STUDY #: NIDA-CPU-0003

PHASE 1, DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE ESCALATING ASSESSMENT OF POTENTIAL INTERACTIONS BETWEEN INTRAVENOUS COCAINE AND RPR 102681

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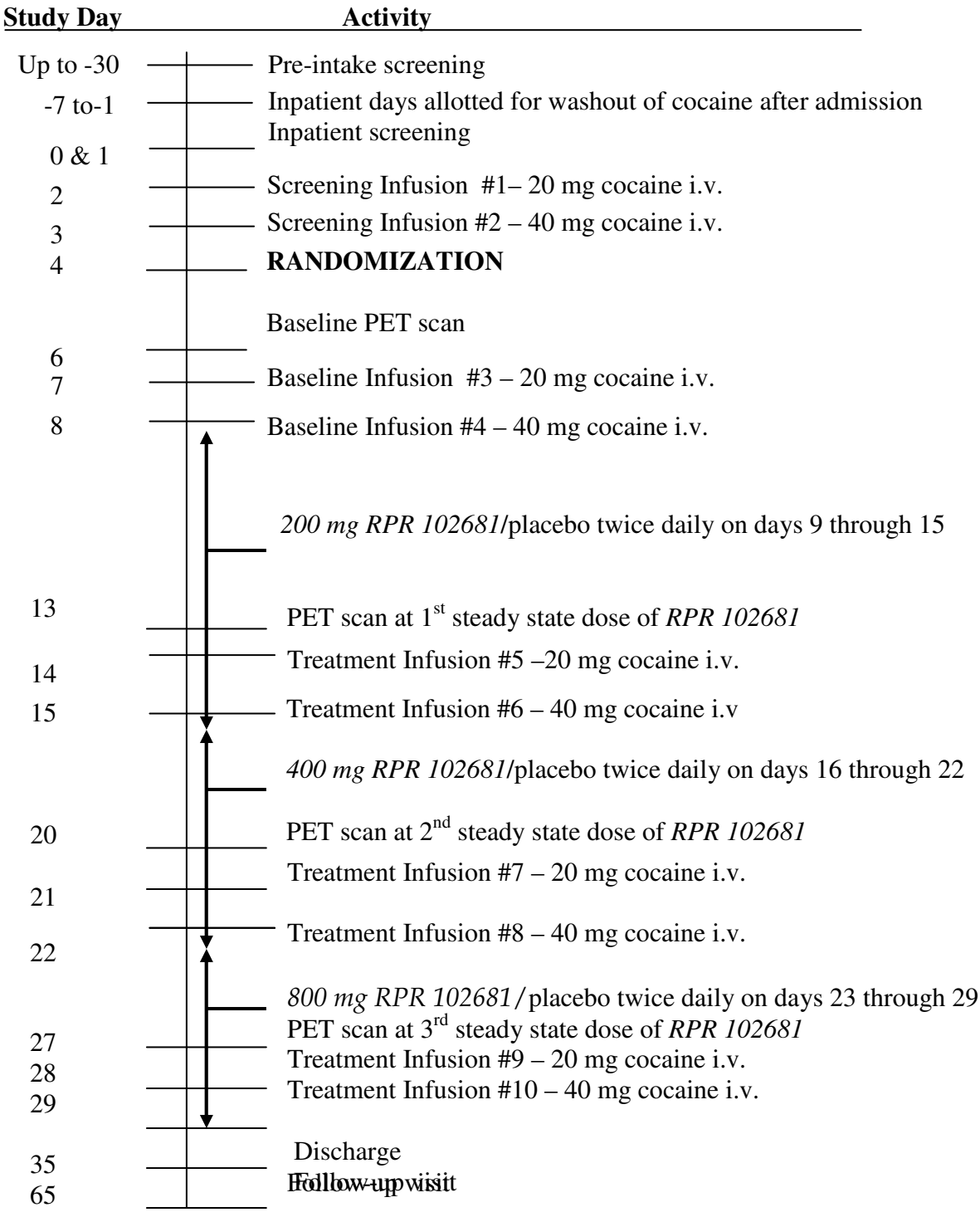
1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ANOVA	analysis of variance
ARCI	Addiction Research Center Inventory
ASI-Lite	Addiction Severity Index-Lite
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	area under the blood concentration-time curve
BE	benzoylecgonine
BDI	Beck Depression Inventory
BP	Blood Pressure
BPRS	Brief Psychiatric Rating Scale
BSCS	Brief Substance Craving Scale
BSI	Brief Symptom Inventory
BUN	blood urea nitrogen
CAP	College of American Pathologists
CCK-B	cholecystokinin-B
CLIA	Clinical Laboratory Improvement Amendment of 1988
COPD	chronic obstructive pulmonary disease
CPU	Clinical Pharmacology Unit
CRF	Case Report Form
CPK	creatinine phosphokinase
DAT	dopamine transporter
DHHS	Department of Health and Human Services
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DSMB	Data and Safety Monitoring Board
DTR&D	Division of Treatment Research and Development
ECG	electrocardiogram
GCP	good clinical practices
HIV	human immunodeficiency virus
HR	heart rate
IRB	Institutional Review Board
i.v.	intravenous(ly)
LDH	lactate dehydrogenase
MAO	monoamine oxidase
mg	milligrams
mL	milliliter
MRI	magnetic resonance imaging
NDA	New Drug Application
NIDA	National Institute on Drug Abuse
PET	positron emission tomography
PK	pharmacokinetic(s)
POMS	Profile of Mood States

Abbreviation	Definition
PPD	purified protein derivative (test for tuberculosis)
RPR	rapid plasma reagin (test for syphilis)
SAE	serious adverse event
SCID	structured clinical interview for DSM-IV
SERT	serotonin transporter
USUHS	Uniformed Services University of the Health Sciences
VAS	Visual Analog Scale

2 STUDY SCHEMA



3 ABSTRACT

STUDY OBJECTIVES: This is a human laboratory clinical pharmacology study to assess potential interactions between intravenous (i.v.) cocaine and RPR 102681 administered in 3 escalating doses.

Primary: The primary objective of this study is to determine if there are significant interactions between RPR 102681 treatment concurrent with i.v. cocaine infusions of 20 and 40 mg by measuring adverse events and cardiovascular responses [heart rate (HR), blood pressure (BP), and electrocardiogram (ECG)].

Secondary:

1. To evaluate whether administration of RPR 102681 alters the pharmacokinetics (PK) of cocaine or its major metabolite, benzoylecgonine (BE).
2. To determine PK of RPR 102681 during treatment at a dose of 200, 400 and 800 mg twice a day (b.i.d.).
3. To evaluate whether RPR 102681 treatment alters the subjective effects of cocaine measured by Adjective Scale and Visual Analog Scale (VAS) and craving measured by Brief Substance Craving Scale (BSCS).
4. To assess the effects of RPR 102681 on mood and personality using Brief Symptom Inventory (BSI), Beck Depression Inventory (BDI), Brief Psychiatric Rating Scale (BPRS) and Profile of Mood States (POMS) assessments and on the abuse liability using the Addiction Research Center Inventory (ARCI).
5. To assess the effects of RPR 102681 on serum prolactin levels.
6. To evaluate whether treatment with RPR 102681 induces changes in baseline DA release in striatum, as assessed by PET scan with [^{11}C]-raclopride.

STUDY DESIGN: This is a dose escalation, double-blind, placebo-controlled inpatient study in which 12 cocaine-experienced volunteers will serve as subjects. Subjects will enter in a block randomization schedule such that in each of 4 blocks, two subjects will receive RPR 102681 and one will receive matched placebo. Subjects in the first two blocks will complete the study before the subjects in the other two blocks proceed; this will make it possible to analyze the PET scans after the first 6 subjects have completed without breaking the blind and to decide whether the PET scans should be administered to the next 6 subjects. If there are significant changes in the PET scans of these first 6 subjects, the PET scans will not be done on the remaining 6 subjects; if the PET scan findings are not definitive, the PET scans will be administered to the next 6 subjects.

After establishing eligibility including cardiovascular responses to screening cocaine infusions of 20 mg and 40 mg i.v. (days 2 and 3), subjects will be randomized to receive either RPR 102681 or matched placebo. Three days after second screening infusion and with urine assay negative for cocaine, all subjects will receive baseline cocaine infusions of 20 mg and 40 mg i.v. on two consecutive days (days 7 and 8) and start treatment the next day (day 9) with 200 mg of RPR 102681 twice daily (b.i.d.) or matched placebo b.i.d. for seven (7) days. After beginning of daily

treatment with either RPR 102681 or placebo, subjects will receive treatment cocaine infusions of 20 mg and 40 mg i.v. on two consecutive days (days 14 and 15). After seven (7) days of treatment with the lowest dose of RPR 102681 (200 mg b.i.d.), the dosing will escalate to the next higher dose sequentially, 400 mg b.i.d and then 800 mg b.i.d. Subjects will receive 7 days at each dose of RPR 102681 with no washout between dosage levels and cocaine infusions of 20 mg and 40 mg i.v. on the two last days of each dosage level. Each cocaine infusion will be preceded or followed by saline i.v. infusion in random order; cocaine and saline infusions will be administered 60 minutes apart. Subjects will receive PET scans with [^{11}C]-raclopride at baseline after uneventful completion of screening cocaine infusions and assignment to RPR 102681 or placebo treatment (day 6) and on the fifth day of each RPR 102681 dose level (days 13, 20 and 27). The subjects will be discharged 5 days after the last infusion of cocaine (day 35). Subjects will be requested to return for follow-up at 1 month after the day of discharge.

STUDY DURATION: Subjects will have up to 30 days for outpatient screening. The inpatient period will include seven days allotted for cocaine washout after admission (days -7 to -1), two days of inpatient screening (days 0 and 1), two days of screening cocaine infusions (days 2 and 3), three days between screening and baseline infusions (days 4-6), two days of baseline cocaine infusions (days 7 and 8), seven days of treatment with the lowest dose of RPR 102681 (days 9-15), seven days of treatment with the next higher dose of RPR 102681 (days 16-22), seven days of treatment with the highest dose of RPR 102681 (days 23-29), and five days of inpatient washout and follow-up (days 30-34). Clinic discharge is on day 35. Subjects will be requested to return for follow up at 1 month after the day of discharge.

SAMPLE SIZE: 12 subjects total. Subjects who receive at least one dose of the study drug will be evaluated as intent-to-treat subjects. Study subjects who complete the inpatient phase of the study will be considered completed subjects. Subjects will continue to be screened until 12 subjects have completed.

POPULATION: Volunteer experienced cocaine users, 18-to-45 years of age, who have used cocaine by the smoked or i.v. route in the past six weeks and provided a positive urine test for cocaine within two weeks prior to entering the study.

TREATMENTS: Subjects will receive 200, 400 and 800 mg of RPR 102681 or matched placebo by oral administration twice a day for 7 days at each dose level.

ASSESSMENTS: The primary outcome measure is safety. Safety of cocaine administration in RPR 102681 dosed subjects will be measured by recording adverse events, BP, and HR, and by performing ECG monitoring. Secondary outcome measures include pharmacokinetic parameters, psychological assessments, and serum prolactin and DA release in striatum. Pharmacokinetic interactions between cocaine and RPR 102681 will be assessed by collecting blood and determining levels of cocaine and BE and peak and trough levels of RPR 102681 during cocaine treatment infusions (sessions #6, 8, and 10). The effect of RPR 102681 on cocaine craving will be assessed by BSCS; other psychological assessments include POMS, BSI, BDI, VAS, ARCI, BPRS and Adjective Scale. Serum prolactin levels will be assessed to determine the effect of RPR 102681. At each RPR 102681dosage level, DA release in striatum

will be estimated using PET scan with [^{11}C]-raclopride to check if treatment with RPR 102681 induces changes in baseline DA release.

4 INTRODUCTION AND RATIONALE

4.1 Therapeutic Strategies for Treating Cocaine Abuse

A variety of neuropharmacological strategies are being pursued in the search for an effective treatment for cocaine abuse. These include: 1) blocking cocaine's effects, 2) restoration of central nervous system homeostasis, 3) reducing craving or enhancing the addict's ability to manage his/her response to craving, 4) treating underlying comorbid conditions that may predispose targeted subpopulations toward dependence, and 5) stress reduction to prevent relapse.

4.1.1 Use of Dopaminergic and Serotonergic Agents to Treat Cocaine Dependency

In the mid-90s, after the earlier pharmacologic trials of tricyclic antidepressants to treat cocaine dependence (Gawin, 1986; Giannini *et al.,* 1986), the search for an effective pharmacotherapy for cocaine addiction was focused on dopaminergic agents (bromocriptine, bupropion, cabergoline) with direct or indirect agonist activity at dopamine receptors (Johanson and Schuster, 1995). Cocaine binds at the dopamine transporter and inhibits neurotransmitter reuptake, thus leading to a build-up of extracellular dopamine levels and potentiation of DAergic neurotransmission in mesolimbocortical pathways (Kuhar *et al*., 1991).

Different approaches to influence drug seeking behavior include restoring dopamine levels by treatment with a) dopamine agonists, b) inhibitors of MAO that convert dopamine into dihydroxyphenylacetic acid and c) inhibitors of catechol-*O*-methyltransferase that converts dihydroxyphenylacetic acid into homovanillic acid. This approach is based on a combination of theory and experimental data suggesting that chronic cocaine use depletes brain dopamine, which is experienced as increased cocaine craving. In addition, the results of recent studies indicating that serotonin and norepinephrine receptors are also involved in cocaine addiction (Sora *et al.,* 2001), fostered concepts that utilize the structure of dopamine transporter (DAT) domains involved in cocaine recognition (Kitayama *et al.,* 1993; Lin *et al.,* 1999) and the sequence homologies between DAT and serotonin transporter (SERT) (Uhl and Hartig, 1992) for a rational design of new drugs to treat cocaine dependence.

4.1.2 Cholecystokinin-B (CCK-B) Receptor Antagonists as Potential Study Agents to Treat Cocaine Dependency

Recently, a new approach that utilizes CCK-B receptor antagonists for treatment of cocaine dependency has evolved. It is based on the ability of activated CCK-B receptors to counteract the effects of dopaminergic systems in the nucleus accumbens, a brain area that plays a crucial role in motivation and reward mechanisms (Tanganelli *et al.,* 2001). The antagonists of CCK-B receptors have been shown to effectively reduce both cocaine consumption and cocaine withdrawal-associated anxiety in animal models of addiction (Costall *et al.,* 1991).

Cholecystokinin is a "gut-brain" peptide that exhibits a variety of physiological effects in the gastrointestinal tract and central nervous system through CCK receptors (Noble and Roques,

1999). CCK was first isolated from the porcine duodenum as a 33-amino acid peptide (CCK_{33}) and subsequently found in high density in the mammalian brain. The C-terminal sulfated octapeptide fragment of CCK (CCK_8) is one of the major neuropeptides of the brain that has been shown to be involved in numerous physiological functions such as feeding behavior, central respiratory control and cardiovascular tonus, vigilance states, memory processes, nociception, and emotional and motivational responses (Crawley, 1991; Noble and Roques, 1999). Two receptor subtypes for CCK have been identified, CCK-A (A for "alimentary") and CCK-B (B for "brain"). The CCK-A receptors are located mainly in the periphery but are also found in some regions of the brain (Hill *et al.,* 1987a,b); they have much higher affinity (1,000-fold) for the sulfated than for the non-sulfated form of CCK_8. The major population of central nervous system CCK receptors is of CCK-B subtype, which is also found in the stomach and vagus nerve (Hill *et al.,* 1987a); they exhibit similar affinity to sulfated and non-sulfated forms of CCK_8 as well as for the shorter fragments down to CCK_4. The gastrin receptor was found to be identical to the CCK-B receptor.

Numerous data support the existence of physiological interactions ("crosstalk") between endogenous CCK and dopaminergic systems in mammalian brain. The neuroanatomical association between DA and CCK in the ventral tegmental area, nucleus accumbens and the ascending mesolimbic pathways (Hokfelt *et al.,* 1980) suggests that CCK may act as a modulator of dopaminergic neurotransmission in midbrain and thus have a role in the regulation of drug dependence-linked motivation and reward mechanisms that are mediated by striatonigral and striatopallidal dopaminergic pathways. Indeed, mesolimbic CCK system is activated in response to repeated cocaine administration (Beinfeld *et al.,* 2002). Thus, cocaine treatment increases extracellular CCK in nucleus accumbens shell, an effect that is enhanced in rats that are behaviorally sensitized to cocaine, which is indicative of the important role of CCK (via modulation of dopamine neurotransmission) in expression of cocaine sensitization (Beinfeld *et al.,* 2002). Recent biochemical and microdialysis studies provide evidence for an antagonistic CCK-B/D2 dopamine receptors interaction in the regulation of DAergic transmission in the nucleus accumbens, a brain area that plays a crucial role in motivation and reward mechanisms (Tanganelli *et al.,* 2001). Injection of CCK_8, a CCK-B agonist, into the rat ventral tegmental area leads to a reduction in electrical stimulation-induced DA release from nucleus accumbens (Xie *et al.,* 2001), and CCK-B receptor-deficient mice exhibit a basal increase in locomotor activity, which is DA-dependent and completely blocked by the D2 DA receptor antagonist sulpiride (Dauge *et al.,* 2001).

It is hypothesized that deregulation of CCK-B/D2 dopamine receptor interaction, induced, for instance, by CCK-B antagonists, may play an important role in diseases, such as addiction, depression and schizophrenia. CCK-B antagonists effectively reduce cocaine consumption and anxiety associated with cocaine withdrawal (Costall *et al.,* 1991), while CCK agonists produce the opposite effect (Crespi *et al.,* 1998). Also, mutant mice lacking CCK-B receptor are less sensitive to cocaine (locomotor activity test) and develop sensitization to morphine more easily than wild type mice (Dauge *et al.,* 2001).

CCK-B receptor antagonists also appear to exert antidepressant effects in humans (Crawley, 1991) and to act as anxiolytics in animal models of fear and anxiety (Dauge and Roques, 1995; Dauge and Lena, 1998). These antidepressant properties of CCK-B receptor antagonists may be

useful for treatment of abstinence syndrome in opioid dependent subjects and thus to prevent the possibility of relapse, which is one of the important issues in addiction treatment strategies. Importantly, in an animal model of chronic ethanol treatment, CCK-B receptor antagonists proved to be effective in protection against anxiety-related behavior produced by ethanol withdrawal (Wilson *et al.,* 1998; Wilson and Little, 1998).

RPR 102681, a potent non-peptide antagonist of CCK-B receptor, is the drug to be investigated in this study as a potential medication for treatment of cocaine abuse. Before clinical investigations to determine RPR 102681 efficacy as a pharmacological treatment for cocaine abuse and dependence can proceed, a thorough study of the safety, tolerability and pharmacokinetics of the agent is required. The results of two phase 1 double-blind placebo-controlled clinical studies of RPR 102681 in healthy volunteers conducted in France (Caplain, 1997, 1998) indicate that RPR 102681 is well tolerated and no serious adverse events have been reported in either single or multiple dose schedules.

4.2 Cocaine

Pharmacology. Cocaine is a potent inhibitor of monoamine transporters including dopamine, serotonin, and norepinephrine transporters (Fleckenstein *et al.,* 2000; Miller *et al.,* 2001). Cocaine binds at the dopamine transporter and inhibits neurotransmitter reuptake, leading to a build-up of extracellular dopamine levels and potentiation of mesolimbocortical pathways (Kuhar *et al*., 1991). Neuroimaging (positron emission tomography) studies of human volunteers who regularly abuse cocaine indicate that doses used by cocaine abusers lead to a significant brain dopamine transporter blockade, which is associated with subjective effects of cocaine (self-reported "high") (Volkow *et al*., 1997). Single gene knockout studies in mice of dopamine, serotonin or norepinephrine transporters indicated that any one of these transporters might be able to mediate cocaine reward in the other's absence (Sora *et al.,* 1998; Xu *et al.,* 2000). Sora *et al.* (2001) found that cocaine reward depends on both DAT and SERT blockade and that serotonin, as well as dopamine, plays a critical role in the development of cocaine addiction. The effects of transporter gene copy numbers on the cocaine place preference test indicated a greater role for DAT than SERT in cocaine reward/reinforcement in mice, consistent with previous pharmacological studies. Thus, mice with even a single DAT gene copy and no SERT copies still experienced reward/reinforcement behavior following cocaine administration, while cocaine-induced reward/reinforcement behavior was totally blocked in mice with no DAT gene and either half-normal or absent SERT.

Cocaine affects nearly every organ and system, with the most dramatic changes being observed in the cardiovascular system and the brain. An important factor of cocaine-induced toxicity is vasoconstriction of coronary arteries and cerebral blood vessels combined with increased platelet aggregation, which can lead to focal or general ischemic episodes and myocardial and cerebral infarctions. In the cardiovascular system, tachycardia, hypertension, ruptures of blood vessels, arrhythmias, and arteriosclerotic lesions are typical complications of cocaine abuse that often precede myocardial ischemia and infarction (Karch, 1993). Chronic use of cocaine can result in serious neuropathies, including optic nerve neuropathy, and can lead to seizures, cerebral infarction, cerebral hemorrhage, multifocal cerebral ischemia, and cerebral atrophy (Majeska *et al*.,1996). Psychiatric impairments associated with cocaine abuse include cognitive deficits, particularly in attention, problem solving, abstraction, arithmetic performance and short-term

memory (Majeska *et al.,*1996). The most significant psychopathologies observed in cocaine addicts include anhedonia, anxiety, anergy, paranoia, depression, and bipolar mood disorder, which may predispose to suicide and are believed to contribute to cocaine craving and relapse. Cocaine seems to be hepatotoxic in humans (Marks and Chapple, 1967); this hepatotoxicity is enhanced by drugs such as barbiturates, alcohol and cocaine adulterants. Cocaine also induces pulmonary disorders, which are particularly severe in cocaine smokers. These disorders include barotrauma, inflammation and lung infections, pulmonary congestion, edema, hypertrophy of pulmonary arteries, and pulmonary necrosis (Karch, 1993).

Cocaine Pharmacokinetics. The distribution half-life of cocaine from an intravenous (i.v.) dose is about 10 min and the elimination half-life of cocaine is about 1 hour (50-80 min) (Jeffcoat *et al.,* 1989).

Cocaine Metabolism. Cocaine is primarily metabolized by esterases in the plasma and liver (Stewart *et al.,* 1977; Dean *et al.,* 1991) to inactive metabolites, benzoylecgonine (BE), ecgonine methyl ester and ecgonine. A very small portion of cocaine is metabolized by hepatic microsomal enzymes to an active metabolite, norcocaine (N-demethyl metabolite). In the presence of ethanol, liver carboxylesterase catalyzes the ethyl transesterification of cocaine to form cocaethylene plus methanol (Dean *et al.,* 1991).

Cocaine Dose Justification. Intravenous cocaine administration spanning the doses proposed for use in this study (20 mg and 40 mg) have been previously investigated in human laboratory clinical trials (Johnson *et al.,* 1998; Walsh *et al.,* 1994). Johnson and colleagues conducted continuous non-invasive cardiovascular monitoring in eight healthy cocaine addicts receiving intravenous doses of cocaine 0.325 mg/Kg or 0.650 mg/Kg. They demonstrated dose dependent increases in pulse and mean arterial pressure following cocaine administration that peaked 5 min post-cocaine infusion with a maximal responses being sustained for a further 15 and 35 min afterwards, respectively. Cocaine administration had no significant effect on peripheral oxygen saturation, and no clinical abnormalities of rhythm or conductivity were seen on ECG. These doses of cocaine (20 mg and 40 mg) and the method of single-dose i.v. cocaine administration as well as procedures for cardiovascular monitoring appear to be relatively safe for laboratory studies of healthy cocaine addicts with no pre-existing cardiovascular disease. Importantly, in a phase 1 clinical trial study of fluoxetine, intravenous cocaine doses of 20 mg and 40 mg did not produce any adverse physiological or subjective reactions in 5 healthy adult male volunteers with histories of cocaine abuse (Walsh *et al.,* 1994).

Prolactin as a Biological Marker for Dopaminergic Tone. Acute cocaine administration alters secretion of anterior pituitary hormones in experimental animals, and cocaine abuse may compromise neuroendocrine function in humans. The effect of cocaine on prolactin release is consistent with both cocaine-induced activation of dopaminergic systems and with dopaminergic inhibitory control of prolactin release from the anterior pituitary. D2 dopamine receptor agonists, such as bromocriptine decrease plasma levels of prolactin (Mastronardi *et al.,* 2000). On the other hand, D2 dopamine receptor antagonists, i.e. haloperidol, increase plasma levels of prolactin. Also, alpha-methyl-*p*-tyrosine (inhibitor of tyrosine hydroxylase and thus of dopamine synthesis) increases plasma levels of prolactin (Tohei *et al.,* 2000). Single intranasal administration of cocaine to 12 healthy male volunteers without a history of drug abuse inhibited

prolactin secretion (Heesch *et al.,* 1996). Also, in cocaine-dependent men plasma prolactin levels decreased significantly after i.v. administration of cocaine (Mendelson *et al.,* 1992). However, cocaine's effects on prolactin are biphasic in 10 of 18 animal studies. Thus, prolactin suppression was followed by rebound elevation within 2 hours post-cocaine that exceeded baseline levels by up to and even over 100% (Mello *et al.,* 1990). During chronic cocaine exposure basal prolactin levels started increasing after 2 months exposure and in 300 days were higher than in drug-free control *Rhesus* monkeys by 227-350% (Mello *et al.,* 1994). This increase of basal prolactin levels was reversed to below the baseline levels by dopamine infusion, confirming the involvement of the dopaminergic system in the effects of cocaine.

The results of animal studies are consistent with clinical reports of hyperprolactinemia in chronic cocaine abusers. Hyperprolactinemia was found in 17 patients hospitalized for cocaine abuse (27.5+/-10.2 ng/mL) and persisted during the course of 4 weeks of hospitalization until discharge (Mendelson *et al.,* 1988). This persistent elevation of plasma prolactin levels after cocaine withdrawal may reflect a chronic cocaine-induced derangement in neural dopaminergic regulatory systems. In this context, a hypothesis of this study is that administration of RPR 102681 will affect the basal plasma prolactin level, which may be elevated in cocaine-dependent subjects with a long history of abuse.

Imaging of Mesolimbic Dopamine Transmission with Positron Emission Tomography (PET). Dopamine transmission in the mesolimbic system plays a critical role in the pathophysiology of reinforcing effects of virtually all drugs of abuse, including cocaine. Dopamine neurotransmission will be evaluated by PET scan with [^{11}C]-raclopride, a D2 dopamine receptor antagonist that competes with endogenous dopamine for binding to the receptor. Dopamine release in striatum will serve as a measure of the effect of RPR 102681 on the dopaminergic system in brain and will be estimated by measuring the density of D2 dopamine receptor binding sites (B_{max}), affinity (K_d) and binding potential (BP). Due to its rapid accumulation in the striatum (a steady state is reached at about 40 minutes after injection), [^{11}C]-raclopride is widely used to monitor changes in the dopaminergic system following administration of opioid dependence medications (Volkow *et al*., 1996; Hietala *et al.,* 1999; Mawlawi *et al.,* 2001).

[^{11}C]-raclopride displacement by endogenously-released dopamine will be used as a measure of the modulatory effect of CCK-B antagonism on dopamine neurotransmission. This will be helpful to demonstrate the mechanism of action of RPR 102681 and identify an effective dose for use in outpatient trials.

4.3 RPR 102681

4.3.1 Chemistry

RPR 102681 has a chemical name of (2S)-2-{3-{3{[(2R,4R)-4-tert-butoxycarbonyl-2-(2-fluorophenyl)-3-thiazolidinyl] carbonylmethyl}ureido}phenyl}propionic acid, a molecular formula of $C_{26}H_{30}FN_3O_6S$, and a molecular weight of 531.61.

RPR 102681 is a slightly hygroscopic, white to slight yellow amorphous powder. Its solubility in water is low (about 0.1 mg/mL), but it is sparingly soluble in 0.1 M sodium phosphate, pH 7.4

(about 20 mg/mL). RPR 102681 is freely soluble in ethyl acetate (about 400 mg/mL) and very soluble in ethanol and dimethylformamide (about 1000 mg/mL for both).

4.3.2 Pharmacology

RPR 102681 is a potent non-peptide antagonist of the cholecystokinin-B (CCK-B) receptors (Boehme *et al.,* 1997). It displays high (nanomolar) affinity for human CCK-B receptors and about 2,000-fold selectivity to CCK-B versus CCK-A receptors. RPR 102681 exhibits potent antagonist properties at central and peripheral CCK-B receptors. In contrast to limited solubility and oral bioavailability of the first generation of CCK-B receptor antagonists (L-362, 260, PD-134,308), RPR 102681 readily penetrates the blood brain barrier and is detected in rat brain as early as 0.25-0.5 hours after oral administration (Archimbaud and Martinet, 1995; Gaillard and Martinet, 1996).

Intraperitoneal administration of RPR 102681 stimulates dopamine release in the ventral striatum (measured by microdialysis), and at the highest dose tested (20 mg/Kg), the release of dopamine is almost tripled compared to baseline values (Imperato *et al*., 1995a; Obinu *et al*., 1997). The ability of RPR 102681 to interfere with psychostimulant abuse has been demonstrated in animal models. Thus, RPR 102681 reduces amphetamine and cocaine self-administration in drug-naïve mice and drug-experienced rats but it does not alter cocaine- or amphetamine-induced place preference (Frata, 1996, a-e). RPR 102681 reduces alcohol and "pleasurable" food consumption in rats and monkeys (Ervin and Palmour, 1995, Imperato *et al.,* 1995b). Importantly, RPR 102681 does not have abuse liability as it is not self-administered in mice, does not induce place preference in rats and does not substitute for cocaine or amphetamine in rats (Frata, 1995, a-c; Obinu *et al*., 1997).

4.3.3 Pharmacokinetics

RPR 102681 is rapidly absorbed from the human gastrointestinal tract with oral bioavailability of about 57%; the peak blood concentrations are reached at 0.5 to 1.5 hours (single dose with escalation) and at 1 to 2 hours (repeated dosing) after ingestion (Caplain, 1997, 1998). The mean elimination half-life of RPR 102681 is 11.7-34.3 hours. The mean plasma peak concentrations (C_{max}) and mean areas under the plasma concentrations-time curves (AUC_{0-24}) increased in a dose-related manner within the dose range of 1 to 50 mg, after which they still increased with dose but not proportionally and in an irregular manner (Caplain, 1997). These parameters (C_{max} and AUC_{0-24}) increased in a linear dose-related manner in all three repeated dosing groups (300, 600 and 800 mg b.i.d.) (Caplain, 1998).

A high inter-individual variability in C_{max} and $AUC_{(0-t)}$ values was observed (up to 87%), especially in 700 and 1300 mg single dose groups (Caplain, 1997) and in all three repeated dosing groups of RPR 102681 (300, 600 and 800 mg b.i.d.) (Caplain,1998). These inter-individual differences in PK of RPR 102681 may result, in part, from variations in the activity of CYP3A4, a ketoconazole-inhibited member of cytochrome P450 (CYP) enzyme family of drug metabolizing monooxygenases that is responsible for biotransformation of RPR 102681 and displays a marked person-to-person variability of the catalytic function (Ozdemir *et al.,* 2000).

4.3.4 Metabolism

Knowledge of the major pathway for RPR 102681 metabolism is necessary to predict the likelihood of metabolism-mediated drug-drug interactions that may affect the clinical outcome of treatment in subjects who receive concomitant medications. Cytochrome P450 3A4 (CYP3A4), a ketoconazole-inhibited member of the cytochrome P450 family of drug-metabolizing monooxygenases, appears to be the major enzyme responsible for RPR 102681 degradation by liver microsomes (Guo *et al*., 1995). The ability of RPR 102681 to induce drug-drug interactions via inhibition of human liver CYP450 enzymes has also been studied, and RPR 102681 did not inhibit any of the following isoforms tested CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 (Guo *et al*., 1996).

4.3.5 Toxicology

In a single dose oral toxicity study in rats, no mortality was observed at doses up to 2000 mg/Kg, the highest dose tested (Caplain, 1998). No serious adverse reactions were reported in a single dose oral toxicity study in rats and in a repeated oral toxicity study in rats and dogs. No electrocardiographic and ophthalmologic findings were noted. The main RPR 102681-related adverse events were noisy/labored respiration in rats (1000 mg/Kg/day and above), soft/liquid feces in rats (300 mg/Kg/day and above) and dogs (100 mg/Kg/day and above), reduced motor activity in rats (1000 mg/Kg/day and above), and excessive salivation in rats (300 mg/Kg/day and above). Decreases in urinary osmolarity and sodium and potassium values have been reported in rats at doses higher than 1000 mg/Kg/day, and urinary sodium values have been decreased in dogs at 100 mg/Kg/day and above. As to clinical chemistry parameters, hyperglycemia was reported in rats at 300 mg/Kg/day and above, and in dogs, alkaline phosphatase activity was increased at 100 mg/Kg/day and above, alanine aminotransferase was increased and total cholesterol values decreased at 500 mg/Kg/day dose. Decrease in white blood cell count at 300 mg/Kg/day and above and increase in red blood cell count at 600 mg/Kg/day were reported in rats. RPR 102681-related organ changes were limited to reduced thymus weights and lymphoid atrophy of thymus cortex in rats at 600 mg/Kg/day and were likely to be associated with stress.

In the reproductive toxicity studies, there was no evidence of negative effects of RPR 102681 on the fertility of female rats. RPR 102681 did not exhibit embryotoxic effects in pregnant rats and rabbits and is not mutagenic.

4.3.6 Previous Human Experience

In a single dose with escalation study (Caplain, 1997), 88 healthy male volunteers received a single oral dose of RPR 102681, ranging from 1 to 1600 mg (1, 5, 20, 50, 100, 200, 400, 700, 1000, 1300 and 1600 mg). RPR 102681 was well tolerated up to the maximum administered dose of 1600 mg with only minor and non-specific adverse events. Dose escalation was stopped prior to reaching the maximum tolerated dose due to evidence of saturation in PK at high doses, most probably caused by high number of capsules to be swallowed (16 capsules required for 1600 mg dosing).

No serious adverse events occurred on this study, and a total of 24 adverse events was recorded in 18 out of 88 subjects (20.5%). The most frequently reported adverse events were postural

hypotension (6 occurrences), headaches (3 occurrences), somnolence (3 occurrences), diarrhea (2 occurrences), and euphoria (2 occurrences). No clear dose relationship was evident in the occurrence of adverse events. No clinically significant changes were observed in physical examination, vital signs and laboratory examinations. Minor ECG abnormalities considered as not drug related were observed in 2 subjects.

A fixed single oral dose of 600 mg RPR 102681 was well tolerated in healthy female subjects (n=8) (Caplain,1998). The only adverse event reported was metrorrhagia (spotting) in 2 subjects (1 receiving RPR 102681 and another receiving placebo).

In a repeated oral doses study (Caplain,1998), RPR 102681 (300, 600 and 800 mg b.i.d.) was administered for 14 days to three groups of healthy male volunteers (n=8 each). RPR 102681 was well tolerated up to the maximum administered dose of 800 mg b.i.d (total daily dose of 1600 mg) with only minor and not-specific adverse events. The most frequent adverse events observed were flatulence (4 subjects receiving 300 mg b.i.d. RPR 102681), pharyngitis (3 subjects receiving 300 mg b.i.d. RPR 102681 and 1 subject receiving 600 mg b.i.d. RPR 102681), headache (1 subject receiving 600 mg b.i.d. RPR 102681 and 2 receiving placebo). Dose escalation was stopped at 1600 mg of RPR 102681 daily due to evidence of saturation in pharmacokinetics at high doses most probably due to the high number of capsules to be swallowed (16 capsules required for 1600 mg dosing).

In both paradigms (single dose with escalation and repeated dosing), RPR 102681 showed no evidence of central effects, and produced no significant or consistent changes in subjective ratings assessed by VAS or sleep questionnaire and in objective measurements of psychomotor performance assessed with a battery of psychometric tests. RPR 102681 had no effect on the plasma concentrations of the following hormones: prolactin, growth hormone, luteinizing hormone, adrenocorticotropin hormone, neuropeptide Y and melatonin. However, it enhanced dose dependently the physiological increase in plasma gastrin levels observed after meal intake (Caplain, 1997, 1998).

4.3.7 Dose Justification.

Oral RPR 102681 administration spanning two of the doses proposed for use in this study (400 mg and 800 mg b.i.d.) have been previously investigated in a human laboratory clinical trial (Caplain, 1998). Thus, repeated oral doses of RPR 102681 (300, 600 and 800 mg b.i.d.) have been well tolerated during 14 days-long treatment up to the maximum administered dose of 800 mg b.i.d (total daily dose of 1600 mg) with only minor and not-specific adverse events. Dose escalation was stopped at 1600 mg of RPR 102681 daily due to evidence of saturation in pharmacokinetics at high doses most probably due to the high number of capsules to be swallowed (16 capsules required for 1600 mg dosing).

4.4 Safety Considerations

4.4.1 RPR 102681 Safety

No serious adverse events occurred in the two clinical studies with RPR 102681 conducted in France (Caplain, 1997, 1998). The principal adverse events in the first clinical study with RPR 102681 (Caplain, 1997) were postural hypotension (6 occurrences), headaches (3 occurrences),

somnolence (3 occurrences), diarrhea (2 occurrences), and euphoria (2 occurrences). The most frequent adverse events observed in the 2nd clinical study with RPR 102681 (Caplain, 1998) were flatulence (4 occurrences), pharyngitis (4 occurrences), and headache (1 occurrence).

Subjects will not be allowed to take concomitant medications, whether prescription or over the counter (OTC), without the permission of the site investigator. Specific medications that will be excluded are ketoconazole, ritonavir and rifampin.

4.4.2 Potential Drug Interactions

In preclinical studies, RPR 102681 reduces cocaine self-administration in drug-naïve mice and drug-experienced rats but does not substitute for cocaine (Obinu *et al*., 1997).

Biotransformation of RPR 102681 is carried out in liver microsomes by cytochrome P450 3A4 (CYP3A4), a ketoconazole-inhibited member of the cytochrome P450 family of drug-metabolizing monooxygenases. Although cocaine is primarily metabolized by esterases in the plasma and liver to inactive metabolites, benzoylecgonine (BE), ecgonine methyl ester, and ecgonine (Stewart *et al.,* 1977; Kloss *et al.,* 1984; Dean *et al.,* 1991), a very small portion of cocaine is oxidized to an active metabolite norcocaine by hepatic microsomal enzyme CYP3A (Ladona *et al.,* 2000). The fact that both RPR 102681 and cocaine are substrates for CYP3A indicates a potential of cocaine-RPR 102681 interaction that may lead to a possible inhibition of each substrate's metabolism by CYP3A. However, norcocaine is a minor metabolite that accounts for only 2 to 6% of the administered cocaine dose (Inaba *et al.,* 1978), and thus the effect of RPR 102681 on cocaine metabolism should be negligible.

4.4.3 Other Safety Considerations

Coadministration of RPR 102681 with specific inhibitors of CYP3A4 such as ketoconazole, ritonavir and rifampin could alter expected therapeutic effects of RPR 102681 as CYP3A4 is the enzyme responsible for metabolism of RPR 102681.

5 STUDY OBJECTIVES

5.1 Primary

The primary objective of this study is to determine if there are significant interactions between RPR 102681 treatment concurrent with i.v. cocaine infusions of 20 and 40 mg by measuring adverse events and cardiovascular responses [heart rate (HR), blood pressure (BP), and electrocardiogram (ECG)].

5.2 Secondary

1. To evaluate whether administration of RPR 102681 alters the pharmacokinetics (PK) of cocaine or its major metabolite, benzoylecgonine (BE).
2. To determine PK of RPR 102681 during treatment at a dose of 200, 400 and 800 mg b.i.d.

3. To evaluate whether RPR 102681 treatment alters the subjective effects of cocaine measured by Adjective Scale and Visual Analog Scale (VAS) and craving measured by Brief Substance Craving Scale (BSCS).
4. To assess the effects of RPR 102681 on mood and personality using Brief Symptom Inventory (BSI), Beck Depression Inventory (BDI), Brief Psychiatric Rating Scale (BPRS) and Profile of Mood States (POMS) assessments and on the abuse liability using the Addiction Research Center Inventory (ARCI).
5. To assess the effects of RPR 102681 on serum prolactin levels.
6. To check if treatment with RPR 102681 induces changes in dopamine release in striatum, as assessed by PET scan with [^{11}C]-raclopride.

6 STUDY DESIGN

This is a dose escalation, double-blind, placebo-controlled inpatient study in which 12 cocaine-experienced volunteers will serve as subjects. Subjects will enter in a block randomization schedule such that in each of 4 blocks, two subjects will receive RPR 102681 and one will receive matched placebo. Subjects in the first two blocks will complete the study before the subjects in the other two blocks proceed; this will make it possible to analyze the PET scans after the first 6 subjects have completed without breaking the blind and to decide whether the PET scans should be administered to the next 6 subjects. If there are significant changes in the PET scans of these first 6 subjects, the PET scans will not be done on the remaining 6 subjects; if the PET scan findings are not definitive, the PET scans will be administered to the next 6 subjects.

After establishing eligibility including cardiovascular responses to screening cocaine infusions of 20 mg and 40 mg i.v. (days 2 and 3), subjects will be randomized to receive either RPR 102681 or matched placebo. Three days after second screening infusion and with urine assay negative for cocaine, all subjects will receive baseline cocaine infusions of 20 mg and 40 mg i.v. on two consecutive days (days 7 and 8) and start treatment the next day (day 9) with 200 mg of RPR 102681 twice daily (b.i.d.) or matched placebo b.i.d. for seven (7) days. After beginning of daily treatment with either RPR 102681 or placebo, subjects will receive treatment cocaine infusions of 20 mg and 40 mg i.v. on two consecutive days (days 14 and 15). After seven (7) days of treatment with the lowest dose of RPR 102681 (200 mg b.i.d.), the dosing will escalate to the next higher dose sequentially, 400 mg b.i.d and then 800 mg b.i.d. Subjects will receive 7 days at each dose of RPR 102681 with no washout between dosage levels and cocaine infusions of 20 mg and 40 mg i.v. on the two last days of each dosage level. Each cocaine infusion will be preceded or followed by saline i.v. infusion in random order; cocaine and saline infusions will be administered 60 minutes apart. Subjects will receive PET scans with [^{11}C]-raclopride at baseline after uneventful completion of screening cocaine infusions and assignment to RPR 102681 or placebo treatment (day 6) and on the fifth day of each RPR 102681 dose level (days 13, 20 and 27). The subjects will be discharged 5 days after the last infusion of cocaine (day 35). Subjects will be requested to return for follow-up at 1 month after the day of discharge.

Subjects who receive at least one dose of the study drug will be evaluated as intent-to-treat subjects. Study subjects who complete the inpatient phase of the study will be considered completed subjects. Subjects will continue to be screened until 12 subjects have completed.

7 STUDY SITE

The study will be conducted at the Uniformed Services University of the Health Sciences (USUHS). On admission, subjects with positive urine drug toxicology will be allowed a seven (7) days-long washout period before first cocaine infusion (session #1).

8 SUBJECT SELECTION

8.1 Inclusion Criteria

In order to participate in the study, subjects must:

1. Be volunteers who are not seeking treatment at the time of the study.

2. Be between 18 and 45 years of age and within 20% of ideal body weight according to the Metropolitan Height and Weight Chart, and weigh at least 45 kg.

3. Meet DSM-IV criteria for cocaine abuse or dependence.

4. Must currently use cocaine by the smoked or i.v. route, and this use must be confirmed by a positive BE urine test once within 30 days prior to entering the study.

5. Be able to verbalize understanding of consent form, able to provide written informed consent, and verbalize willingness to complete study procedures.

6. If female and have a negative pregnancy test within 72 hours prior to receiving the first dose of investigational agent and agree to use one of the following methods of birth control, or be postmenopausal, or have had hysterectomy, or have been sterilized, or be male.

    a) complete abstinence from sexual intercourse
    b) diaphragm and condom by partner
    c) intrauterine device and condom by partner
    d) sponge and condom by partner

Note: oral contraceptives, Depo-Provera, Norplant and intrauterine progesterone contraceptive system are not allowed.

7. Have a history and brief physical examination that demonstrate no clinically significant contraindication for participating in the study.

8. Be able to comply with protocol requirements, Clinical Pharmacology Unit (CPU) rules and regulations, and be likely to complete all the study treatments.

8.2 Exclusion criteria

In order to participate in the study, subjects must not:

1. Have a current or past history of seizure disorder, including alcohol- or stimulant-related seizure, febrile seizure, or significant family history of idiopathic seizure disorder.

2. Have any previous medically adverse reaction to cocaine, including loss of consciousness, chest pain, or seizure.

3. According to DSM-IV criteria as determined by structured clinical interview (SCID), have any history of major psychiatric illness, such as bipolar disorder, depression, manic or dysthymic illness, other than drug dependence or disorders secondary to drug use as determined by a National Institute of Mental Health trained technician.

4. Be pregnant or lactating.

5. Have a history of liver disease or current elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) exceeding the upper limit of normal.

6. Have donated a unit of blood or participated in any other clinical investigation within 4 weeks of enrolling on the study.

7. Have a history of any illness, or a family history of early significant cardiovascular disease, or a history of behavior, that in the opinion of the investigator might confound the results of the study or pose additional risk in administering the investigational agents to the subject.

8. Be seropositive for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) type 1.

9. Have a diagnosis of adult onset asthma (i.e., 21 years or older), or chronic obstructive pulmonary disease (COPD), including those with a history of acute asthma within the past two years, and those with current or recent (past 2 years) treatment with inhaled or oral beta-agonist.

10. Have any illness, condition, and use of medications, that in the opinion of the principal investigator and the admitting physician, would preclude safe and/or successful completion of the study.

11. Currently use illicit drugs besides cocaine and marijuana.

12. Have used any prescription drugs within 14 days of the start of the study or non-prescription drugs within 7 days of the start of the study.

13. Be unable to distinguish between a 20 mg and 40 mg dose of cocaine intravenously during the administration of screening and baseline infusions.

14. Have had prior exposure to radiation for a research study. This excludes having x-rays for medical purposes.

15. Have had tatoos within the last 6 months.

16. Have any metallic body art (such as eye rings, navel rings) that cannot be removed.

17. Have an abnormal MRI finding discovered as part of the PET Scan procedure. (Subjects will be notified immediately of results and advised to contact their primary care physician.)

9 INVESTIGATIONAL AGENTS

9.1 RPR 102681

RPR 102681 capsules, 200 mg, and matching placebo capsules were manufactured by Murty Pharmaceuticals, Lexington, Kentucky, for NIDA. Both the active drug and placebo are in size 0, white opaque hard gelatin capsules.

RPR 102681 capsules, 200 mg: each capsule contains 200 mg of RPR 102681 and excipients such as microcrystalline cellulose, sodium starch glycolate, and magnesium stearate.
Placebo capsules, 200 mg: each placebo capsule contains microcrystalline cellulose, sodium starch glycolate, and magnesium stearate.

The active drug product and placebo are supplied in an amber bottle with 30 capsules per bottle with a bag of desiccant. It is recommended that RPR 102681 capsules and the matching placebo capsules be stored at 4^{o}C in the presence of desiccant to protect from humidity. Exposure to direct light should be avoided.

9.2 Cocaine

Cocaine Hydrochloride solutions, 10 mg/mL in 2 mL ampoule (20 mg dose) and 20 mg/mL in 2 mL ampoule (40 mg dose), were manufactured by Murty Pharmaceuticals for NIDA. The Cocaine Hydrochloride solutions should be stored in the pharmacy vault under refrigerated conditions. Standard controlled substance procedures will govern access to the drug. Cocaine will be administered by i.v. infusion over 60 seconds by the study physician. Any unused drug will be disposed according to standard practices.

10 TREATMENT PLAN

10.1 RPR 102681 and Placebo

Each subject will receive 200 mg of RPR 102681 or matched placebo b.i.d. on study days 9-15, 400 mg of RPR 102681 or matched placebo b.i.d. on study days 16-22, and 800 mg of RPR 102681 or matched placebo b.i.d. on study days 23-29.

10.2 Cocaine

All subjects will receive cocaine infusions on ten days: days 2, 3, 7, 8, 14, 15, 21, 22, 28, and 29. Cocaine will be administered by i.v. push over 60 seconds by the study physician. Subjects will receive 20 mg cocaine i.v. on days 2, 7, 14, 21, and 28 and 40 mg cocaine i.v. on days 3, 8, 15, 22, and 29. For each session (screening, baseline and treatment), subjects will be randomly assigned (1:1 ratio) to receive either saline (at 8:00 a.m.) followed one hour later by cocaine or cocaine (at 8:00 a.m.) followed one hour later by saline in a double-blind fashion (subjects and research staff will be blinded). During the treatment sessions #5-10 (study days 14, 15, 21, 22, 28 and 29), the subjects will take the morning dose of RPR 102681 at 6:05 a.m., and after that will get the infusions at 8:00 a.m. and 9:00 a.m.

10.3 Prior and Concomitant Medication(s)

No prescription medication for 14 days and non-prescription medications (including dietary health food supplements) for 7 days are to be taken by subjects prior to the start of the study. Female subjects must not use oral contraceptives, Depo-Provera, Norplant or intrauterine progesterone contraceptive system, 30 days prior to study participation and during the study. Addition of any medication during the course of the study must be discussed with the NIDA medical monitor prior to administration. Should there be a clinical indication for any additional medication during the course of the study, the name of the drug, dosage, reason for administration, and duration of administration must be recorded on the appropriate case report form (CRF). One multivitamin per day that does not exceed 100% of the recommended daily allowance (RDA) for each component is permitted for ingestion by each subject except during inpatient periods.

10.4 Dietary, Physical Activity, and Other Restrictions

Diet. The consumption of grapefruit juice should be excluded during the study as grapefruit juice is considered to be a clinically important CYP3A4 inhibitor (Ameer and Weintraub, 1997) and may thus increase the bioavailability of RPR 102681, which is metabolized by CYP3A4. For all dosages of RPR 102681, subjects must take both daily doses one hour before meals. Food and drink must be provided by the site (USUHS).

Exercise. Subjects will be instructed to refrain from participation in contact sports and weight lifting from 48 hours before inpatient period until completion of the study.

Tobacco Products. Subjects will be allowed to smoke during the study in designated areas and accompanied by site staff at scheduled times according to the rules of the site (USUHS). Smoking is not permitted from one (1) hour prior to until two (2) hours after drug administration.

Alcohol. Subjects will be questioned about their estimated daily intake of alcohol during the pre-study evaluation of eligibility. Any subject who shows physiological dependence on alcohol requiring medical detoxification will be excluded. Alcoholic beverages are not permitted from 48 hours before the inpatient period until the discharge from the study. Subjects will have a breath analyzer test on admission; if a subject is found to be test positive for alcohol, the investigator or his designee may at his discretion decide if the subject should be rescheduled

11 STUDY PROCEDURES

Appendices IA and IB provide detailed tables of the timing of study activities.

11.1 Screening

Subjects will have up to 30 days for screening. The first seven inpatient days (Days -7 through -1) are allotted for the subjects' urine to become negative for cocaine. Day 0 and day 1 are the days of inpatient screening.

Interested candidates between the ages of 18 and 45 who have been determined to have used cocaine by the smoked or i.v. route, are not seeking treatment, and are available to participate in an inpatient study for 30 days will meet with the investigator 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 study informed consent form approved by the local site's Institutional Review Board *(*IRB). After providing informed consent, the subject will proceed to the screening/baseline assessments phase of the study. The number of subjects that may sign the informed consent is not specified, as subjects will continue to be screened until 12 subjects have completed the study.

Screening of subjects to establish eligibility will occur initially before clinic intake and be completed after intake. Assessments performed before intake include collection of demographic information and completion of a subject locator form, a timeline follow back interview for cocaine use for the past 30 days, medical history, a 12-lead ECG, and physical examination including vital signs (HR and BP). Blood will be collected for complete blood count, chemistries, including liver function tests, infectious disease panel, including human immunodeficiency virus (HIV) type 1, pregnancy and alcohol assessments. Urine will be collected for routine urinalysis. A urine drug toxicology screen will also be conducted for drugs of abuse; it will be repeated until a negative test for cocaine is obtained. With the exception of cocaine, cocaine metabolites, and marijuana, the urine drug toxicology screen must be negative to enroll in the study. Candidates deemed eligible based on the screening assessments mentioned above will be administered a structured clinical interview (SCID) by a trained mental health professional, to determine if there are any underlining psychiatric conditions that might exclude the potential subject from participation. These assessments must be completed within 30 days before clinic intake.

Subjects will be instructed that no prescription/non- prescription medications are to be taken within 14 and 7 days of the start of the study, respectively. Subjects will also be instructed to refrain from using any alcohol from 48 hours before clinic intake until discharge from the study. Subjects will also be instructed to refrain from participation in contact sports and weight lifting from 48 hours before the inpatient period until study completion.

Subjects must be informed of the unknown risks of becoming pregnant and must agree not to become pregnant during the time they are participating in this study. Women of childbearing potential can be enrolled; however, appropriate contraception must be used throughout the study. No oral contraceptives, Depo-Provera, Norplant and intrauterine progesterone contraceptive system are to be taken or used within 30 days prior to the start of the study. Abstinence (starting

at least 14 days prior to study) or double barrier contraception techniques, such as diaphragm and condom (by the partner), intrauterine device and condom, or sponge and condom must be used during the study. If there is any question that a subject will not be reliable in the use of these double-barrier contraceptive methods, she will not be entered into the study.

Women participating in the study will be tested for serum beta-human chorionic gonadotropin (ß-HCG) to detect pregnancy at pre-study screening and within 72 hours prior to receiving study drug. In the case of a positive or borderline serum ß-HCG pregnancy test at the pre-study visit, the subject will not enter the study. Subjects will again be tested prior to discharge from the study. In the case of a positive or borderline test at the end of the inpatient period, the NIDA clinical monitor will be contacted and the pregnancy will be recorded as an adverse event. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been terminated or completed. The outcome of the pregnancy test will be reported to the NIDA clinical monitor without delay within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The result of each pregnancy test will be recorded on a CRF.

All drug-abusing applicants for study participation will receive counseling about drug dependence and be advised that treatment for drug abuse is indicated and available. Applicants not participating in the study will receive treatment referral information as appropriate. At the completion of their participation, study participants will again be advised that treatment is indicated and available, and will be given treatment referral information and assistance.

11.2 Intake Screening

Potential candidates whose screening assessment results do not exclude them from study participation will complete intake procedures and reside full-time as inpatients until discharge or completion of the study. Screening procedures after intake will be completed on the days 0 or 1 before first cocaine infusion and include brief physical exam, vital signs, 12-lead ECG, serum prolactin, urine drug toxicology screen, a ß-HCG (pregnancy test), a blood chemistry, a breathalyzer test, and BSCS, BPRS, BDI, BSI, POMS, ASI-Lite, VAS, ARCI, and Adjective Scale assessments.

11.3 Enrollment and Randomization

A prospective subject who meets all of the study inclusion criteria and does not meet any of the exclusion criteria may be enrolled onto the study. After completing screening cocaine infusions (sessions #1 and #2), subjects will be randomized to receive either RPR 102681 or matched placebo. Twelve (12) subjects will enter in a block randomization schedule such that in each of 4 blocks, two subjects will receive RPR 102681 and one will receive matched placebo. Subjects in the first two blocks will complete the study before the subjects in the other two blocks proceed; this will make it possible to analyze the PET scans after the first 6 subjects have completed without breaking the blind and to decide whether the PET scans should be administered to the next 6 subjects. If there are significant changes in the PET scans of these first 6 subjects, the PET scans will not be done on the remaining 6 subjects; if the PET scan findings are not definitive, the PET scans will be administered to the next 6 subjects.

The data-coordinating center will supply the Research Pharmacist with pre-coded envelopes with treatment assignments. On study day 4, the investigator or study coordinator will obtain the treatment assignment from the Research Pharmacist. The Research Pharmacist will dispense the coded bottle of investigational agent for the subject to the investigator. If a subject is terminated before completing all of the cocaine infusion sessions, a replacement subject will be randomized until 12 subjects have completed the study.

11.4 Cocaine Infusion Sessions

11.4.1 Schedule

Intravenous cocaine infusions will be conducted according to the schedule shown in Table 1. Each series of repeated administrations (screening, baseline, and treatment) will consist of two infusion sessions over two consecutive days and will be conducted in a random saline/cocaine order (Table 1). During the screening and baseline infusion assessments, the subject's responses to cocaine without concomitant RPR 102681 or placebo administration will be assessed. During the treatment infusion sessions, the subject's responses to cocaine with concomitant RPR 102681 or placebo administration will be assessed. Each infusion session will be on different days. The fixed ascending sequence each week is a safety precaution.

Table 1. Cocaine Infusion Session Schedule

Study Phase	Session Number	Study Day	Infusion
Screening	Session 1	2	Saline/20 mg cocaine followed by 20 mg cocaine/saline 1 hr later
Screening	Session 2	3	Saline/40 mg cocaine followed by 40 mg cocaine/saline 1 hr later
Baseline	Session 3	7	Saline/20 mg cocaine followed by 20 mg cocaine/saline 1 hr later
Baseline	Session 4	8	Saline/40 mg cocaine followed by 40 mg cocaine/saline 1 hr later
Treatment	Session 5	14	RPR 102681 200 mg b.i.d./placebo followed by saline/20 mg cocaine 1 hr later and then followed by 20 mg cocaine/saline 1 hr later
Treatment	Session 6	15	RPR 102681 200 mg b.i.d./placebo followed by saline/40 mg cocaine 1 hr later and then followed by 40 mg cocaine/saline 1 hr later
Treatment	Session 7	21	RPR 102681 400 mg b.i.d./placebo followed by saline/20 mg cocaine 1 hr later and then followed by 20 mg cocaine/saline 1 hr later
Treatment	Session 8	22	RPR 102681 400 mg b.i.d./placebo followed by saline/40 mg cocaine 1 hr later and then followed by 40 mg cocaine/saline 1 hr later
Treatment	Session 9	28	RPR 102681 800 mg b.i.d./placebo followed by saline/20 mg cocaine 1 hr later and then followed by 20 mg cocaine/saline 1 hr later
Treatment	Session 10	29	RPR 102681 800 mg b.i.d./placebo followed by saline/40 mg cocaine 1 hr later and then followed by 40 mg cocaine/saline 1 hr later

11.4.2 Conduct of Cocaine/Saline Infusion Sessions

All subjects will receive cocaine infusions on ten days: days 2, 3, 7, 8, 14, 15, 21, 22, 28, and 29. Subjects will receive 20 mg cocaine i.v. on days 2, 7, 14, 21, and 28 and 40 mg cocaine i.v. on days 3, 8, 15, 22, and 29. A study physician will administer each i.v. infusion dose over 1 minute duration. For each infusion session (screening, baseline and treatment), subjects will be randomly assigned (1:1 ratio) to receive either saline at 8:00 a.m. followed one hour later at 9:00 a.m. by cocaine or cocaine at 8:00 a.m. followed one hour later at 9:00 a.m. by saline in a double-blind fashion (subjects and research staff will be blinded). During the treatment infusions (sessions #5-10), the subjects will take the morning dose of RPR 102681 at 6:05 a.m., and after that will get the infusions at 8:00 a.m. and 9:00 a.m. (Table 1).

For a subject to receive the first screening cocaine infusion of 20 mg i.v. (session #1), s/he must have a drug toxicology screening that shows negative urine drug/metabolite levels for drugs of abuse (except marijuana) before conduct of cocaine infusion session. Subjects with positive urine drug toxicologies will be allowed a seven day washout period before screening cocaine

infusion (session #1). The screening infusions are to ensure that volunteers safely tolerate the cocaine test doses.

The baseline cocaine infusions of 20 and 40 mg i.v. (sessions #3 and 4) are performed 3 days after screening cocaine infusion of 40 mg i.v. (session # 2) or when urine is negative for cocaine. The baseline infusions provide cardiovascular and psychological response data in the absence of the investigational agent RPR 102681. Only subjects safely tolerating both 20 mg and 40 mg of cocaine and who can distinguish between the psychoactive effects of these two doses at either the screening or baseline infusions, as assessed by Visual Analog Scale (VAS) and Adjective Scale scores, will continue in the study.

For all dosages of RPR 102681, subjects must take both daily doses one hour before meals. Cigarette-smoking subjects may not smoke from 1-hour prior to infusion session initiation until 90-minutes after the infusion.

Before and after each i.v. infusion, the subjects' physiologic responses will be closely monitored using repeated HR, BP, and ECG readings. During infusion sessions #1-10, BP and HR will be recorded at the following time points relative to infusions: -10, -8, -6, -4, -2, 0 (first infusion), 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 45, 50, 52, 54, 56, 58, 60 (second infusion), 62, 64, 66, 68, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120 minutes and then every 30 minutes for the next five hours (Table 2). ECG will be monitored continuously from 15 minutes before the first infusion until 24 hours after second infusion. 12-lead ECG will be performed at 40 minutes after each infusion. Subjects will be monitored for at least 1 hour after the second infusion by study personnel and staff. Thereafter, nursing staff will monitor participants and take vital signs according to the above schedule until vital signs revert to being within 10% of the baseline.

The Visual Analog Scale (VAS), which assesses psychoactive response to cocaine, will be administered before and at 5, 15, 25 and 35 minutes after each cocaine/placebo infusion, and will be continued every 30 minutes for as long as the symptoms remain. The Adjective Scale will be administered at the same time points as VAS. These scales will allow assessment of cocaine related "high" as well as dysphoric reactions to cocaine withdrawal.

11.4.3 Safety Precautions

A physician will perform the infusions and will be present at least 1 hour after the completion of the infusions. Thereafter, the physician will remain on the medical campus and be available by pager for prompt response, if needed, for at least four hours post-infusion. If a subject demonstrates a significant adverse reaction to cocaine, the cocaine administration will be halted, appropriate medical response will be implemented, and the subject will be discontinued from the remainder of the study. The BPRS will be performed within 1 hour of the completion of each infusion to assess possible acute psychosis due to cocaine.

11.4.4 Stopping Criteria for Further Cocaine Infusion

Cocaine intravenous administration will be discontinued if any of the following events occurs:

1. Systolic BP > 165 mm Hg;

2. Diastolic BP > 100 mm Hg;
3. HR > 130 bpm;
4. Behavioral manifestation of cocaine toxicity, e.g., agitation, psychosis, inability to cooperate with study procedures.

11.4.5 Stopping Criteria for Further Study Participation

Further participation of the subject is stopped if any of the following events occur:

1. Acute chest pain, shortness of breath;
2. Systolic BP > 180 mm Hg sustained for 5 minutes or more;
3. Diastolic BP > 120 mm Hg sustained for 5 minutes or more;
4. Heart rate > (220 - age x 0.85) bpm sustained for 5 minutes or more;
5. Neurological or psychiatric events (e.g., panic or psychosis);
6. A clinically significant ECG abnormality, such as:
    - ST segment elevations in two or more continuous leads of greater than 0.1 mV.
    - ST segment depression of greater than 1 mm that are flat or down-sloping at 80 msec after the J point.
    - New bundle branch block.
    - Mobitz II 2^0 or 3^0 heart block.
    - Atrial fibrillation or atrial flutter or activation of any tachyarrhythmia for greater than 10 seconds.
    - Three or more consecutive ectopic ventricular complexes at a rate of greater than 100 per minute.
7. Any condition that in the clinical judgment of the investigator is of sufficient magnitude to present a danger to the subject.

11.4.6 Volunteer Discontinuation

Subjects will be excluded or discharged if their behavior is disruptive, non-compliant with study procedures, or otherwise not consistent with remaining in the hospital.

11.4.7 Subject Discharge and Follow-Up

The subjects will be discharged from the hospital 5 days after the last infusion of cocaine (session #10) on day 35. Subjects will be requested to return for follow up at 1 month after the day of discharge.

11.4.8 Subject Payment

Subject payment will consist of payment for screening procedures, payment for all in-patient procedures, and final payment at the completion of the outpatient visit. Payments will be back-loaded to provide incentive for subjects to complete the outpatient follow-up.

12 CLINICAL AND LABORATORY EVALUATIONS

Tables summarizing the timing of the clinical and laboratory assessments to be conducted over the entire study period are shown in Appendices IA and IB.

12.1 Screening

Screening evaluations will be performed initially before clinic intake and then in the inpatient setting.

Screening Assessments before Intake. The following evaluations will be performed before clinic intake and must be performed within 30 days prior to intake:

1. Informed Consent;
2. Locator Form;
3. Demographics Information;
4. Cocaine use for prior 30 days using timeline follow back method;
5. Urine drug toxicology screen;
6. Medical history;
7. Physical examination and vital signs (oral temperature, BP, HR and respiratory rate);
8. 12-lead ECG;
9. Hematology;
10. Blood chemistry, including liver function tests;
11. Infectious disease serology;
12. Serum ß-HCG (pregnancy test);
13. Plasma alcohol;
14. Routine urinalysis;
15. SCID.

Inpatient Screening Assessments. The following evaluations will be performed after intake before the first cocaine infusion:

1. Vital signs (BP and HR);
2. 12-lead ECG;
3. Urine drug toxicology screen;
4. Breathalyzer test;
5. Serum prolactin;
6. Blood chemistry, including liver function tests;
7. Serum ß-HCG (pregnancy test);
8. BDI, BSI, BPRS and POMS;
9. ASI-Lite;
10. BSCS;
11. VAS, ARCI, and Adjective Scale;
12. Adverse events daily.

12.2 Evaluations Performed Daily, Every Other Day or Weekly While Inpatient

1. Adverse events will be monitored daily starting as soon as the subject signed the informed

consent form;
2. BSI, BDI, POMS and BSCS will be performed every other day;
3. PET scan with [^{11}C]-raclopride will be performed on each subject in the first two blocks (6 subjects total) after the subject completes screening cocaine infusions uneventfully and is assigned to RPR 102681 or placebo treatment (day 6) and then on days 13, 20 and 27. If there are significant changes in the PET scans of these 6 subjects, the PET scans will not be done on the remaining 6 subjects; if the PET scan findings are not definitive, the PET scans will be administered to the next 6 subjects;
4. Serum prolactin levels will be evaluated on days 15, 22, and 29.

12.3 Evaluations Performed During Infusion Sessions

Table 2 shows the series of activities that occur on days when cocaine infusion sessions are scheduled. Refer to Table 1 for the timing of the infusion sessions according to the study day. Note that not all activities occur at each infusion session. Those activities that do not occur at each infusion session are noted.

Table 2. Cocaine Infusion Sessions Daily Schedule

Time-point	Activity (occurs at all sessions unless otherwise indicated)

Time-point	**Activity (occurs at all sessions unless otherwise indicated)**
6:00 a.m.	Draw blood for prolactin assay (sessions #6, 8 & 10)
6:05 a.m.	**Administer morning dose of RPR 102681/placebo (sessions #5-10)**
7:00 a.m.	Breakfast
7:10 a.m.	BSI, BDI, POMS, BSCS
7:30 a.m.	Draw blood for liver function tests (sessions # 4, 6, 8 & 10)
7:35 a.m.	Insert catheters (catheter for blood may already be in place)
7:40 a.m.	Draw blood for cocaine assay (sessions #4, 6, 8, 10) Draw blood for RPR 102681 assay (sessions #5-10)
-15 min (7:45 a.m.)	**Start continuous monitoring of ECG until 24 hours after last infusion** VAS, ARCI, Adjective Scale, BP, HR
-10 min	BP, HR
-8 min	BP, HR
-6 min	BP, HR
-4 min	BP, HR
-2 min	BP, HR
Time 0 (8:00 a.m.)	**Inject saline/cocaine i.v. 1 min push; BP, HR**
2 min	BP, HR
4 min	BP, HR
5 min	VAS, ARCI, Adjective Scale
6 min	BP, HR
8 min	BP, HR
10 min	BP, HR
15 min	VAS, ARCI, Adjective Scale, BP, HR
20 min	BP, HR
25 min	VAS, ARCI, Adjective Scale, BP, HR
30 min	BP, HR Draw blood for prolactin assays (sessions #6, 8 & 10)
35 min	VAS, ARCI, Adjective Scale, BP, HR
40 min	12-lead ECG, BP, HR
45 min	Draw blood for cocaine assay (session #4, 6, 8, 10) BPRS, BP, HR
50 min	BP, HR
52 min.	BP, HR
54 min.	BP, HR
56 min	BP, HR
58 min	BP, HR
60 min (9:00 a.m.)	**Inject cocaine/saline i.v. 1 min push; BP, HR**
62 min	BP, HR
64 min	BP, HR
65 min	VAS, ARCI, Adjective Scale
66 min	BP, HR
68 min	BP, HR
70 min	Draw blood for cocaine assay (sessions #4, 6, 8, 10)

Time-point	Activity (occurs at all sessions unless otherwise indicated)
	BP, HR
75 min	VAS, ARCI, Adjective Scale, BP, HR
80 min	Draw blood for cocaine assay (sessions #4, 6, 8, 10) BP, HR
85 min	VAS, ARCI, Adjective Scale, BP, HR
90 min	Draw blood for cocaine assay (sessions #4, 6, 8, 10) Draw blood for RPR 102681 assay (sessions #5-10) Draw blood for prolactin assay (sessions #6, 8 & 10) BP, HR
95 min	VAS, ARCI, Adjective Scale, BP, HR
100 min	12-lead ECG, BP, HR
105 min	Draw blood for liver function tests (session #4, 6, 8 & 10) BPRS, BP, HR
110, 115 min	BP, HR
120 min (10:00 a.m.)	Draw blood for cocaine assay (sessions #4, 6, 8, 10) BP, HR
150 min	Draw blood for cocaine assay (sessions #4, 6, 8, 10), BP, HR
180 min	Draw blood for cocaine assay (sessions #4, 6, 8, 10), BP, HR
210, 240, 270 min	BP, HR
300 min (1:00 p.m.)	BP, HR Draw blood for cocaine assay (sessions #4, 6, 8, 10)
330, 360, 390, 420 min	BP, HR

12.4 Evaluations at Discharge and Follow-up

The subjects will be discharged from the hospital 5 days after the last infusion of cocaine (session #10) on day 35. Subjects will return for follow-up visit at 30 days (day 65) after discharge.

The following evaluations will be performed at time of discharge and during the follow-up visit. The same evaluations will be performed in the case of early study discontinuation.

1. Vital signs (BP and HR);
2. Hematology;
3. Brief physical
4. Blood chemistry, including liver function tests;
5. 12-lead ECG;
6. Serum ß-HCG (pregnancy test);
7. Urine drug toxicology screen;
8. Adverse events.

12.5 Clinical and Laboratory Assessment Methods

The following describes the methods to be used for collection of clinical and laboratory evaluations.

12.5.1 Intake Assessments

A variety of standardized psychosocial assessments and information will be collected during screening and intake in order to describe fully the characteristics of participants and in order to facilitate future contact for follow-up. Study personnel who will administer the questionnaires and interviews are extensively trained and experienced in working with a drug abusing population.

12.5.1.1 Addiction Severity Index (ASI)-Lite CF Version

The ASI-Lite CF version will be administered by a research staff member having at least a bachelor's degree in the social sciences or equivalent training and experience as determined by the principal investigator. The ASI-Lite is the interviewer's estimate of the severity of the subject's status in seven areas (medical, employment, drug use, alcohol use, legal, family/social, and psychological). Composite scores will be calculated according to the procedures described by McGahan *et al*. (1982) and Carroll *et al*. (1994). The Lite version is a shorter version of the ASI that still retains all questions used to calculate the ASI composite scores. The ASI-Lite will be completed after intake.

12.5.1.2 Cocaine Use by Timeline Follow Back Method

Detailed histories of cocaine use over the past 30 days prior to screening will be obtained using the timeline follow-back method. The timeline follow-back method was described and validated by Sobell *et al.,* (1986) for reporting alcohol use. It has also been found to be a reliable method for assessing the history of psychoactive substance use in drug-abusing populations (Fals-Stewart *et al.,* 2000).

12.5.1.3 SCID

This instrument (Spitzer *et al*., 1995) will be administered during screening and serves to determine whether the subject meets the DSM-IV criteria for drug dependence and to rule out any major psychiatric disorders (e.g., affective disorders, schizophrenia).

12.5.1.4 Breathalyzer Test

The breathalyzer or breath alcohol test will be administered at intake to assess recent alcohol use.

12.5.2 Medical Assessments

12.5.2.1 Physical Exam

A physical exam 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.

12.5.2.2 Medical History

To monitor the health of all potential study subjects, health profiles and medical history will be collected during screening.

12.5.2.3 Vital Signs

Vital signs to be assessed at intake include oral temperature, sitting blood pressure, pulse rate, and respiratory rate.

12.5.3 Eligibility Checklist

The Eligibility Checklist must be completed prior to randomization and enrollment. This information will be used to determine whether the patient may be enrolled in the study. This form will document final eligibility and, if applicable, the reason the subject was not enrolled in the study.

12.5.4 Urine Toxicology

Urine toxicology for marijuana, opiates, cocaine, and amphetamines will be done at screening and admission. Upon admission to the CPU subjects will be tested for the presence of cocaine or cocaine metabolites once daily (8 a.m.). The first seven days of the inpatient stay (Days -7 through -1) will be allotted for washout after admission to document when subject's urine becomes negative for cocaine. This test will be also performed at the time of discharge and at the follow-up visit.

12.5.5 Laboratory Tests

12.5.5.1 Hematology

Blood will be collected in anticoagulant containing vacutainer tubes for hematologic assessments. Analysis of hemoglobin, hematocrit, mean corpuscular volume, white blood cell count, differential white blood cell count and platelet count will be performed. Analyses will be performed in the local clinical laboratory. The laboratory performing these assessments will be either directly regulated by the College of Pathologists (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. Hematologic assessments will occur during screening, at discharge and at follow-up.

12.5.5.2 Blood Chemistry/Liver Function Tests

Blood will be collected in serum separation vacutainer tubes and serum separated according to standard procedures. Quantitative analysis will be performed for the following analytes: creatinine, blood urea nitrogen (BUN), glucose, creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), and electrolytes (Na, K, Cl, HCO_3). Liver function tests will include total bilirubin, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), and alkaline phosphatase (ALP). The laboratory performing these assessments will be either directly regulated by CAP or CLIA or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification. Blood chemistry, including liver function tests, will be performed during screening, at admission, at discharge and at follow-up. In addition, liver function tests will also be conducted on days 8, 15, 22 and 29.

12.5.5.3 Serum Prolactin

Serum prolactin levels will be evaluated at baseline on day 0 and on days 15, 22 and 29, when treatment infusions with 40 mg cocaine (sessions #6, 8 and 10) are scheduled. On day 0, prolactin assay will be drawn once at 6:00 a.m. and the subjects will have breakfast at 7:00 a.m. On days 15, 22 and 29, blood for prolactin assay will be drawn three times, first at 6:00 a.m. before the morning dose of RPR 102681 (6:05 a.m.), and then 30 minutes after each i.v. infusion (Table 2). Blood will be collected in serum separation vacutainer tubes and serum separated according to standard procedures. Quantitative analysis will be performed for prolactin by a central laboratory. Normal ranges for serum prolactin at this laboratory are 3.1-16.5 ng/mL for adult males and 3.6 - 18.9 ng/mL for nonpregnant females.

12.5.5.4 PET Scan with [^{11}C]-Raclopride

The PET scans will be performed at the Department of Nuclear Medicine, Johns Hopkins Medical Center (Appendix III). Each subject in the first two blocks (6 subjects total) will receive four (4) PET scans after the morning dose of RPR 102681. If there are significant changes in the PET scans of these 6 subjects, the PET scans will not be done on the remaining 6 subjects; if the PET scan findings are not definitive, the PET scans will be administered to the next 6 subjects. A baseline PET scan will be performed after the subject completes screening cocaine infusions uneventfully and after assignment to RPR 102681 or placebo treatment (day 6) and then on the 5th day of each dose level when the subjects are at anticipated steady dose levels of the drug: days 13, 20, and 27. PET scan will be performed with [^{11}C]-raclopride, a D2 receptor antagonist that competes with endogenous DA for binding to the receptor. Binding potential (BP) is defined as B_{max}/K_d, where B_{max} is maximal density of receptor binding , and K_d is affinity. We will measure BP and change in BP as the indicator of the occupancy of the D2 receptor sites due to dopamine released in response to RPR 102681 at baseline (day 6) and on days 13, 20, and 27.

12.5.5.5 Pregnancy Test

A blood-based pregnancy test designed to measure human chorionic gonadotropin will be performed during screening, at intake, at discharge and at follow-up.

12.5.5.6 Infectious Disease Panel

Blood will be collected in a serum separation evacuated venous blood collection tubes (e.g., Vacutainer^{TM}) and serum separated according to standard procedures. Qualitative analysis reporting positive/negative results will be performed during screening for the following analytes: hepatitis B surface antigen, hepatitis C virus antibody and HIV type 1. An HIV test informed consent must be obtained before collecting blood for this test.

12.5.6 Methods for Assessment of Primary Outcome Measures

12.5.6.1 Primary Outcome Measures

The primary outcome measures are adverse events and cardiovascular responses (HR, BP, ECG measurements).

12.5.6.2 Adverse Events (AEs)

AEs will be assessed daily by an investigative staff nurse or physician starting as soon as the subject signed the informed consent. If an AE is reported to a nurse that requires medical attention, it should be reported to a study physician immediately. The investigator or study physician will assess subjects for any medical or psychiatric side effects. All AEs will be recorded on an AE CRF that is completed weekly.

12.5.6.3 Cardiovascular Assessments

Before and after each i.v. infusion, the subjects' physiologic responses will be closely monitored using repeated HR, BP, and ECG readings. During infusion sessions #1-10, BP and HR will be recorded at the following time points relative to infusions: -10, -8, -6, -4, -2, 0 (first infusion), 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 45, 50, 52, 54, 56, 58, 60 (second infusion), 62, 64, 66, 68, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120 minutes and then every 30 minutes for the next five hours (Table 2). ECG will be monitored continuously from 15 minutes before the first infusion until 24 hours after second infusion. 12-lead ECG will be performed at 40 minutes after each infusion. Subjects will be monitored for at least 1 hour after the second infusion by study personnel and staff. Thereafter, nursing staff will monitor participants and take vital signs according to the above schedule until vital signs revert to being within 10% of the baseline.

12.5.7 Methods for Assessment of Secondary Outcome Measures

12.5.7.1 Secondary Outcome Measures

The secondary outcome measures include PK of study agent RPR 102681, PK of cocaine and BE, craving for cocaine assessed using BSCS, psychological and mood and personality tests including BPRS, BSI, BDI, POMS, VAS, and Adjective Scale, abuse liability assessment of RPR 102681 using ARCI, serum prolactin levels and DA release in striatum measured by PET scan with [^{11}C]-raclopride.

12.5.7.2 Blood Sample Collections for Pharmacokinetic Determinations

A schedule of blood collections and volumes is provided in Appendix II including collection of samples for cocaine and RPR 102681 blood levels for pharmacokinetic calculations.

An intravenous catheter will be inserted for each infusion session, and can be maintained in place for the two days of infusion sessions in one week, if the subject wishes. Two intravenous catheters will be placed for infusion sessions that involve repeated blood draws on days 8, 14, 15, 21, 22, 28 and 29; one will be for cocaine administration, the other for blood sample collection.

Samples will be collected for assessment of cocaine pharmacokinetics on days 8, 15, 22, and 29 in 10 cc grey-stoppered Vacutainer™ tubes containing sodium fluoride and potassium oxalate. In order to assess study agent RPR 102681 pharmacokinetics, peak and trough levels, blood will be collected in heparin-containing green-stoppered Vacutainers™ on days 13, 14, 15, 20, 21, 22, 27, 28 and 29.

Blood drawn from all subjects should be considered infectious and extreme 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.

Samples will be collected during baseline 40 mg i.v cocaine infusion (session #4) and treatment i.v. cocaine infusions (sessions #5-10). Samples will be collected for assessment of cocaine pharmacokinetics on days for scheduled sessions #4, 6, 8, and 10 (days 8, 15, 22, and 29) and for RPR 102681 pharmacokinetics on days 13, 14, 15, 20, 21, 22, 27, 28 and 29. Total blood loss during the study will be 532 mL (Appendix II).

12.5.7.3 Subjective Responses

During and after the saline and cocaine infusions subjects' subjective responses will be closely monitored. VAS will be administered 15 minutes before, and at 5, 15, 25 and 35 minutes after each i.v. infusion. For this scale, subjects will report the degree to which they feel “any drug effect”, "high", “good effects”, “bad effects”, “like cocaine”, "desire for cocaine", "depressed", "anxious", “stimulated”, and “likely to use” on a continuous scale digitized between 0 to 100 for computing a score. In addition, they will be asked to answer the question: How much do you think this is worth in dollars. ARCI and Adjective Scale will be administered at the same time points as VAS, which is 15 minutes before and at 5, 15, 25 and 35 minutes after each i.v. infusion. The ARCI consists of 49 statements in a true/false format and the Adjective Scale contains 22 adjectives on which a response on a scale of 0-4 is required, ranging from “not at all” to “extremely”. For training purposes, VAS, ARCI and Adjective Scale will be also administered once a day on days -2, -1, 0 and 1.

12.5.7.4 Brief Substance Craving Scale (BSCS)

The BSCS is a self-administered assessment that asks the subject to rate his or her craving for cocaine. The BSCS used for this study is a modification of the State of Feelings and Cravings Questionnaire (Mezinskis *et al.*,1998). If the subject is unable to self-administer this assessment (e.g. physical handicap, poor reading skills) study personnel can assist by reading the questions out loud to the subject and/or marking the subject's response on the CRF. However, study personnel are not to offer interpretations of the questions.

12.5.7.5 Beck Depression Inventory (BDI)

The BDI is a 22-item self-report inventory that focuses on the subject's subjective feelings of depression and is sensitive to changes in feeling status. Subjects will start the measure at baseline and continue to complete this questionnaire on an every other day basis, until the end of the study.

12.5.7.6 Brief Symptom Inventory (BSI)

The BSI is a 53-item self-report clinical rating scale used to assess psychological distress. Subjects will start the measure at baseline and continue to complete this questionnaire on an every other day basis, until the end of the study.

12.5.7.7 Profile of Mood States (POMS)

The POMS is a questionnaire that measures dimensions of affect or mood. It consists of 65 adjectives to which the client responds according to a 5-point scale ranging from "not at all" to "extremely". Subjects will start the measure at baseline and continue to complete this questionnaire on an every other day basis, until the end of the study.

12.5.7.8 Brief Psychiatric Rating Scale (BPRS)

The BPRS is an interview that may be administered by a trained research nurse and conducted either by remote video or in face-to-face format to evaluate the severity of subject's psychopathology, including anxiety, depression and symptoms of schizophrenia. The BPRS may be dichotomized into subjective items based on patients' verbal reports and objective items based on visual observation of patients' behavior. The BPRS total score ratings serve as indicators of psychiatric comorbidity in drug-dependent subjects and as predictors of mental health services utilization. Subjects will start the measure at baseline and will be administered this interview on the days of all cocaine infusions within one hour of the completion of infusion (sessions #1-10), as an indicator of possible acute psychotic effects of cocaine.

12.5.8 Concomitant Medications

Concomitant medications will be assessed once per week by an investigative staff member. Any medications to be taken during the study must be approved by the site principal investigator/study physician.

12.5.9 End of Trial Form

The End of Trial CRF will document all data relevant to subject discharge: reason for discharge; date of discharge; and study day of discharge.

13 REGULATORY AND REPORTING REQUIREMENTS

13.1 Good Clinical Practices

This study will be conducted in accordance with the most current version of the International Conference on Harmonization Guide for Good Clinical Practices (GCP). An Operations Manual will be provided to all investigational sites as a study quality assurance tool.

13.2 FDA Form 1572

The investigator agrees to sign and submit a Statement of Investigator (FDA Form 1572) to the sponsor prior to initiating this study.

13.3 IRB Approval

Prior to initiating the study, the investigator 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, IRBs will approve all advertising materials used for subject recruitment and any educational materials given to the subject. Annual reports and progress reports will be submitted to the IRB annually or at a frequency requested by the IRB.

The investigator will ensure that a duly constituted IRB at the study site that conforms with FDA regulations (21 CFR part 56) will review the protocol and the volunteer informed consent form. Each investigator will follow IRB and FDA guidance regarding reporting of adverse events. Each investigator will promptly report to the IRB all changes in research activity and all unanticipated problems involving risks to human subjects or others and will not make any changes in the protocol without IRB approval, except where necessary to eliminate immediate hazards to human subjects. Following procedures outlined by the IRB, each investigator will describe the study, its risks and benefits, to each subject and ensure that each subject understands the study prior to obtaining the subject's signature. A copy of the consent form will be given to the subject.

13.4 Informed Consent

All potential candidates for the study will be given a current copy of the Informed Consent Form to read. The investigator or other study physician will explain all aspects of the study in lay language and answer all of the candidate's questions regarding the study. If the candidate desires to participate in the study, s/he will be asked to sign the Informed Consent. No study procedure will be performed prior to signing Informed Consent. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice. The number of subjects that may sign the informed consent is not specified, as subjects will continue to be screened until 12 subjects have completed the study.

13.5 Risks and Benefit Assessment

The primary risks of this study are those of possible adverse reaction to the study drugs, cocaine and RPR 102681. There is extensive experience with these cocaine infusion procedures and they appear to be safe. The doses used are modest, the exposure periods to the agents are brief, the safety screening and monitoring are appropriate, and there have been no significant prior adverse events with these procedures. No serious adverse events occurred in the two clinical studies with RPR 102681 conducted in France (Caplain, 1997, 1998). The most frequent adverse events reported in these clinical studies with RPR 102681 were postural hypotension, headache, somnolence, diarrhea, euphoria, flatulence, and pharyngitis (Caplain, 1997, 1998). It is possible that the dopaminergic activities of cocaine and RPR 102681 might be additive or potentiated when they are administered together. The ascending order of cocaine doses is one protection against this risk. There is the risk of a breach of confidentiality regarding study records, but this is unlikely, since staff is well trained and experienced in this area.

The study does not offer direct therapeutic benefit to participants. But, because it is directed toward the identification and development of effective treatment for cocaine abuse, it does offer the potential of future benefit to this same population group.

Overall, we believe that the risks are modest, that appropriate precautions have been taken, that there is potential societal health benefit, and that therefore the risk/benefit ratio is favorable.

13.6 Drug Accountability

Upon receipt, the investigator/pharmacist or a licensed designate is responsible for taking inventory of the investigational agents. A record of this inventory must be kept and usage must be documented. Any unused or expired investigational agents shall be returned to the study sponsor.

13.7 Outside Monitoring

Compliance With NIDA Policy On Monitoring Plans: In June 2000, the National Institutes of Health (NIH) issued a policy that extended the requirement for inclusion of monitoring plans to phase 1 and 2 clinical trials. (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html) That Further Guidance followed the policy issued in June 1998 on data and safety monitoring (http://grants.nih.gov/grants/guide/notice-files/not98-084.html), which required the establishment of Data and Safety Monitoring Boards (DSMBs) for all NIH-supported or -conducted multi-site clinical trials involving interventions that entail potential risk to the participants. NIH requires each Institute to have a system of oversight of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data.

This protocol is in compliance with that policy. The procedures for reporting Serious Adverse Events (SAEs) to NIDA, the IRB and FDA are contained under section 13.8. A DSMB will be reviewing the data and safety information from this trial.

Medical Monitor: A 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.

Clinical Monitors: All investigators will allow representatives of the sponsor to periodically audit, at mutually convenient times during and after the study, all source documents for each subject. 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 GCP 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 investigators and other site personnel in study procedures and compliance with good clinical practice guidelines and

FDA regulations, 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 medication. The site should anticipate visits by sponsor, sponsor's representatives, NIDA, and the FDA.

13.8 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 principal investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and Appendix IV.

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 medication-related or clinically significant**.** For this study, AEs will include events reported by the subject, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study investigators until satisfactory resolution. AEs should be reported up to 2 weeks following completion of, or termination from treatment.

13.9 Serious Adverse Events

Each adverse event or reaction will be classified by the study investigator as serious or non-serious. Based on the seriousness of the adverse event 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 patient 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.

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

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. The sponsor will inform NIDA of all SAEs that occur during the study.

There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA regulations governing the reporting of SAEs to FDA. The study investigators in this study have the responsibility of promptly reporting all SAEs to the sponsor in order that the sponsor can comply with these regulations.

If a study subject withdraws from the study or if an investigator 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

14.1 Outcome Measures

14.2 Primary Outcome Measures

The primary outcome measures are adverse events and cardiovascular responses (HR, BP, ECG).

14.3 Secondary Outcome Measures

Secondary outcome measures are intended to determine if there are any changes in RPR 102681 or cocaine pharmacokinetics and to assess the effects of RPR 102681 on a variety of neuropsychological measures and its abuse liability. Secondary outcome measures include:

1. PK parameters of cocaine and BE including:

AUC_{0-24}	Area under the plasma concentration time-curve from 0 to 24 hours at steady state
C_{max}	Maximum observed concentration
T_{max}	Time for maximum concentration
k_e	Elimination rate constant (if data permit)
$t_{1/2}$	Elimination half-life (0.693/(z))
CL/F	Clearance of the study agent determined by the formula $CL=Dose/AUC_{0-24}$ (if data permit)
V_d/F	Volume of distribution (if data permit)

2. PK of study agent RPR 102681 (peak and trough levels)
3. Craving for cocaine, assessed using BSCS
4. Psychological assessments including VAS and Adjective Scale
5. Abuse liability using ARCI
6. Mood and personality assessments (BPRS, BSI, BDI, and POMS)
7. Serum prolactin level
8. Release of dopamine in striatum determined by PET scan with [^{11}C]-raclopride

14.4 Analysis Plan

14.4.1 Primary Outcome Measures

HR and BP measures during saline infusions will be compared to HR and BP after each cocaine infusion (20 mg and 40 mg doses). Changes in HR and BP induced by cocaine infusion along with RPR 102681 will be compared to those without RPR 102681, by cocaine dose level (20 mg and 40 mg doses), using repeated measures analysis of variance (ANOVA).

Changes in ECG readings during saline infusion as compared to those taken during cocaine infusions will be reported as summary statistics.

Adverse event data will be compiled for RPR 102681 and placebo cohorts and presented as summary statistics.

14.4.2 Secondary Outcome Measures

Plasma concentration-time profiles of cocaine after baseline cocaine infusion (session #4) will be analyzed to obtain pharmacokinetic parameter estimates of cocaine (T_{max}, $C_{max,}$ AUC_{0-24}, apparent $t_{½}$, CL/F, V_d/F, and k_e) by individual and the means computed (between subjects comparison) will be compared with data from the post-treatment cocaine infusions for each RPR 102681 dose level (sessions #5 and #6 for 200 mg RPR 102681 b.i.d level, sessions #7 and #8 for 400 mg RPR 102681 b.i.d level, and sessions #9 and #10 for 800 mg RPR 102681 b.i.d level)

being averaged by subject. Blood for cocaine/BE PK determinations will be collected at the following time points: 80 and 15 minutes prior to and 10, 20, 30, 60, 90, 120, and 240 minutes post infusion (sessions #4, 6, 8, 10).

PK parameters determined for treatment infusions (sessions #6, 8, 10) will be compared between RPR 102681 dose levels by *t*-tests. Confidence intervals (90%) for each parameter will be determined. To be certain that there are no inherent differences between the pharmacokinetics of cocaine between the RPR 102681 and placebo cohorts, pharmacokinetic parameters between these two cohorts will also be compared during the baseline 40 mg i.v. cocaine infusion (session #4).

Blood for RPR 102681 PK determinations will be collected at 95 and 205 minutes after the morning dose on days 13, 14, 15, 20, 21, 22, 27, 28 and 29. Pharmacokinetics (peak and trough levels) of RPR 102681 during treatment at a dose of 200 mg (day 13), 400 mg (day 20) and 800 mg (day 27) b.i.d. will be determined. These data will be compared to PK of RPR 102681 obtained during the treatment cocaine infusions for each dose level, i.e. sessions #5 & 6 for 200 mg b.i.d., sessions #7 & 8 for 400 mg b.i.d, and sessions #9 & 10 for 800 mg b.i.d, by *t*-tests.

Blood for prolactin level determinations will be collected on day 0 at 6:00 a.m. before breakfast (7:00 a.m.) and also three times a day on days 15, 22 and 29 with first blood draw performed at 6:00 a.m. before the morning dose of RPR 102681 (6:05 a.m.) and the other two at 30 minutes after each i.v. infusion. Prolactin levels on days 15, 22, and 29 will be compared between RPR 102681 and placebo cohorts to determine the extent to which prolactin levels are modified by the administration of RPR 102681 using repeated measures ANOVA. Changes in prolactin level induced by 40 mg cocaine infusion along with RPR 102681 (days 15, 22 and 29) will be compared for each subject by RPR 102681 dose level using repeated measures ANOVA.

DA release in striatum measured by PET scans with [^{11}C]-raclopride (B_{max}, K_d and BP values) will be compared between RPR 102681 and placebo cohorts to determine the extent to which administration of RPR 102681 modulates dopamine neurotransmission using repeated measures ANOVA. RPR 102681-induced changes in DA release in striatum will be also compared for each subject by dose level to identify an effective dose of RPR 102681 for prospective Phase 2 clinical trials using repeated measures ANOVA.

Psychological outcome measures (including VAS, Adjective Scale, ARCI) obtained during saline infusions will be compared between RPR 102681 and placebo cohorts to those during cocaine infusions by cocaine dose level to determine the extent to which these measures are modified by the administration of RPR 102681 using repeated measures ANOVA.

Changes in BSCS, BSI, BDI, POMS and BPRS scores will be compared before and after RPR 102681 administration using repeated measures ANOVA or generalized estimating equations.

Population demographics will be tabulated for both treatment cohorts (RPR 102681 and placebo) and presented in a tabular form.

15 DATA MANAGEMENT AND CASE REPORT FORMS

15.1 Data Collection

Data will be collected at the study sites on source documents that will be entered at the site into electronic case report forms (eCRFs). eCRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. eCRFs should be completed according to the instructions in the study operations manual. The principal investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. The principal investigator 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-coordinating center will be reviewed. If incomplete or inaccurate data are found a data clarification request will be forwarded to the site for a response. The site will resolve data inconsistencies and errors prior to returning data to the data-coordinating center. All corrections and changes to the data will be reviewed prior to being entered into the main study database.

Participating investigators agree to routine data audits by the sponsor's designated staff. Monitors will routinely visit the site to assure that data submitted on the appropriate forms are in agreement with source documents. They will also verify that study agents have been properly stored and accounted for, subject informed consent for study participation has been obtained and documented, all essential documents required by GCP 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 established procedures specified in the study Operations Manual.

15.3 Data Entry, Processing, and Analyses

Data will be collected at the study sites on source documents that will be entered into CRFs. 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 data coordinating center's statisticians in accordance with the analytical plan section of this protocol.

15.4 Study Documentation and Records Retention

Study documentation includes all case report forms, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, Ethics or Institutional Review Committee correspondence and approved consent form and signed subject consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records).

Source documents include 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, patient diaries, biopsy reports, ultrasound photographs, patient 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 an 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 a New Drug Application (NDA).

15.5 Confidentiality

15.5.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

15.5.2 Confidentiality of Patient 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 securely. Only research staff and sponsor or sponsor's representative will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by the FDA or sponsor. 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, the sponsor or any regulatory agency may consult and/or copy study documents in order to verify case report form data.

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

16 PUBLICATIONS OF THE STUDY RESULTS

Publications derived from this study will include input from the principal investigator, his or her colleagues, and sponsor personnel. Such input should be reflected in publication authorship, and agreement regarding order of authors should be established before writing a manuscript. Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this study 60 days prior to submission for presentation.

17 SIGNATURES

SPONSOR REPRESENTATIVES

Typed Name	Signature	Date
Ann Montgomery, R.N. NIDA Project Manager	_____	_____
Ahmed Elkashef, M.D. NIDA Investigator	_____	_____
Roberta Kahn, M.D. NIDA Investigator	_____	_____
Nora Chiang, Ph.D. NIDA Investigator	_____	_____
Moo Kwang Park, Ph.D. NIDA Investigator	_____	_____
Ann Anderson, M.D. NIDA Medical Monitor	_____	_____

INVESTIGATOR (S)

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 13.8 of this protocol.

Typed Name	Signature	Date
Louis Cantilena, Jr., M.D., Ph.D Principal Investigator	_____	_____
_____ Co-Principal Investigator	_____	_____
_____ Subinvestigator	_____	_____

18 LITERATURE CITED

Ameer B, Weintraub RA. Drug interactions with grapefruit juice. *Clin Pharmacokinet* 1997; 33:103-121.

Archimbaud Y and Martinet M. ^{14}C-RPR 102681. Distribution by whole body autoradiography in rats following a single oral administration at 10 mg/Kg. Rhone Poulenc Rorer Report IBP/Biodyn 1907, 1995.

Beinfeld MC, Conolly KJ, Pierce RC. Cocaine treatment increases extracellular cholecystokinin (CCK) in the nucleus accumbens shell of awake, freely moving rats, an effect that is enhanced in rats that are behaviorally sensitized to cocaine. *J Neurochem* 2002; 81:1021-1027.

Boehme GA, Bertrand P, Piot O, Boudeau P, Jantaud B, Pauchet C, Guyon C, Manfre F, Imperato A, Dubroucq MC. Pharmacological properties of RPR 102681, a novel CCK-B antagonist. *Abstr Soc Neurosci Meet* 1997; 23:A2409.

Caplain H. A phase 1, double blind, placebo-controlled, randomized tolerability and pharmacokinetic study of RPR 102861 administered as single rising oral doses to parallel groups of healthy male volunteers. Rhone-Poulenc Rorer Inc. (France) Internal Report, 1997.

Caplain H. A phase 1, double blind, placebo-controlled, randomized tolerability, pharmacokinetic and pharmacodynamic study of RPR 102861 administered as repeated oral doses for 14 days to parallel groups of healthy male volunteers and as a single oral dose to one group of healthy female volunteers. Rhone-Poulenc Rorer Inc. (France) Internal Report, 1998.

Carroll KM, Rounsaville BJ, Gordon LT, *et al.* Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. *Arch Gen Psychiatry* 1994; 51:177-187.

Costall B, Domeney AM, Huges J, Kelley ME, Naylor RJ and Woodruff GN. Anxiolytic effects of CCK-B antagonists. *Neuropeptides* 1991; 19:65-73.

Crawley JN. Cholecystokinin-dopamine interactions. *Trends Pharmac Sci* 1991; 12:232-236.

Crespi F. The role of cholecystokinin (CCK), CCK-A or CCK-B receptor antagonists in the spontaneous preference for drug abuse (alcohol or cocaine) in naïve rats. *Methods Find Exp Clin Pharmacol* 1998; 208:679-697.

Dauge V, Lena I. CCK in anxiety and cognitive processes. *Neurosci Biobehav Rev* 1998; 22: 815-825.

Dauge V, and Roques BP. Opioid and CCK systems in anxiety and reward. In: *Cholecystokinin and Anxiety: from Neuron to Behavior* (Eds. Bradwejn J. and Vasar E.) RG Landes Company, Austin, 1995, pp. 151-171.

Dauge V, Beslot F, Matsui T and Roques BP. Mutant mice lacking the cholecystokinin$_2$ receptor show a dopamine-dependent hyperactivity and a behavioral sensitization to morphine. *Neurosci Lett* 2001; 306:41-44.

Dean RA, Christian CD, Sample RHB, and Bosron WF. Human liver cocaine esterases: ethanol mediated formation of ethylcocaine. *FASEB J* 1991; 5: 2735-2739.

Ervin FR, Palmour RM. RPR 102681: A randomized, dose-response study of the effect of the oral administration on voluntary ethanol consumption in alcohol-preferring velvet monkeys. Rhone Poulenc Rorer Report 9503, 1995.

Fleckenstein AE, Gibb JW, Hanson GR. Differential effects of stimulants on monoaminergic transporters: pharmacological consequences and implications for neurotoxicity. *Eur J Pharmacol* 2000; 406:1-13.

Fals-Stewart W, O'Farrell TJ, Freitas TT, McFarlin SK, Rutigliano P. The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. *J Consult Clin Psychol* 2000; 68:134-44.

Frata W. RPR 102681: Intravenous self-administration in drug-naïve mice. Rhone Poulenc Rorer Report 95-001, 1995a.

Frata W. RPR 102681: Conditioned place preference in rats after intraperitoneal treatment. Rhone Poulenc Rorer Report 95-002, 1995b.

Frata W. RPR 102681: Lack of substitution for the discriminative stimulus effects of amphetamine and cocaine after intraperitoneal administration in rats. Rhone Poulenc Rorer Report 95-003, 1995c.

Frata W. RPR 102681: Inhibition of cocaine self-administration in drug-naïve mice. Rhone Poulenc Rorer Report 96-006, 1996a.

Frata W. RPR 102681: Effect on intravenous cocaine self-administration in drug-experienced rats. Rhone Poulenc Rorer Report 96-007, 1996b.

Frata W. RPR 102681: Effect on intravenous d-amphetamine self-administration in drug-experienced rats. Rhone Poulenc Rorer Report 96-010, 1996c.

Frata W. RPR 102681: Effect on cocaine-induced conditioned place preference in rats. Rhone Poulenc Rorer Report 96-009, 1996d.

Frata W. RPR 102681: Effect on d-amphetamine-induced conditioned place preference in rats. Rhone Poulenc Rorer Report 96-008, 1996e.

Gaillard C and Martinet M. Metabolic profiles of ^{14}C-RPR 102681 in rats after single oral administration of 50 mg/Kg. Rhone Poulenc Rorer Report CPD/DMP/FR.2033, 1996.

Gawin FH. New use of antidepressants in cocaine abuse. *Psychosomatics* 1986; 275:24-29.

Giannini AJ, Malone DA, Giannini MC, et al. Treatment of depression in chronic cocaine and phencyclidine abuse with desipramine. *J Clin Pharmacol* 1986; 26:211-214.

Guo Z, Stevens JC and Marietta MP. *In vitro* metabolism of RPR 102681 in human and rat liver microsomes. Rhone Poulenc Rorer Report 95-194, 1995.

Guo Z, Stevens JC and Martinet M. Interaction of RPR 102681 with human hepatic microsomal cytochrome P450 forms. Rhone Poulenc Rorer Report 96-019, 1996.

Heesch CM, Negus BH, Bost JE, Keffer JH, Snyder RW, Eichhorn EJ. Effects of cocaine on anterior pituitary and gonadal hormones. *J Pharm Exp Ther* 1996; 278:1195-2000.

Hietala J, Nagren K, Lehikoinen P, Ruotsalainen U, Syvalahti E. Measurement of striatal D2 dopamine receptor density with [^{11}C]-raclopride in vivo: a test-retest analysis. *J Cereb Blood Flow Metab* 1999; 19: 210-217.

Hill DR, Campbell NJ, Shaw TM and Woodruff GN. Autoradiographic localization and biochemical characterization of peripheral type CCK receptors in rat CNS using highly selective non-peptide CCK antagonists. *J Neurosci* 1987a; 7: 2967-2976.

Hill DR, Shaw TM and Woodruff GN. Species differences in the localization of "peripheral" type CCK receptors in rodent brain. *Neurosci Lett* 1987b; 79: 286-298.

Hokfelt T, Rehfeld JF, Skirboll L, Ivemark B, Goldstein M and Markey K. Evidence for coexistence of dopamine and CCK in mesolimbic neurons. *Nature* 1980; 285: 476-478.

Imperato A, Obinu MC, Bohme GA. RPR 102681: Effects on brain dopamine release after intraperitoneal administration in freely moving rats. Rhone Poulenc Rorer, Preclinical Report 681, 1995a.

Imperato A, Obinu MC, Bohme GA. RPR 102681: Effects after intraperitoneal administration on ethanol intake in alcohol-dependent rats. Rhone Poulenc Rorer, Preclinical Report 617, 1995b.

Inaba T, Stewart DJ, Kalow M. Metabolism of cocaine in man. *Clin Pharmacol Ther* 1978; 23:547-552.

Jeffcoat AR, Perez-Reyes M, Hill JM, Sadler BM and Cook CE. Cocaine disposition in humans after intravenous infusion, nasal insufflation (snorting), or smoking. *Drug Metab Dispos* 1989; 17:153-159.

Johanson C-E, Schuster CR. In *Psychopharmacology: The Fourth Generation of Progress* (F.E. Bloom and D.J. Kupfer, Eds.), Raven, New York, 1995.

Johnson B, Overton D, Wells L, Kenny P, Abramson D, Dhother S, Chen YR, Bordnick P. Effects of acute intravenous cocaine on cardiovascular function, human learning, and performance in cocaine addicts. *Psychiatry Res* 1998; 16:35-42.

Karch SB. Psychopathology of Drug Abuse. Boca Raton, FL:CRC Press, 1993.

Kitayama S, Wang JB, Uhl GR. Dopamine transporter mutants selectively enhance MPP^+ transport. *Synapse* 1993; 15:58-62.

Kloss MW, Rosen G, Rauckman EJ. Cocaine-mediated hepatotoxicity – a critical review. *Biochem Pharmacol* 1984; 33:169-173.

Kuhar MJ, Ritz MC, Boja JW. The dopamine hypothesis of the reinforcing properties of cocaine. *Trends Neurosci* 1991; 14:299-301.

Ladona MG, Gonzalez ML, Rane A, Peter RM, de la Torre R. Cocaine metabolism in human fetal and adult liver microsomes is related to cytochrome P450 3A expression. *Life Sci* 2000; 68: 431-443.

Lin Z. Wang W, Kopajtic T, Revay RS, Uhl GR. Dopamine transporter: transmembrane phenylalanine mutations can selectively influence dopamine uptake and cocaine analog recognition. *Mol Pharmacol* 1999; 56:434-447.

Majeska MD. Cocaine addiction as a neurological disorder: implications for treatment. In: Neurotoxicity and Neuropathology Associated with Cocaine Abuse. *NIDA Research Monography* 1996, 163:1-26.

Marks V and Chapple P. Hepatic disfunction in heroin and cocaine users. *Br J Addict* 1967; 62:189-195.

Mastronardi CA, Walczewska A, Yu WH, Karanth S, Parlow AF, McCann SM. The possible role of prolactin in the circadian rhythm of leptin secretion in male rats. *Proc Soc Exp Biol Med* 2000; 224:152-158.

Mawlawi O, Martinez D, Slifstein M. *et al*. Imaging human mesolimbic dopamine transmisssion with positron emission tomography: I. Accuracy and precision of D2 receptor parameter measurements in ventral striatum. *J Cereb Blood Flow Metab* 2001; 21:1034-1057.

McGahan PL, Griffith JA, Parante R, McLellan AT. Composite scores from the Addiction Severity Index. Washington, DC: National Institute on Drug Abuse Project DA02554 and the Veterans Administration, 1982.

Mello NK, Mendelson JH, Drieze JM, Kelly M. Acute effects of cocaine on prolactin and gonadotropins in female rhesus monkey during the follicular phase of the menstrual cycle.*J Pharm Exp Ther* 1990; 254, 815-823.

Mello NK, Mendelson JH, Drieze JM, Teoh SK, Kelly ML, Sholar JW. Effects of dopamine on prolactin: interactions with cocaine self-administration by phemale rhesus monkeys. *J Pharm Exp Ther* 1994; 270:1110-1120.

Mendelson JH, Teoh SK, Lange U,Mello NK, Weiss R, Skrupny A, Ellingboe J. Anterior pituitary, adrenal and gonadal hormones during cocaine withdrawal. *Amer J Psychiatry* 1988; 145:1094-1098.

Mendelson JH, Teoh SK, Mello NK, Ellingboe J, Rhoades E. Acute effects of cocaine on plasma adrenocorticotropic hormone and prolactin levels in cocaine-dependent men. *J Pharm Exp Ther* 1992; 263:505-509.

Mezinskis J, Dryenforth S, Goldsmith R, Cohen M, Somoza E. Craving and withdrawal symptoms for various drugs of abuse. *Psychiatric Annals* 1998; 28.10:577-583.

Miller GM, Yatin SM, De La Garza R, Goulet M, Madras BK. Cloning of dopamine, norepinephrine and serotonin transporters from monkey brain: relevance to cocaine sensitivity. *Brain Res Mol Brain Res* 2001; 87:124-143.

Noble F and Roques BP. CCK-B receptor: chemistry, molecular biology, biochemistry and pharmacology. *Prog Neurobiol* 1999; 58:349-379.

Obinu C, Bohme GA, Martellota MC, Piot O, Dauge V, Pauchet C, Roques BP, Fratta W and Imperato A. RPR 102681 increases limbic dopamine release, shows antidepressant activity and reduces the rewarding properties of psychostimulants. *Abstr Soc Neurosci Meet*, 1997.

Ozdemir V, Kalowa W, Tang BK, Paterson AD, Walker SE, Endrenyi L, Kashuba AD. Evaluation of the genetic component of variability in CYP3A4 activity: a repeated drug administration method. *Pharmacogenetics* 2000; 10: 373-388.

Sobell MB, Sobell LC, Klajner F, Pavan D, Basian E. The reliability of a timeline method for assessing normal drinker college students' recent drinking history: utility for alcohol research. *Addict Behav* 1986;11:149-61.

Sora I, Wichems C, Takahashi N, Li XF, Zeng Z, Revay R, Lesch KP, Murphy DL, Uhl GR. Cocaine reward models: conditioned place preference can be established in dopamine and serotonin transporter knockouts mice. *Proc Natl Acad Sci* 1998; 95:7699-7704.

Sora I, Hall FS, Andrews AM, Itokawa M., Li XF, Wei HB, Wichems C, Lesch KP, Murphy DL, Uhl GR. Molecular mechanisms of cocaine reward: combined dopamine and serotonin transporter knockouts eliminate cocaine place preference. *Proc Natl Acad Sci* 2001; 98:5300-5305.

Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for the DSM-IV (SCID). Washington, D.C.: American Psychiatric Press, 1995.

Stewart DJ, Juaba T, Tang BK, Kalow W. Hydrolysis of cocaine in human plasma by cholinesterase. *Life Sci* 1977; 20:1557-1563.

Tanganelli S, Fuxe K, Antonelli T, O'Connor WT, Ferraro L. Cholecystokinin/dopamine/GABA interactions in the nucleus accumbens: biochemical and functional correlates. *Peptides* 2001; 22: 1229-1234.

Tohei A, VandeGarde B, Arbogast LA, Voogt JL. Calcitonin inhibition of prolactin secretion in lactating rats: mechanism of action. *Neuroendocrinology* 2000; 71, 327-332.

Uhl GR, Hartig PR. Transporter explosion: update on uptake. *Trends Pharmacol Sci* 1992; 13: 421-425.

Volkow ND, Wang GJ, Fowler JS et al. Measuring age-related changes in dopamine D2 receptors with 11C-raclopride and 18F-N-methylspiroperidol. *Psychiatry Res* 1996; 67: 11-16.

Volkow ND, Wang GJ, Fischman MW et al. Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature* 1997; 386:827-830.

Walsh SL, Preston KL, Sullivan JT, Fromme R, Bigelow GE. Fluoxetine alters the effects of intravenous cocaine in humans. *J Clin Psychopharmacol* 1994; 14:396-407.

Webster J. Dopamine agonist therapy in hyperprolactinemia. J Reprod Med 1999; 44:105-1110.

Wilson J, Little HJ. CCK(B) antagonists protect against some aspects of the ethanol withdrawal, syndrome. *Pharmacol Biochem Behav* 1998; 59:967-973.

Wilson J, Watson WP, Little HJ. CCK(B) antagonists protect against anxiety-related behavior produced by ethanol withdrawal, measured using the elevated plus maze. *Psychopharmacol* 1998; 137:120-131.

Xie JX, Tang M, Zhang C. Effect of cholecystokinin-8 microinjection into ventral tegmental area on dopamine release in nucleus accumbens of rats: an in vivo voltammetric study. *Prog Neuropsychopharmacol Biol Psychiatry* 2001; 25: 427-434.

Xu F, Gainetdinov RR, Wetsel WC, Jones SR, Bohn LM, Miller GW, Wang YM, Caron MG. Mice lacking the norepinephrine transporter are supersensitive to psychostimulants. *Nat Neurosci* 2000; 3:465-

Appendix IA: Screening Time and Events Schedule (until the day of 1st cocaine infusion)

Study Phase	Pre-intake Screening	Intake Screening
Study day	**Up to -30**	**-7* to -1**
Informed consent	X	
Locator form/ Demographics	X	
Cocaine use by timeline follow back	X	
Breathalyzer test		X
12-lead ECG	X	X
SCID	X	
Medical History/Physical Exam	X	
ASI-Lite		X
Vital Signs	X	X
Chemistries plus liver function tests	X	X
Hematology	X	
Pregnancy Test	X	X
Infectious disease serology	X	
Serum prolactin		X[a]
Plasma alcohol	X	
Urine toxicology screen	X	X
BSI, BDI, POMS, BSCS, BPRS		X[b]
Adverse Events		X
VAS, ARCI, Adj Scale		X[c]
Routine Urinalysis	X	

*Days -7 through -1 are inpatient days allotted for washout of cocaine after admission.

Subjects' urine will be tested daily to document when it becomes negative for cocaine.

X[a] - Prolactin will be assessed on day 0.
X[b] - BSI, BDI, POMS, BSCS, BPRS will be performed at intake.
X[c] - VAS, ARCI and Adjective Scale will be performed on days -2, -1, 0, and 1.

Appendix IB: Inpatient Time and Events Schedule (starting from the day of 1st cocaine infusion)

Study Phase	**Screening Infusions**				**Baseline Infusions**				**Treatment Infusions**										**Dis-charge**	**Follow-up**
Study Day	**2**	**3**	**4-5**	**6**	**7**	**8**	**9-12**	**13**	**14**	**15**	**16-19**	**20**	**21**	**22**	**23-26**	**27**	**28**	**29**	**35**	**65**
12-lead ECG	X	X			X	X			X	X			X	X			X	X	X	X
Brief Physical																			X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistries Plus Liver Function Test																			X	X
Liver FunctionTests						X				X				X				X		
Hematology																			X	X
Pregnancy Test																			X	X
Serum Prolactin										X[a]				X				X		
Pet Scan with [^{11}C]-raclopride				X[b]				X				X				X				
Urine Toxicology Screen																			X	X
BSI, BDI, POMS, BSCS	X[c]																			
RPR 102681 or Placebo Administration							X[d]	X	X	X	X	X	X	X	X	X	X	X		
RPR 102681 Blood PK								X[e]	X	X		X	X	X		X	X	X		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cocaine Infusion Session #	**1**	**2**			**3**	**4**			**5**	**6**			**7**	**8**			**9**	**10**		
20 mg Cocaine i.v.	X				X				X				X				X			
40 mg Cocaine i.v.		X				X				X				X				X		
VAS, ARCI, Adj Scale	X	X			X	X			X	X			X	X			X	X		
Continuous BP, HR, ECG Monitoring	X	X			X	X			X	X			X	X			X	X		
BPRS	X	X			X	X			X	X			X	X			X	X		
Cocaine Blood PK						X				X				X				X		

X[a] - Prolactin will be assessed on days 15, 22, and 29.
X[b] - PET Scan will be done after screening cocaine infusions and assignment to RPR 102681 or placebo (day 6) and on days 13, 20 and 27.
X[c] - BSI, BDI, POMS, BSCS will be performed every other day.
X[d] - 200 mg RPR 102681 b.i.d. will be administered on days 9-15, 400 mg RPR 102681 b.i.d. - on days 16-22, and 800 mg RPR 102681 b.i.d. - on days 23-29.
X[e] - RPR 102681 will be assessed on days 13-15, 20-22, 27-29.
X[f] - VAS, ARCI and Adjective Scale will be performed on days 2, 3, 7, 8, 14, 15, 21, 22, 28, and 29.

APPENDIX II: Schedule of Blood Collections

Analysis	Volume Per Sample	Type[a]	Number of Samples per Day[b]														Total Volume
Study Day			Screening	D 0	D 8	D 13	D 14	D 15	D 20	D 21	D 22	D 27	D 28	D 29	D 35	D 65	
Chemistries plus liver function tests	7 mL	S	1	1											1	1	28 mL
Liver function tests	7 mL				2			2			2			2			56 mL
Hematologies	7 mL	P	1												1	1	21 mL
Infectious disease serology	10 mL	S	1														10 mL
Prolactin	5 mL	S		1				3			3			3			50 mL
PK Samples for cocaine	7 mL	P			9			9			9			9			252 mL
PK Samples for RPR 102681	5 mL	P				2	2	2	2	2	2	2	2	2			90 mL
Pregnancy Test	5 mL	S	1	1											1	1	20 mL
Alcohol Test	5 mL	P	1														5 mL
Total																	**532 mL**

[a]S = serum, P = plasma
[b]D = day

APPENDIX III: Displacement of Dopamine Binding by RPR 102681 Dosing in Normal Volunteers

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* National Institute on Drug Abuse (NIDA), Division of Treatment Research and Development
** Uniformed Services University of the Health Sciences (USUHS), Division of Clinical Pharmacology and Medical Toxicology
*** Johns Hopkins Medical Center, Department of Nuclear Medicine

A. RATIONALE

Cocaine addiction in the United States is currently estimated at 2.1 million individuals. Cocaine usage constitutes a significant social problem in terms of health risks and increases in crime. Currently there are no Food and Drug Administration (FDA) approved medications for the treatment of cocaine dependence. The identification of pharmacotherapy for cocaine dependence is, therefore, a major public health priority.

The basis of short term and long term addictive effects of cocaine are not well understood. It is known cocaine blocks the reuptake of dopamine in the synaptic cleft by the dopamine transporter (DAT) (also known as dopamine reuptake sites), and therefore increases the amount of dopamine available for dopamine receptors. This increase in available dopamine leads to the activation of the dopaminergic pathway. The mesolimbic dopamine system appears to play a critical role in the reinforcing effects of cocaine. Cocaine's effects may involve other neurotransmitter systems such as those mediated by serotonin and norepinephrine.

RPR 102681 is a potent, orally bioavailable non-peptide antagonist of the cholecystokinin-B (CCK-B) receptor. CCK-B has been shown to have a mediating role in dopamine release in the central nervous system. Experimentally, intraperitoneal administration of RPR 102681 stimulated the release of dopamine in the ventral striatum, which is behaviorally associated with antidepressant and anxiolytic effects (Costall *et al.,* 1991). Tested in animal models of psychostimulant abuse, RPR 102681 reduced intravenous self-administration of cocaine and amphetamine in drug-naïve mice and antagonized rewarding properties of cocaine and amphetamine in drug-experienced rats (Frata, 1996). Preliminary Phase I safety studies in normal volunteers have demonstrated that oral doses of RPR 102681 in the range from 1 mg up to 1600 mg were well tolerated, with only minor and nonspecific adverse events (Caplain, 1997, 1998).

The National Institute on Drug Abuse (NIDA) Division of Treatment Research and Development and the Uniformed Services University of the Health Sciences (USUHS) will be testing the safety of RPR 102681 in a rising dose, cocaine interaction study in cocaine-experienced volunteers. By measuring [^{11}C]-raclopride binding to dopamine receptors under pre-treatment and post-treatment steady-state conditions at each dose of RPR 102681, we hope to demonstrate that the displacement of [^{11}C]-raclopride from striatal binding sites correlates with a measurable effect of RPR 102681 on dopamine release.

We anticipate that this study will provide crucial information about the sites of dopamine binding at different doses of RPR 102681. This information is potentially important in determining the therapeutic dose in clinical practice. In addition, PET studies will reveal the degree of chronic dopamine depletion in cocaine abusing subjects prior to any medication, which may be helpful in identifying the potential of RPR 102681 as a means to restore normal dopamine concentrations in critical subcortical areas.

AIMS AND HYPOTHESIS:

Aim 1: To demonstrate that RPR 102681 exerts its effects by release of dopamine in the striatum.
Hypothesis 1: A dose-response for RPR 102681 at which any significant subjective effects are experienced can be correlated with enhanced release of dopamine.

Aim 2: To identify whether cocaine users demonstrate chronic depletion of dopamine in the drug-free state.
Hypothesis 2: Pre- and post-treatment dopamine concentrations and subjective experiences of drug craving can be correlated.

PROTOCOL:

The PET scan portion of this study consists of four (4) PET studies each of approximately 120 minutes duration. The scanning technique will not require arterial sampling, so an indwelling arterial catheter will not be placed. It is expected that an *in situ* intravenous catheter placed for the purpose of the cocaine interaction study will be used for performing PET scanning; however, displacement or malfunction of the intravenous catheter will necessitate venipuncture for purpose of the PET scan. Every attempt will be made to place the intravenous catheter so that it can be functionally preserved for use during both portions of the study, in order to avoid unnecessary repeated needle sticks to the subject. All of the subjects are dosed and medically managed by the USUHS Clinical Pharmacology team led by Dr. Louis Cantilena. All subjects will be asked to consent to and voluntarily participate in PET scanning separately from their consent to participate in the safety interaction protocol, and no subject will be excluded from participation in the safety interaction protocol based on their desire to be excluded from PET scanning. Complete blood counts, electrocardiograms, urine for toxicology and pregnancy testing will be obtained to confirm that each subject lacks any physical abnormalities to exclude the subject from participation.

12 healthy adult cocaine-experienced volunteers will serve as subjects in this study. Subjects will enter in a block randomization schedule such that in each block, two subjects will receive RPR 102681 and one will receive matched placebo. After the first six (6) subjects are scanned, the PET scan data will be analyzed without breaking the study blind, to see whether there are definitive medication-induced changes in dopamine release. If these first six subjects' scans are non-specific, we will proceed to scan all twelve subjects per protocol. Subjects who agree to participate in PET scanning as part of their inpatient participation in the cocaine interaction study will undergo a pre-treatment baseline study, and then up to three (3) additional PET studies following establishment of steady-state conditions at each of the three (3) doses of

RPR 102681, 200 mg, 400 mg and 800 mg b.i.d. Due to scheduling and radiation dose limitations, they cannot have more than four (4) of such PET scans within 12 months.

Each dosing period for RPR 102681 will be seven (7) days in duration, with no washout between doses. The PET studies will be performed at study entry and on the fifth day of administration at each dose level. Every attempt will be made to perform the scan to coincide with the anticipated peak blood concentration of RPR 102681 after the afternoon oral dose. A venous sample will be obtained at the time of the PET scan to correlate the blood level of RPR 102681 with the scan results. On the sixth and seventh days of RPR 102681 administration at each dose level, subjects will be undergoing cocaine administration sessions in the Clinical Pharmacology Unit at USUHS. Subjects will not be receiving any cocaine on the days of PET scans. Pharmacokinetic blood sampling will be performed on the days of cocaine interaction sessions. There will be a seven (7) day interval between each PET scan.

Each subject will have a custom-fitted face mask to facilitate maintaining the same head position for both magnetic resonance imaging (MRI) and positron emission tomography (PET) studies. Each subject will undergo a cranial MRI to identify the anatomy of the brain for coregistration with the PET images.

If a freely-running intravenous line is not available, one will be inserted into a vein of one arm for injection of the radiotracer. Just prior to the injection of radiotracer, a venous sample will be obtained for plasma concentration of RPR 102681. The subject will receive a bolus intravenous injection of 20 mCi of [^{11}C]-raclopride followed by acquisitions over 120 minutes by the PET scanner. The plasma radioactivity of centrifuged whole venous blood obtained during each scan will be measured with a gamma counter. Plasma radiometabolites will also be assayed with column-switching high performance liquid chromatography (Hilton *et al.,* 2000). The metabolite-corrected plasma input function will be used for kinetic modeling. Binding potential will be calculated by mathematical modeling as done with other radiotracers (Cumming *et al.,* 1999). After the completion of the PET scans, the intravenous catheter will be sterilely capped and "hep-locked" to preserve *in situ* for the cocaine infusion studies that will be conducted on the following days.

The subject will be monitored for physiologic measures including heart rate, blood pressure, electrocardiogram and pulse oximetry from the baseline period before the first scan, throughout the procedure period until the completion of the final scan. If subjects experience anxiety, inability to hold still, restlessness or increased activity during the study, they will be dropped from the study and administered appropriate symptomatic treatment, e.g. intravenous lorazepam. The subject will not be discharged for transportation to USUHS until monitoring personnel are satisfied that the subject's vital signs and level of consciousness have returned to the conditions observed on admission.

RPR 102681 is rapidly absorbed from the gastrointestinal tract, and peak blood concentrations are reached at 0.5-1.5 hours after single dose ingestion, and 1-2 hours after repeated dosing. The mean elimination half-life is 11.7-33.4 hours (Caplain, 1997, 1998). The pharmacokinetics of RPR 102681 that have been described in normal subjects are expected to justify our assumption that subjects will be at steady-state conditions by the fourth day of dosing at each dose level.

USUHS will transport the subjects from the Clinical Pharmacology Unit at USUHS. Subjects will be accompanied by a nurse and undergo routine observation and monitoring.

Injection of the PET radiotracer [^{11}C]-raclopride will be done one hour following the morning dose of RPR 102681. All dosing will be done by USUHS staff.

INCLUSION CRITERIA

The inclusion criteria are designed to select healthy adults who are cocaine-experienced but without physical or mental illness. Subjects must meet all of the following inclusion criteria at screening, and continue to meet these criteria during the study.

1. Be volunteers who are not seeking treatment at the time of the study
2. Be between 18 and 45 years of age and within 20% of ideal body weight according to the Metropolitan Height and Weight Chart, and weigh at least 45 kg.
3. Meet DSM-IV criteria for cocaine abuse.
4. Be currently using cocaine by the smoked or intravenous route, and use is confirmed by a positive BE urine test within two (2) weeks prior to entering the study
5. Be able to verbalize understanding of the consent form, able to provide written informed consent, and verbalize willingness to complete the study procedures.
6. If female, have a negative pregnancy test within 72 hours prior to receiving the first dose of investigational agent and agree to one of the following methods of birth control, or be postmenopausal, or have had a hysterectomy, or have been sterilized.
    a) complete abstinence from sexual intercourse
    b) diaphragm and condom by partner
    c) intrauterine device and condom by partner
    d) intravaginal sponge and condom by partner
7. Have a history and brief physical examination that demonstrate no clinically significant contraindication for participating in the study.
8. Be able to comply with protocol requirements, Clinical Pharmacology (CPU) rules and regulations, and be likely to complete all study treatments.

Exclusion criteria

In order to participate in the study, subjects must <u>not</u>:

1. Have a current or past history of seizure disorder, including alcohol- or stimulant-related seizure, febrile seizure, or significant family history of idiopathic seizure disorder.

2. Have any previous medically adverse reaction to cocaine, including loss of consciousness, chest pain, or seizure.

3. According to DSM-IV criteria as determined by structured clinical interview (SCID), have any history of major psychiatric illness, such as bipolar disorder, depression, manic or dysthymic illness**,** other than drug dependence or disorders secondary to drug use as determined by a National Institute of Mental Health trained technician.

4. Be pregnant or lactating.

5. Have a history of liver disease or current elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) exceeding the upper limit of normal.

6. Have donated a unit of blood or participated in any other clinical investigation within 4 weeks of enrolling on the study.

7. Have a history of any illness, or a family history of early significant cardiovascular disease, or a history of behavior, that in the opinion of the investigator might confound the results of the study or pose additional risk in administering the investigational agents to the subject.

8. Be seropositive for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) types 1 and 2.

9. Have a diagnosis of adult onset asthma (i.e., 21 years or older), or chronic obstructive pulmonary disease (COPD), including those with a history of acute asthma within the past two years, and those with current or recent (past 2 years) treatment with inhaled or oral beta-agonist.

10. Have any illness, condition, and use of medications, that in the opinion of the principal investigator and the admitting physician, would preclude safe and/or successful completion of the study.

11. Currently use illicit drugs besides cocaine and marijuana.

12. Have used any prescription drugs within 14 days of the start of the study or non prescription drugs within 7 days of the start of the study.

13. Be unable to distinguish between a 20 mg and 40 mg dose of cocaine intravenously during the administration of screening and baseline infusions.

14. Have had prior exposure to radiation for a research study. This excludes having x-rays for medical purposes.

15. Have had a tatoos within the last 6 months.

16. Have any metallic body art (such as eye rings, belly button rings) that cannot be removed.

17. Have an abnormal MRI finding discovered as part of the PET Scan procedure. (Subjects will be notified immediately of results and advised to contact their primary care physician.)

18. Have a history of any congenital or acquired neurologic pathology, including cerebrovascular accidents or insufficiency, encephalitis, head trauma, intracranial neoplasm, normal or low-pressure hydrocephalus, or any progressive central nervous system atrophy or progressive polyneuropathy.

OUTCOME VARIABLES:

The primary outcome variable is the safety of three dosing regimens of RPR 102681 at steady state concentrations and in the presence of concurrent administration of intravenous cocaine under controlled conditions.

The secondary outcome variables include:

1. Binding potentials of raclopride in the striatum at 200 mg, 400 mg and 800 mg b.i.d. doses of RPR 102681 without cocaine, as compared to baseline;
2. Pharmacokinetics of cocaine and its metabolites in the presence of RPR 102681;
3. Effects of RPR 102681 on serum prolactin levels;
4. Effects of RPR102681 on mood and personality using Brief Symptom Inventory (BSI), Beck Depression Inventory (BDI), Brief Psychiatric Rating Scale (BPRS) and Profile of Mood States (POMS) assessments, and on the subjective effects of cocaine measured by Adjective Scale and Visual Analog Scale (VAS) and craving measured by Brief Substance Craving Scale (BSCS).

RISKS AND BENEFITS:

The risks of PET studies include those due to intravenous lines, blood withdrawal, and radiation exposure.

The risks of intravenous catheters are bleeding, possible hematoma at the site of injection, and possible phlebitis at the catheter site. Sampling of venous blood may cause pain, bruising, lightheadedness, and on rare occasions, infection.

[^{11}C]-raclopride, a medication studied in Europe for many years, is an investigational agent in the United States. The adverse effects of [^{11}C]-raclopride are more likely when people are administered therapeutic doses daily for months or years. The risk of long-term adverse effects of [^{11}-C]-raclopride is much less in this study because the subjects will receive a small dose. Long-term side effects are sometimes seen in people who take much larger doses of [^{11}C]-raclopride every day for months or years. One of these is tardive dyskinesia, a condition with involuntary movements of the mouth, face, tongue, cheeks, arms, and/or legs. Tardive dyskinesia may be permanent, and there is no effective treatment for it.

The rad dosimetry per PET scan is 18 mCi, resulting in an effective dose equivalent (17mrem/mCi) that will not exceed 5 rems to the whole body annually. Naturally occurring radiation (cosmic radiation and radon) produces whole body radiation exposures of about 340 mrems per year. A pregnancy test will be performed on all female subjects at the beginning, conclusion, and one-month follow-up of the study, and subjects will remain in a controlled inpatient environment for the duration of the study. If a subject becomes pregnant before the study is completed, she must inform the investigator.

The investigational medication, RPR 102681, has never been administered with [^{11}-C]-raclopride. In prior clinical trials of RPR 102681 (120 healthy volunteers, total), in which doses equal to those proposed for this trial were administered, the adverse events observed were minor and included headache (7 occurrences), somnolence (3), euphoria (2), postural hypotension (6), diarrhea (2), flatulence (4), and pharyngitis (3). In one placebo-controlled trial in 8 healthy females, metrorrhagia was reported in 1 active and 1 placebo subject. No serious adverse events have been reported in prior clinical trials of RPR 102681.

All subjects will be monitored by a physician present during the PET study. The rest of the time to and from NIHCC they will be monitored by USUHS medical staff. Specifically all dosing, monitoring, psychological and medical evaluations will be carried out at USUHS. Only

the MRI and each of up to four (4) PET scans will be carried out at JHH and each visit at JHH may last up to about eight (8) hours, but subjects will never be held over night except in the event of an emergency. All subjects will be recruited by USUHS and consent for the PET and MRI provided jointly at USUHS after they have received a complete explanation of all aspects of the proposed trial.

There are no direct benefits to the subjects. The results will contribute to the development of a medication that is safe and effective for the treatment of cocaine abuse and/or relapse.

COMPENSATION:

Subjects will be compensated for their time at a rate of $20/hour for the PET portion (in addition to their compensation at USUHS) and will receive a physical exam, routine blood work, ECG and MRI free of charge.

CONSENT:

Consent will be obtained from the subjects or their surrogates by the Principal Investigator or Sub-investigator at the research offices at USUHS. Subjects or their surrogates will be asked to state in their own words the study procedure to verify that they understand the information. The subjects and their surrogate may take as much time as they want to make a decision to participate (Brasic and Davis, 1998).

REFERENCES:

Brasic JR, Davis E: Obtaining informed consent for research from persons with Parkinson's disease and movement disorders. *Movement Disorders* 1998; 13 (Suppl2): 206 [abstract]

Caplain H. A phase 1, double-blind, placebo-controlled, randomized tolerability and pharmacokinetic study of RPR 102681 administered as single rising oral doses to parallel groups of healthy male volunteers. Rhone-Poulenc Rorer, Inc. (France). Internal Report, 1997.

Caplain H. A phase 1, double-blind, placebo-controlled, randomized tolerability, pharmacokinetic and pharmacodynamic study of RPR 102681 administered as repeated oral doses for 14 days to parallel groups of healthy male volunteers and as a single oral dose to one group of healthy female volunteers. Rhone-Poulenc Rorer, Inc. (France). Internal Report, 1998.

Costall B, Domeney AM, Huges J, Kelley ME, Naylor RJ, Woodruff GN. Anxiolytic effects of CCK-B antagonists. *Neuropeptides* 1991; 19: 65-73.

Cumming P, Yokoi F, Chen A, Deep P, Dagher A, Reutens D, Kapinski F, Wong DF, Gjedde A. Pharmacokinetics of radiotracers in human plasma during positron emission tomography. *Synapse* 1999; 34:124-134.

Hilton J, Yokoi F, Dannals RF, Ravert HT, Szabo Z, Wong DF. Column switching HPLC for the analysis of plasma in PET imaging studies. *Nucl Med Biol* 2000; 27: 627-630.

Schlaepfer TE, Pearlson GD, Wong DF, Marenco S, Dannals RF: PET study of competition between intravenous cocaine and [^{11}C]-raclopride at dopamine receptors in human subjects. *Am J Psychiatry* 1997;154: 1209-1213.

APPENDIX IV: Instructions For Evaluating and Reporting Adverse Events and Serious Adverse Events

A. GENERAL INSTRUCTIONS

1. Report the severity of the event following the guidance in section B below.

2. 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 investigator 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).

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 Medical Monitor and the IND sponsor.

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
- 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 Medical Monitor/Alternate and the IND sponsor 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 or a change in status from outpatient to inpatient. 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 and the IND sponsor 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 followup 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 V: 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, or
- if required by law.

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.

Applying for a Certificate of Confidentiality

A 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).

Investigators will obtain a certificate 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 Investigator will submit the application, as outlined in the Confidentiality Certificate Application Instructions (http://www.nida.nih.gov/Funding/ConfidentialityInstruct.html), along with IRB review documentation and a copy of the informed consent/assent forms to be used in the study. The Principal Investigator must sign the application and submit everything to:

Ms. Jacqueline R. Porter
NIDA Certificate of Confidentiality Coordinator
or
Ms. Sandra Solomon,
Certificate of Confidentiality Assistant

Office of Extramural Affairs
6001 Executive Boulevard, Room 3158, MSC 9547
Bethesda, Maryland 20852-9547
Rockville, MD 20852 (courier or express mail)
TEL: 301-443-2755
FAX: 301-443-0538
E-MAIL: jporter@nida.nih.gov or ssolomo1@nida.nih.gov

Since a certificate is generally issued to a sponsoring research institution, the application and its assurances, must be signed by a faculty member or a senior official. The principal investigator, or their staff, will not represent the issuance of a Certificate to potential participants as an endorsement of the research project by DHHS or use it in a coercive manner for recruitment of subjects. The investigator must use the authority of the Certificate to resist compulsory disclosure of individually identifiable research data.

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.