hours after the 1400 hour dose).

For PK assessments during smoking sessions in both study Parts 1 and 2, an intravenous catheter will be inserted prior to the start of each smoking session, and can be maintained in place for the two days consecutive days of smoking sessions in a row. Blood (5 mL) will be collected into heparinized tubes approximately 5 minutes before the start of the first of the two active marijuana cigarette smoking periods and at approximately 5, 15, 25, 40, and 55 minutes after the completion of the first puff of each marijuana cigarette, and at 2 and 3 hours after completing smoking the last marijuana cigarette of the day.

Blood drawn from all subjects should be considered infectious and caution should be used to avoid needle sticks and direct contact with blood or plasma. Using appropriate Vacutainers:

a. Draw blood and invert tube 8-10 times.

b. Centrifuge the blood (3000 x g for 15 min.) immediately to prevent hemolysis.
c. Using a disposable pipet, immediately transfer the plasma from the tubes to a single plastic plasma storage vial and secure the cap tightly.
d. Label the vial as described below.
e. Freeze sample at -20°C immediately after transferring to shipping vial. Store in an upright position. Keep frozen until shipment to a laboratory for analysis.

THC and THC-COOH will be assayed using a chemical ionization gas chromatography/mass spectrometry by a modification of the method of Foltz et al.(1983).[49] This method has a 0.5 ng/mL limit of detection.

### 12.21 VAS-Drug Effects

Drug effects will be assessed using three VAS questions for which the response will be scored on a 100-mm line labeled none at all on the left and extremely on the right. The three questions are:

How high do you feel now?
How stoned on marijuana are you now?
How strong is the drug effect you feel now?

The individual scores and the mean of the three individual scores as a composite score will be analyzed. This VAS has been used by Heustis et al. (2001)[43] to evaluate the subjective effects of marijuana. The VAS assessments are performed after the MWSC except on smoking session days when it is taken prior to and approximately 7, 10, 20, 30, and 50 minutes after each of the 3 smoking periods on these days.

## 13 REGULATORY AND REPORTING REQUIREMENTS

### 13.1 FDA Form 1572

The PI will sign a Statement of Investigator (FDA Form 1572) prior to initiating this study.

### 13.2 IRB Approval

Prior to initiating the study, the PI will obtain written IRB approval to conduct the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to the IRB by the investigator for IRB approval prior to implementation. In addition, the IRB will approve all advertising materials used for subject recruitment. Progress reports will be submitted to the IRB annually or at a frequency requested by the IRB.

### 13.3 Informed Consent

All potential candidates for the study will be given a current copy of the Informed Consent Form to read and take home. All aspects of the study will be explained in lay language. After the subject has read the consent form, a short questionnaire will be given to the subject before signing the form. This questionnaire will review all aspects of the study discussed in the consent form. A research staff member will review the answers provided by the subject. Any subject who

does not successfully complete the questionnaire will re-read the consent with a research staff member. The subject will retake the questionnaires until s/he shows complete understanding of the information discussed in the consent form before providing consent. Any subject who is unable to demonstrate understanding of the information contained in the informed consent will be excluded from study participation and assisted in finding other sources of treatment. Subjects who refuse to participate or who withdraw from the study also will be assisted in finding other sources of treatment without prejudice.

### 13.4 Drug Accountability

Upon receipt, the investigator/pharmacist is responsible for taking inventory of the investigational agents(s). A record of this inventory must be kept and usage must be documented. Any unused or expired investigational agent(s) shall be returned to the sponsor (or responsible party) unless otherwise instructed. Dronabinol and marijuana cigarettes are controlled substances. Thus in accordance with the Controlled Substance Act, 21 CFR, Part 13, Section 801, all individuals and firms must be registered and are required to maintain complete and accurate inventories and records of all transactions involving controlled substances, as well as security for the storage of controlled substances.

### 13.5 Outside Monitoring

**Medical Monitor:** An independent medical monitor will be appointed for the study. The medical monitor will be responsible for establishing concurrence with the investigator on the severity of any SAEs, the relatedness to the study treatments, and for determining if the SAE should be reported to the FDA in a 7 or 15 day expedited report or an annual report. The medical monitor will also be responsible for tracking and assessing trends in the SAEs reported.

**Safety Committee:** A Safety Committee comprised of the Principal Investigator, NIDA Investigator's and the NIDA Medical Monitor will review the safety data collected after all subjects have completed Study Part 1 and make any recommendations for changes to the study design if deemed warranted.

**Clinical Monitors:** The PI will allow representatives of the sponsor to periodically audit, at mutually convenient times during and after the study, all CRFs and corresponding source documents for each subject. These monitoring visits provide the sponsor with the opportunity to evaluate the progress of the study and to inform the sponsor of potential problems at the study site. The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that investigational agents are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by good clinical practices guidelines are appropriately filed.

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training site personnel in study procedures and good clinical practice's guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by the sponsor's representatives will be scheduled at appropriate intervals but more frequently at the beginning of the study. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines. At the end of the study they will advise on storage of study records and return of unused study agents. The site should anticipate visits by NIDA and the FDA.

### 13.6 Adverse Events Reporting

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the PI or study physicians according to the specific instructions detailed in this section of the protocol and Appendix I. The occurrence of AEs will be assessed daily after clinic intake.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered related to the investigational agent 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 which are present prior to clinical trial entry and do not worsen are not considered AEs. All AEs must be recorded on the AE CRF.

Each week, a study investigator must review the AE CRF completed for the previous week 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 physicians until satisfactory resolution.

### 13.7 Serious Adverse Events

Each AE or reaction will be classified by the study investigator as serious or non-serious. Based on the seriousness of the AE or reaction appropriate reporting procedures will be followed. The International Conference on Harmonization (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995, as implemented by the U.S. Food and Drug Administration defines serious adverse event (SAE) or reaction as any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening; *(NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)*
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

An unexpected event is one that is not described with respect to nature, severity, or frequency in the current Investigator's Brochure or product package insert.

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug reaction, when based on appropriate medical judgment, that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

Any SAEs due to any cause, that occur during the course of this investigation, whether or not related to the investigational agent, must be reported within 24-hours by telephone to: the Study Medical Monitor and the NIDA Study Director. 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 Medication Form, and the Medical History Form from the subject's CRFs. Any serious medical events are also to be reported to the responsible IRB according to local regulatory requirements. The PI will be notified of any serious and unexpected AE requiring submission to the FDA in an IND safety report from the sponsor.

Any fatal or life-threatening SAE that is investigational agent related and unexpected must be reported by the sponsor initially to the FDA within 7 calendar days via telephone, facsimile or e- mail. A follow-up written report must be submitted in 8 days to the FDA. All AEs that are both serious and unexpected but not life-threatening or lethal must be reported to the FDA, in writing, within 15 calendar days of notification of the sponsor of the SAE. All other SAEs will be reported in an annual report or more frequently as necessary. Any additional clinical information that is obtained must be reported to the FDA, as it becomes available in the form of an information amendment.

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 PI has the responsibility of promptly reporting all SAEs to NIDA in order that the sponsor can comply with these regulations.

If a study subject withdraws from the study or if the PI decides to discontinue the subject from the study because of 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.

## 14 ANALYTICAL PLAN

The main objective of this study is to determine the safety of oral THC when combined with smoked THC particularly in relation to cardiovascular responses in marijuana dependent volunteers. In study Part 1, cardiovascular responses to two sequential one-hour apart marijuana

smoking sessions will be thoroughly investigated in 6 subjects. In the second part of the study, this data will be extended to an additional group of 12 subjects. In addition, in the second part of the study, the comparison between cardiovascular effects during smoking sessions of the 6 subjects who received placebo capsules and the 6 subjects who received dronabinol capsules will also be performed.

Secondary objectives include:

1) Characterizing the subjective effects of oral drabinol, smoked marijuana, and the combination of the two,
2) Measuring PK parameters of THC after smoking marijuana in the presence and absence of oral drabinol, and,
3) Determining the effect of dronabinol on marijuana withdrawal symptoms compared to a placebo control.

### 14.1 Primary Outcome Measures

The primary outcome measures are cardiovascular responses, HR and BP during active marijuana smoking periods, in the presence and absence of dronabinol treatment.

### 14.2 Secondary Outcome Measures

Secondary outcome measures include:

1. AEs and ECG abnormalities.

2. PK parameters of THC and THC-COOH during various periods in the study. Measures to be calculated include:

| | |
|---|---|
| $AUC_{0\text{-}55min}$ | Area under the plasma concentration time-curve from 0 to 55 minutes after smoking each active marijuana cigarette |
| $AUC_{0\text{-}4hr}$ | Area under the plasma concentration time-curve from 0 to 4 hours (where time 0 is the time smoking of the first marijuana cigarette of the day was started) |
| $AUC_{0\text{-}¥}$ | Area under the plasma concentration time-curve from time 0 to infinity (where time 0 is the time smoking of the first marijuana cigarette of the day was started) |
| $C_{max}$ | Maximum observed concentration after smoking each active marijuana cigarette |
| $T_{max}$ | Time for maximum concentration after smoking each active marijuana cigarette |
| $k_e$ | terminal exponential rate constant (if data permit) |
| $t_{1/2}$ | Elimination half-life (0.693/(z)) (if data permit) |

3. Peak and trough THC and THC-COOH plasma levels on Study Days 4, 6, and 8.

4. Urine kinetics for THCV-COOH including excretion rate constant and half-life.
5. Subjective effects of THC as measured by VAS (single item and 3-item mean score).
6. Withdrawal symptoms as measured with individual item and the total WDS of the MSWC.

## 14.3 Analysis Plan

### *14.3.1 Descriptive Statistics*

Mean HR and BP over time will be plotted for each of the three sequential smoking periods per day for smoking sessions 1 and 2 for all 18 subjects in study parts 1 and 2. Each daily sessions' data will be examined separately. Time to peak change and peak changes in HR and BP may be compared between the first and second active marijuana cigarettes smoked during one day, if it appears that the effects do not parallel one another during each of these two smoking periods.

There are essentially, three study groups in this study as follows:

1) the first 6 volunteers enrolled in study Part 1
2) 6 volunteers enrolled in study Part 2 and randomized to placebo capsules
3) 6 volunteers enrolled in study Part 2 and randomized to dronabinol

Changes in ECG readings during placebo marijuana smoking sessions and active marijuana smoking sessions will be reported for each of the three groups of six subjects (the first 6 subjects enrolled during study Part 1 and the 6 subjects in each of the placebo capsule and dronabinol capsule groups in study Part 2) as summary statistics. Likewise, the severity and frequency of AEs for these three groups will also be presented as summary statistics. AEs will be coded using Medical Dictionary of Regulatory Affairs (MedDRA) preferred terms and grouped by system, organ, and class (SOC).

Summaries of the demographic, marijuana and other drug use history characteristics of the subject populations in Part 1 of the study and both of the treatment groups in study Part 2 will be prepared.

The mean and 90% confidence intervals for plasma THC and THC-COOH PK parameters for the subjects in each of the two Part 2 study groups during each of the following study periods will be summarized:

1. The 55-minute period that blood was collected after each separate active marijuana cigarette was smoked ($AUC_{0\text{-}55min}$, $C^{max}$, and $T_{max}$).
2. The 4-hour period that blood was collected after the start of smoking of the first marijuana cigarette of the day ($AUC_{0\text{-}4hr}$ and $AUC_{0\text{-}\infty,}$ $C_{max}$ and $T_{max}$)
3. Peak and trough levels of THC and THC-COOH on study days 4, 6, and 8.

In addition, mean plasma THC and THC-COOH concentrations over time will be plotted for all samples in each of the two treatment groups collected on smoking days.

Urine kinetics for THCV-COOH including excretion rate constant and half-life will be presented as summary statistics with means, standard deviation, and minimum and maximum values reported for each smoking session by treatment group.

### *14.3.2 Between Group Comparisons (Study Part 2 Subjects)*

The primary safety outcome measures, change in HR and BP, collected during each of the two active marijuana cigarette smoking periods per day will be compared separately between the group treated with dronabinol and the group treated with placebo capsules using repeated measures analysis of variance (ANOVA). These same comparisons will be performed for subjective effects outcomes measures including VAS scores.

Scores of individual items and total WDS score generated from the MWSC will be plotted over time to examine trends in the severity of withdrawal symptoms. Mean scores in the group treated with dronabinol and that treated with placebo capsules will be compared on individual days using a t-test or appropriate non-parametric test. No adjustments for multiple comparisons will be made.

All statistical comparisons will be two-sided and a $p<0.05$ will be considered significant.

## 15 DATA MANAGEMENT AND CASE REPORT FORMS (CRF)

### 15.1 Data Collection

Data will be collected at the study site and transcribed into CRFs that should be completed according to the instructions in the study operations manual. The site PI is responsible for maintaining accurate, complete and up-to-date records for each subject. The site PI is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

### 15.2 Data Editing and Control

Data received at the data management center will be reviewed. If incomplete or inaccurate data are found, a data clarification request will be forwarded to the clinical site for a response. The site will resolve data inconsistencies and errors prior to returning data to the data management center. All corrections and changes to the data will be reviewed prior to being entered into the main study database.

Study monitors will routinely visit the study site to assure that data submitted on the appropriate forms are in agreement with source documents. They will also verify that the investigational agents have been properly stored and accounted for, subject informed consent for study participation has been obtained and documented, all essential documents required by Good Clinical Practice regulations are on file, and the site is conducting the study according to the research protocol. Any inconsistencies will be resolved, and any changes to the data forms will be made using the data management center procedures.

## 15.3 Data Processing and Analyses

When the study is completed and all data have been entered into the clinical database and the database has been checked by Quality Assurance and is locked, statistical analysis of the data will be performed by the study statisticians in accordance with the analytical plan section of this protocol. Periodically, during the investigation, data sets will be submitted to the NIDA DPMC central data repository according to procedures specified in the study operations manual.

## 15.4 Study Documentation and Records Retention

Study documentation includes all CRFs, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, IRB correspondence and approved consent form and signed informed consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

Government agency regulations and directives require that the investigator must retain all study documentation pertaining to the conduct of a clinical trial. These documents must be kept for a minimum of two years after discontinuation of the IND or 2 years after the approval of an NDA.

## 15.5 Confidentiality

### 15.5.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical investigators and IRBs will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and the IRB.

By signing this protocol the investigator affirms to NIDA that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

### *15.5.2 Confidentiality of Subject Records*

To maintain subject confidentiality, all laboratory specimens, CRFs, reports and other records will be identified by a coded study subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff and NIDA program officials will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by the FDA, the NIDA monitoring contractor, or NIDA. Upon approval of the study by an IRB, an application will be filed with NIDA for a certificate of confidentiality. By signing the protocol the investigator agrees that within local regulatory restrictions and ethical considerations, NIDA or any regulatory agency may consult and/or copy study documents in order to verify CRF data.

The procedure for applying for a certificate of confidentiality is provided in Appendix II.

## 16 PUBLICATIONS OF THE STUDY RESULTS

NIDA and the investigative group agree that data will be made available to the investigator to publish. Review of manuscripts resulting from this study or from data generated during this study must occur according to the NIDA DPMC Publications Policy prior to submission for publication. Authorship shall be consistent with NIDA and DPMC policies.

## 17 SIGNATURES

### NIDA REPRESENTATIVES

| Typed Name | Signature | Date |
|---|---|---|
| Ahmed Elkashef, M.D.<br>NIDA Investigator | _____ | _____ |
| Roberta Kahn, M.D.<br>NIDA Investigator | _____ | _____ |
| Nora Chiang, Ph.D.<br>NIDA Investigator | _____ | _____ |
| Jurij Mojsiak<br>Project Manager | _____ | _____ |
| Ann Anderson, M.D.<br>Medical Monitor | _____ | _____ |

### SITE INVESTIGATOR

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in section 13.7 of this protocol.

| Typed Name | Signature | Date |
|---|---|---|
| Louis Cantilena, Jr., M.D., Ph.D<br>Principal Investigator | _____ | _____ |

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## APPENDIX I: INSTRUCTIONS FOR EVALUATING AND REPORTING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### A. GENERAL INSTRUCTIONS

1. The Adverse Event (AE) CRF must be completed daily and reviewed by a study physician.
2. Start recording AEs after clinic intake.
3. Report the severity of the event following the guidance in section B below.
4. Report the relatedness of the event to the study agent administration according to the guidance in section C.

### B. DEFINITIONS – SEVERITY OF EVENTS

| | |
|---|---|
| Mild: | Awareness of symptom, but easily tolerated. |
| Moderate: | Discomfort enough to cause interference with usual activity. |
| Severe: | Incapacitating with inability to work or do usual activity. |

### C. DEFINITIONS – RELATEDNESS OF EVENTS

The study physician is responsible for defining, in his/her best judgment, the relationship of the AE/SAE to the study drug/placebo. The degree of certainty for which the AE/SAE is attributed to the study drug or alternative causes (e.g. natural history of the underlying disease, concomitant therapies, etc.) should be determined by how well the experience can be understood in terms of one or more of the following:

- ***Exposure:*** Is there evidence that the subject was actually exposed to the drug/placebo?
- ***Timing of the study drug/placebo:*** Did the AE/SAE follow in a reasonable temporal sequence from administration of the drug test?
- ***Consistency with study drug profile:*** Known pharmacology and toxicology of the study drug in animals and man; reaction of similar nature having been previously described with the study drug.
- ***Alternative explanations*** for the adverse event such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding findings.
- ***Response to discontinuation*** of the study drug/placebo.

Terms and definitions to be used in assessing the study agent relationship to the AE/SAE are:

- ***Unknown:***
  Use this category only if the cause of the AE/SAE is not possible to determine

- ***Definitely Not Related:***
  The subject did not receive the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is not reasonable, or there is another obvious cause of the AE/SAE.

- ***Remotely Related:***
  There is evidence of exposure to the test drug or there is another more likely cause of the AE/SAE.

- ***Possibly Related:***
  There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, but the AE/SAE could have been due to another equally likely cause.

- ***Probably Related:***
  There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, and the AE/SAE is more likely explained by the test drug than by any other cause.

- ***Definitely Related:***
  There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, the AE/SAE is more likely explained by the test drug than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the test drug or test drug class.

## D. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

A laboratory or ECG AE is any clinically significant worsening in a test variable that occurs during the course of the study, whether or not considered to be study agent related. For each such change, provide the information requested on date of test, severity, likelihood of a relationship to investigational agent, change in investigational agent dosage due to the AE, and treatment required.

All laboratory AEs should be specified as an increased or decreased test result (e.g. “increased glucose”, “decreased potassium”) or as a term that implies an abnormality (e.g., hypercalcemia, azotemia, hypokalemia, or bradycardia). Any abnormal laboratory value that is considered not clinically significant will be recorded as such on the clinical laboratory report CRF along with a comment providing justification for that determination.

## E. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

***24 hour Reporting Requirements***

Any serious adverse event, including death due to any cause, which occurs to any subject from the time of admission through discharge whether or not related to the study drug/placebo, must be reported within 24 hours to the NIDA Medical Monitor, the NIDA Project Officer, and the PI.

**NIDA Medical Monitor:** Ann Anderson, M.D., 301/443-2281

**NIDA Project Officer:** Jurij Mojsiak, M.S., 301/443-9804

**NIDA Project Manager**: Jurij Mojsiak, M.S., 301/443-9804

**Principal Investigator:** Louis Cantilena, M.D., 301/295-3239

The following information must be provided with the initial report of an SAE or unexpected AE:

- Name of person reporting the SAE/unexpected AE
- Subject's I.D. number
- Name of the principal investigator and institution
- Date the subject signed informed consent
- Date of first treatment
- Description of the SAE/unexpected AE
- Date and time of Onset
- Date/time of administration of last dose of study agent/placebo prior to the SAE/unexpected AE
- Severity of the SAE/unexpected AE
- Investigator's assessment of the relationship of the SAE/unexpected AE to study drug (related, possibly related, probably related, unlikely related, not related)
- Any action taken with the study drug, alteration to protocol defined schedule, diagnostics, and treatments secondary to the SAE/unexpected AE.

***3-day Supporting Documentation Requirements***

Written documentation for all SAEs/unexpected AEs must be received by the NIDA Medical Monitor/Alternate, and the NIDA Project Manager within 3 days of reporting the event. Required documents that must be submitted include the following:

- SAE Form
- Concomitant Medication CRF pages
- Adverse Events CRF pages

- Copies of source documents pertinent to the event (lab reports, ECG tracings, medical chart notes, etc.)
- Any other relevant information necessary to facilitate the investigator's judgment regarding the SAE's relatedness to the severity OR by request of the Medical Monitor/Alternate

***Follow-Up of All Adverse Events/Serious Adverse Events***

All adverse medical events must be followed until they are resolved, or until all attempts to determine the resolution of the AE/SAE are exhausted. This may require an extended inpatient period. All treatments, outcomes and information regarding whether or not the subject was referred to their Primary Care Provider for additional follow-up must be recorded in the source document. All serious and unexpected adverse events occurring 30 days after administration of the last dose of study drug/placebo must be reported.

The investigator is required to provide the Medical Monitor/Alternate with all relevant follow-up information necessary to facilitate a thorough understanding of the event and judgment regarding the relationship to the study drug/placebo.

***Reporting to the FDA***

The IND sponsor is required to report SAEs to the FDA:

- in 7 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), life-threatening or lethal, and at least possibly related to the study agent, with a follow-up written report in 8 days;

- in 15 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), but not immediately life-threatening; and

- in an annual report in all other cases.

## APPENDIX II: Procedure for Applying for a Certificate of Confidentiality

The only people who will know the identity of the subjects are members of the research team and, if appropriate, the physicians and nurses. No information about the subjects, or provided by the subjects during the research, will be disclosed to others without the subjects' written permission, except:

- if necessary to protect subjects' rights or welfare

When the results of the research are published or discussed in conferences, no information will be included that would reveal subjects' identity. Authorized representatives of the FDA and NIDA study monitors may need to review records of individual subjects. As a result, they may know subjects' names, but they are bound by rules of confidentiality not to reveal their identity to others. The results of this study including laboratory results and clinical information collected during this study will be submitted to the FDA and may be used for research purposes. The results of this study may be published but will not personally identify any subjects. All records will be kept in locked storage locations that will be accessible only to authorized study personnel.

**NIDA will apply for a Certificate of Confidentiality for the participating site.**

This Certificate of Confidentiality helps researchers protect the privacy of subjects in health research projects against compulsory legal demands (e.g., court orders and subpoenas) that seek the names or other identifying characteristics of research subjects. The certificate was developed to protect against the involuntary release of personally identified research information of a sensitive nature sought through any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. This authority was granted under the Comprehensive Drug Abuse Prevention and Control Act of 1970, Public Law No. 91-513, Section 3(a).

This certificate is necessary for investigators to avoid being required to involuntarily disclose personally identifiable research information about individual study subjects. Under this statute:

"The Secretary [of the Department of Health and Human Services] may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, and on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals" (Public Health Service Act 301 (d), 42 U. S. C. 241 (d), as amended by Public Law No. 100-607, Section 163 (November 4, 1988)).

Accordingly, this special privacy protection can be granted only to research (i.e., a systematic investigation, designed to develop or contribute to generalizable knowledge). It is granted only when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives.

The study subjects should be informed that a Certificate is in effect, and be given a fair and clear explanation of the protection it affords, including the limitations and exceptions. This information will be included in the informed consent. Please see below some suggested wording:

"We have received a Certificate of Confidentiality from the National Institute on Drug Abuse, which will help us protect your privacy. The Certificate protects against the involuntary release of information about your participation in this study. The researchers involved in this project cannot be forced to disclose your identity or your participation in this study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, you or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests disclosure of your participation, the researchers will provide research data. The Certificate does not protect against that voluntary disclosure.

Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or a Food and Drug Administration request under the Food, Drug and Cosmetics Act."

or

"A Certificate of Confidentiality has been obtained from the Federal Government for this study to help insure your privacy. This Certificate means that the researchers cannot be forced to tell people who are not connected with the study, including courts, about your participation, without your written consent. If we see [learn] something that would immediately endanger you, your child, or others, we may discuss it with you, if possible, or seek help."

Study subjects will be notified that a Certificate has expired if they are recruited to the study after the expiration date of the Certificate and an extension of the Certificate's coverage has not been granted.

If the research scope of a project covered by a Certificate should change substantially, the PI will request an amendment to the Certificate; however, the NIDA Certificate Coordinator may require a new Certificate depending on the extent of the change in scope. An extension of coverage must be requested if the research extends beyond the expiration date of the original Certificate, as research information collected after the expiration of a Certificate is not protected from compelled release.

A Certificate of Confidentiality is a legal defense against a subpoena or court order, and is to be used by the researcher to resist disclosure. The researcher should seek legal counsel from his or her institution if legal action is brought to release personally identifying information protected by a certificate. The Office of General Counsel for DHHS is willing to discuss the regulations with the researcher's attorney.