DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE ESCALATING, SAFETY AND PHARMACOLOGY STUDY WITH THREE DOSAGES OF GBR 12909 IN COCAINE EXPERIENCED VOLUNTEERS

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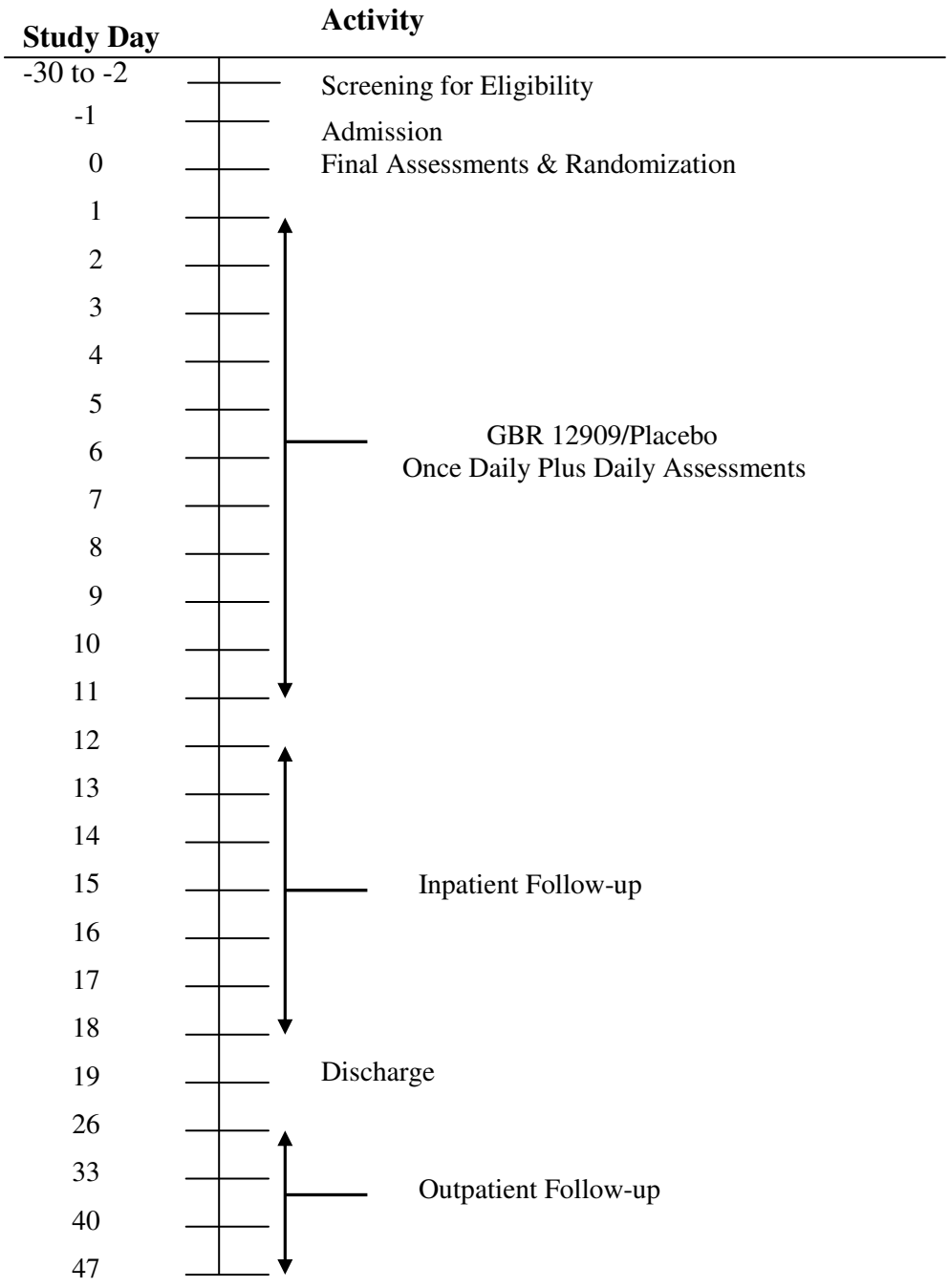
1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADME	adsorption, distribution, metabolism, and excretion
AE	adverse event
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ARCI	Addiction Research Center Inventory
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	area under the blood concentration-time curve
BE	benzoylecgonine
BP	blood pressure
BSCS	Brief Substance Craving Scale
CAP	College of American Pathologists
CLIA	Clinical Laboratory Improvement Amendment of 1988
COPD	chronic obstructive pulmonary disease
CRF	Case Report Form
CPU	clinical pharmacology unit
CSFQ	Change in Sexual Function Questionnaire
CYP3A	cytochrome P450 isoform 3A
DA	dopamine
DAT	dopamine transporter
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
FDA	Food and Drug Administration
HPLC	high performance liquid chromatography
HR	heart rate
IRB	Institutional Review Board
i.v.	intravenous(ly)
MOASCL	McClean Hospital Event Overt Aggression Checklist
mg	milligrams
NIDA	National Institute on Drug Abuse
PET	positron emission tomography
PK	pharmacokinetic
p.o.	orally (per os)
RDA	recommended daily allowance
SAE	serious adverse event
SAFTEE	Systematic Assessment for Treatment Emergent Effects
SCID	structured clinical interview for DSM-IV
SERT	serotonin transporter
USUHS	Uniformed Services University of the Health Sciences
UCSF	University of California San Francisco

2 SCHEMA


Study Day
Activity
-30 to -2
Screening for Eligibility
-1
Admission
0
Final Assessments & Randomization
1
2
3
4
5
6
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Inpatient Follow-up
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3 ABSTRACT

STUDY OBJECTIVES: This is a human laboratory study that will assess the clinical pharmacology, safety and tolerance of three escalating oral doses of GBR 12909, which is 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl) piperazine dihydrochloride, in cocaine experienced volunteers.

STUDY DESIGN: This is a single dose with escalation, double-blind, placebo-controlled inpatient study, in which 24 cocaine experienced volunteers that meet the protocol eligibility criteria during a 30 day (maximum) screening period will be randomized into three dose groups (n=8 each). In each group, 6 subjects will be randomized to receive a single daily dosage of 50, 75 or 100 mg of study agent and 2 will receive matched placebo for 11 days. Each cohort of 8 subjects will complete all inpatient study procedures and be released from the clinic before starting the next cohort. Prior to initiating dosing of the next cohort, the safety data of the completed cohort including the ECG parameters (not limited to prolongation of the QT interval) will be reviewed by the NIDA medical monitor, site investigators, and if applicable, a physician representative of the governing Institutional Review Board (IRB) for a determination to proceed to dosing of the next cohort. Dosing will start at the lowest dose of GBR 12909 (50 mg), and escalate to the next higher doses sequentially (75 then 100 mg). Subjects will be followed weekly for 4 weeks after clinic discharge.

STUDY DURATION: The total duration of the study is 20 to 25 inpatient days which includes a washout period if the subject is drug positive on admission, 11 days of treatment (days 1 through 11) with pharmacokinetic (PK) sampling and seven days of inpatient follow-up PK sampling and safety assessments or until the vital signs return to baseline values. After discharge, subjects will be assessed weekly for 4 weeks for safety assessments. This is a total of 54 to 59 study days per subject.

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SAMPLE SIZE: 24 subjects total (three groups of eight). Subjects dropping out due to medical reasons not related to drug toxicity may be replaced at the discretion of the investigational team.

POPULATION: The study population will include male and female healthy, volunteer experienced cocaine users with a diagnosis of cocaine abuse or dependence according to Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria and are 18-to-45 years of age.

TREATMENTS: Subjects will receive 50, 75 or 100 mg of GBR 12909 or matched placebo by oral administration daily for 11 days. No subject will start a higher dose level until all 8 subjects (2 receiving placebo and 6 receiving GBR 12909) have completed all inpatient procedures.

ASSESSMENTS: Safety of GBR 12909 will be determined by monitoring adverse events (AE), blood pressure (BP), heart rate (HR), and electrocardiogram (ECG) responses as well as hematology/serum chemistry/urinalyses data and psychometric evaluations. GBR 12909 plasma concentrations will be determined at the following time points for pharmacokinetic (PK) analysis at predose (trough) on inpatient days 0, 3, 8, 9, 10, and 11 and post dose starting on the 11th day at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours. Urine samples will

be collected for PK at pre-GBR 12909 dosing on days 1 and 11 and at 8-hour intervals during the first 24 hours after day 11 dosing.

4 INTRODUCTION AND RATIONALE

4.1 Therapeutic Strategies for Treating Cocaine Abuse

Cocaine abuse and dependency in the United States have achieved epidemic proportions in the past decade and constitute a significant public health concern. The development of a pharmacological treatment for cocaine abuse and dependence is a major objective of the National Institutes on Drug Abuse (NIDA) that is being coordinated by Division of Treatment Research and Development (DTRD). The present study will examine the safety of the investigational compound, GBR12909, in cocaine-experienced volunteers prior to subsequent randomized trials designed to assess therapeutic efficacy for the treatment of cocaine abuse and dependence. GBR12909 has been investigated previously in European clinical studies for the treatment of depression and Parkinson's disease and for safety in healthy human volunteers. Limited reinforcing properties of GBR 12909 may be advantageous in the context of addiction treatment programs by contributing to better patient's compliance and enhanced effectiveness of medication (Howell and Wilcox, 2001).

Cocaine is a stimulant as well as a local anaesthetic with potent vasoconstrictor properties (i.e., cocaine rapidly increases HR and BP in a dose related manner). It induces a complex pattern of subjective effects that have been described as intense euphoria and alertness, mood enhancement, increased confidence and strength, heightened sexual feelings and indifference to concerns or cares. The neurobiological mechanism underlying the effects of cocaine are not well understood. There is considerable evidence that the initiation and continuation of cocaine use is associated with the effects of the drug on the dopaminergic, serotonergic and noradrenergic modulation of the central nervous system function. Animal studies suggest that the mesocorticolimbic dopaminergic pathways are important mediators of cocaine's reinforcing properties.

Although many compounds have been evaluated for the treatment of cocaine dependence, so far there is no pharmacotherapy for this indication. Cocaine is known to produce its major abuse-related effects via dopaminergic mechanisms in the midbrain. It binds at the dopamine transporter (DAT) and inhibits dopamine (DA) reuptake, thus leading to a build-up of extracellular DA levels and stimulation of reward-associated mesolimbocortical pathways (Kuhar *et al.,* 1991). Cocaine is a potent inhibitor of not only DAT; it also inhibits transporters for serotonin and norepinephrine (Fleckenstein *et al.,* 2000; Miller *et al.,* 2001). Single gene knockout studies of dopamine, serotonin or norepinephrine transporters in mice indicate 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. Still, the effects of transporter gene copy numbers on the cocaine place preference test indicate a greater role for DAT than serotonin transporter (SERT) in cocaine reward/reinforcement in mice, consistent with previous pharmacological studies.

Given the obvious importance of DAT in the addictive properties of cocaine, the development of compounds that target DAT represents a logical approach for treatment of cocaine dependence.

In vitro preclinical studies have shown that GBR12909 has a strong affinity for the dopamine transporter. GBR12909 produces dopamine like agonist effects in preclinical studies and the finding that GBR12909 has a long duration suggests it may be a potential agonist medication. Furthermore, nonhuman primate studies have demonstrated that GBR12909 can selectively block cocaine self-administration (Villemagne *et al.,* 1999a).

4.2 GBR 12909

4.2.1 Pharmacology

GBR 12909, 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl) piperazine dihydrochloride], is a DA uptake inhibitor structurally different from cocaine. GBR 12909 binds to the DA transporter (DAT) and inhibits reuptake of DA from the synaptic cleft. GBR 12909 exhibits high affinity to DAT (K*i* for human DAT is 9 nM), which is 20-fold higher than that of cocaine (NIDA, unpublished data). *In vivo* and *in vitro* pharmacological and biochemical studies have demonstrated that GBR 12909 is a selective DA uptake inhibitor with specificity for DA uptake 100-fold higher compared to noradrenaline and serotonin uptake (Andersen, 1989; Sogaard *et al.,* 1990). GBR 12909 is a long-acting inhibitor of DA uptake, and duration of its effect on DAT availability and increase in DA in conscious monkey brain is 5.5 and 7 hrs, respectively, as evaluated by positron emission tomography (PET) studies combined with microdialysis (Tsukada *et al.,* 2000).

GBR 12909 produces a persistent and non-competitive blockade of DAT and substantially reduces cocaine-induced increases in extracellular DA in the nucleus accumbens of the rats (Rothman *et al.,* 1991; Baumann *et al.,* 1994). *In vivo* microdialysis studies in rodents showed that GBR 12909 attenuates cocaine and amphetamine-induced increases in mesolimbic DA that mediate the addictive and reinforcing properties of drugs of abuse (Rothman *et al.,* 1991; Baumann *et al.,* 1994).

Early data showed that GBR 12909 can decrease cocaine-maintained response in *Rhesus* monkeys without affecting similar levels of food-maintained response (Glowa *et al.,* 1995a,b). Furthermore, a decanoate ester of a hydroxylated analog of GBR 12909, DBL-583, can decrease cocaine-maintained response by 80% without affecting food-maintained response; this effect lasts almost 30 days with a single injection (Glowa *et al.,* 1996). Intravenous (i.v.) infusion of GBR 12909 (1 mg/Kg) to *Papio anubis* baboons inhibits amphetamine-induced striatal DA release by 74% as measured by raclopride PET scans (Villemagne *et al.,* 1999b). Importantly, GBR 12909 reduces (1 mg/Kg, i.v.) and eliminates (3 mg/Kg, i.v.) cocaine self-administration in *Rhesus* monkeys (Villemagne *et al.,* 1999a). The doses of GBR 12909 that suppress cocaine self-administration in non-human primates produce high occupancy of DAT; thus, doses of 1, 3 and 10 mg/Kg occupy 26, 53, and 72% of DAT, respectively (measured by WIN35,428 PET scans) (Villemagne *et al.,* 1999a). GBR 12909 produces a dose-dependent DAT occupancy in humans as well, and at 100 mg oral doses, the DAT occupancy by GBR 12909, as assessed by PET imaging with WIN35,428, is reported to be 30 to 40 % (Wong *et al.,* 1999). The results of the studies in non-human primates and in human volunteers indicate that GBR suppresses cocaine self-administration via inhibition of DAT and that human laboratory studies testing the efficacy of orally administered GBR 12909 for cocaine addiction should use doses that produce sufficiently high occupancy of DAT.

4.2.2 Pharmacokinetics

The results of GBR 12909 pharmacokinetics studies in humans indicate that:

1. GBR 12909 metabolism follows first order kinetics with elimination half-life of about 48 hours (Sogaard *et al.,* 1990).
2. Steady-state concentrations of GBR 12909 are reached by day 8 of repetitive dosing (Sogaard *et al.,* 1990; NIDA Communication, 2001).
3. Food intake increases oral bioavailability of GBR 12909 (Ingwersen *et al.,* 1993b).
4. GBR 12909 is rapidly absorbed with a mean T_{max} of less than 1.5 hours (NIDA Communication, 2001).

4.2.3 Metabolism

GBR 12909 is metabolized by human liver microsomes and by human hepatocytes to a single metabolite, the chemical structure and biological activity of which remains to be elucidated (Cherstniakova *et al.,* 2001). A recent study of GBR 12909 biotransformation by human liver microsomes (Cherstniakova *et al.,* 2001) indicated that CYP3A, a ketoconazole-inhibited member of the cytochrome P450 family of drug-metabolizing monooxygenases, appears to be the major enzyme responsible for GBR 12909 degradation. The results of this study indicate that coadministration of GBR 12909 with specific inhibitors or inducers of CYP3A such as ketoconazole, ritonavir and rifampin could alter expected therapeutic effects in cocaine-dependent subjects.

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 GBR 12909 and cocaine are substrates for CYP3A indicates a potential of cocaine-GBR 12909 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 GBR 12909 on cocaine metabolism should be negligible.

4.2.4 Previous Human Experience with GBR 12909

Two randomized placebo-controlled double-blind cross-over studies in normal human volunteers (20-45 years old) have been conducted by Sogaard *et al.* (1990) with rising dose levels of GBR 12909 in an aqueous solution. The first single dose study was conducted in four subjects with dose levels of 100, 200 and 300 mg with a 7 day washout period between each dose level. Subjects fasted from 8 hours before and 2 hours after the dosing. C_{max} ranged from 29-102 nM after the 100 mg dose, from 119-348 nM after the 200 mg dose and from 266-831 nM after the 300 mg dose. GBR 12909 was rapidly absorbed with T_{max} ranging from 0.5-1 hr. The elimination half-life was not characterized due to lack of assay sensitivity.

A multiple dose study has been performed with dose levels of 50, 100 and 150 mg administered for 7 days in four subjects (Sogaard *et al.,* 1990). Subjects fasted from 8 hours before and 30 minutes after the dosing. Serum concentrations observed 24 hours after the last dose ranged from 33-70 nM after the 100 mg dose and 83-153 after the 150 mg dose. Concentrations after

the 50 mg dose were below the detection limit (20 nM). The terminal half-life was not calculated in this study. However, rough estimates indicated a value between 36-57 hours. Subjects, in that study, demonstrated mild to moderate side effects such as difficulties in concentration, asthenia, feeling of drug influence and palpitations. In addition, a dose related effect on ECG T-wave amplitude was mentioned in the report. One of 4 subjects demonstrated an abnormal prolongation in the QT-interval at the highest doses. No signs of arrhythmia or cardiac decompensation during exercise until exhaustion were observed. In addition, dose related sedation was observed in the single dose study assessed by psychomotor performance. The report also noted that there were no changes in hematologic and blood chemistry parameters. Finally, the study noted that pharmacokinetics observed in individuals appeared to be first order in nature with elimination half-life estimated at one to two days. The authors concluded that steady state serum concentrations of GBR 12909 appeared to be obtained within one week of once daily dosing and that the expected "therapeutic" doses of the agent appeared to be well tolerated in the subjects.

In a three-way cross-over study in 14 healthy volunteers, GBR 12909 exhibited nonlinear pharmacokinetics after multiple administrations of daily doses of 25, 75 and 125 mg for 14 days. Near-steady state concentrations were achieved in 9-11 days. The mean elimination half-life was approximately 60 hours at 75 and 125 mg doses (Ingwersen *et al,* 1993a).

An increase in oral bioavailability following administration of a single dose of 100 mg of GBR 12909 with food was observed in a study conducted in 12 healthy male volunteers. The AUC_{0-t} increased from 110 to 194 nM.h after a low fat diet and from 110 to 391 nM.h after a high fat diet (Ingwersen *et al,* 1993b).

A recent NIDA-sponsored phase 1, dose escalation protocol was completed at the NIDA-Uniformed Services University of the Health Sciences (USUHS) Clinical Pharmacology Unit (CPU). This study examined 12 healthy male and female volunteers, ages 18-to-45 years old, in a dose escalation scheme incorporating 25, 50, 75, and 100 mg daily dosages of GBR 12909 (NIDA Communication, 2001). The primary finding of this study was a slight increase in heart rate and systolic blood pressure in the majority of subjects. In addition, two of the 12 subjects completing the protocol experienced an increased sexual drive at the two higher dosages of GBR 12909. There were no serious adverse events or dose-limiting toxicity. A slight, clinically insignificant increase in the QTc interval was seen, which was attributed entirely to the increase in HR.

4.3 Rationale for the Current Study

Before clinical investigations to determine GBR 12909 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 European studies with GBR 12909 in patients with depression and Parkinson's disease utilized only small numbers of subjects in both single dose and multiple dose schedules.

The preliminary NIDA-USUHS CPU study was not placebo-controlled and was conducted in healthy volunteers. A more thorough study of potential hemodynamic effects of GBR 12909 in the indicated population (cocaine users) is required for further development of this compound as

a potential therapy to treat cocaine dependency. An expert consultant meeting convened by NIDA in June, 2001 recommended that a phase I absorption, distribution, metabolism, and excretion (ADME) clinical trial of GBR 12909 be conducted in cocaine experienced healthy volunteers before proceeding to phase I interaction studies with cocaine and subsequent outpatient clinical trials.

Planned dosage levels for the present phase 1 clinical investigation encompass the expected "therapeutic" dose of 50-100 mg of GBR 12909 per day. Furthermore, the three dose levels planned for study in this investigation (50, 75 and 100 mg) are well within those levels, which have previously been used in human subjects in Europe.

4.4 Safety of GBR 12909

The pharmacokinetics of GBR 12909 may be affected by drugs that alter (induce or inhibit) CYP3A activity that is responsible for biotransformation of GBR 12909 (Cherstniakova *et al.,* 2001). Thus, coadministration of GBR 12909 with specific inhibitors/inducers of CYP3A such as ketoconazole, ritonavir and rifampin should be done with caution because that can alter expected therapeutic effects of GBR 12909 in cocaine-dependent subjects. These agents can either reduce GBR 12909 metabolism and increase its plasma concentrations leading to toxicity or increase clearance of GBR 12909, resulting in lower plasma levels of this drug and, perhaps, sub-effective dosing. Also, as GBR 12909 potently inhibits human recombinant CYP2D6 *in vitro* (K_i 0.13 nM) (NovaScreen Biosciences, N01DA-8-8089), it may have the potential to decrease the metabolism and consequently increase the toxicity of drugs known to be metabolized by CYP2D6 such as clozapine, codeine, risperidone, haloperidol, dextromethorphan, and fenfluramine. Thus, close monitoring of plasma GBR 12909 concentration and its adverse effects will be performed.

Adverse events reported in subjects receiving GBR 12909 include mild to moderate difficulties in concentration, asthenia, feelings of drug influence and palpitations. In addition, a dose related effect on ECG T-wave amplitude was mentioned in one report. In one study, 1 of 4 subjects, demonstrated a slightly abnormal prolongation in the QT-interval at a 150 mg daily dose. In studies conducted by NIDA with 25 to 100 mg daily dosages of GBR 12909, a slight increase in heart rate and systolic blood pressure was reported in the majority of subjects (NIDA Communication, 2001).

5 STUDY DESIGN

This is a single dose with escalation, double-blind, placebo-controlled inpatient study, in which 24 cocaine experienced volunteers that meet the protocol eligibility criteria during a 30 day (maximum) screening period will be randomized into three dose groups (n=8 each). In each group, 6 subjects will be randomized to receive a single daily dosage of 50, 75 or 100 mg of study agent and 2 will receive matched placebo for 11 days. Each cohort of 8 subjects will complete all inpatient procedures and be released from the clinic before starting the next cohort. Dosing will start at the lowest dose of GBR 12909 (50 mg), and escalate to the next higher doses sequentially (75 then 100 mg). Subjects will be followed weekly for 4-weeks after clinic discharge. Subjects will be confined in the CPU for the duration of the inpatient period to ensure proper monitoring for safety and compliance. An inpatient period is defined as the period

between the day of admission and 168 hrs after the last dose at the specific dose level of study drug. There will be one inpatient period for each cohort of 8 patients corresponding to each of the 3 dose levels of GBR 12909 with two patients in each cohort receiving matched blinded placebo according to the same schedule. Plasma concentrations for GBR 12909 will be measured at specified time-points during the inpatient period and during the 168 hours following the morning dose on the 11th day of each inpatient period.

Prior to initiating dosing of the next cohort, the safety data of the completed cohort including the ECG parameters (not limited to prolongation of the QT interval) will be reviewed by the NIDA medical monitor, site investigators and if applicable, a physician representative of the governing Institutional Review Board (IRB). Their recommendation to advance to the next dose level will be required prior to the initiation of the next dose cohort.

Safety will be assessed by physical examinations, vital signs, 12-lead and digital ECGs, routine hematology, routine serum chemistry, urinalyses, and monitoring for adverse experiences. Subjects will be monitored for central nervous system (CNS) effects using psychometric determinations during the inpatient period and during the outpatient follow-up visits.

6 STUDY OBJECTIVES

To assess the safety, tolerance, and pharmacokinetics of multiple escalating dosages of oral GBR 12909 in cocaine experienced volunteers.

7 STUDY SITE

The study will be conducted at the Clinical Pharmacology Unit (CPU) at the National Naval Medical Center, Uniformed Services University of the Health Sciences (USUHS), Bethesda, MD.

8 STUDY SPONSOR

This study will be conducted under IND No. 57,007 held by NIDA.

9 SUBJECT SELECTION

9.1 Inclusion Criteria

In order to participate in this study, subjects must:

1. Be between 18 and 45 years-of-age.

2. Be within 20% of ideal body weight and must weigh at least 45 kg.

3. Understand the study procedures and provide written informed consent.

4. Be volunteers who are dependent on or abusing cocaine according to DSM-IV criteria and are non-treatment seeking at time of study.

5. Currently use cocaine as determined by self report and a positive urine test for BE within 30 days of the start of the study.

6. Be 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. Be judged by the examining physician or his/her designee after a history and physical examination to be in good health, without clinically significant abnormalities.

8. Have an ECG performed that demonstrates normal sinus rhythm and no clinically significant arrhythmias.

NOTE: Recent intermittent alcohol or other illicit drug use without physical dependence is allowable.

9.2 Exclusion Criteria

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

1. According to DSM-IV criteria as determined by structured clinical interview (SCID), have any current diagnosis or history of major psychiatric illness other than drug dependence or disorders secondary to drug use or be mentally or legally incapacitated.

2. According to DSM-IV criteria be dependent upon or abusing drugs other than cocaine, marijuana, nicotine, and alcohol or have physiological dependence upon alcohol requiring medical detoxification.

3. Currently be physically dependent on illicit drugs besides cocaine and marijuana as determined by the SCID. Note: The subjects that are not physically dependent on other illicit substances but during pre-study screening have a positive urine drug screen for amphetamines, barbiturates, benzodiazepines, methadone, opiates, PCP, or propoxyphene will be allowed to participate after a wash-out period and providing a negative urine drug screen.

4. Use any prescription drugs within 14 days of enrollment or non-prescription drugs within 7 days of enrollment, or if female, have used an oral contraceptive, Depo-Provera, Norplant or intrauterine progesterone contraceptive system within 30 days of enrollment.

5. Be pregnant or lactating.

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

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

8. 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.

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

10. Have a diagnosis of adult (i.e., 21 years or older) asthma, 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 INVESTIGATIONAL AGENTS

10.1 GBR 12909 and Placebo

The chemical name of GBR 12909 is 1-(2[bis(4-fluorophenyl)methoxy[ethyl)-4-(3-phenylpropyl) piperazine dihydrochloride. GBR 12909 will be supplied as 25 mg and 50 mg gelatin capsules along with matched placebo capsules by the National Institute on Drug Abuse (NIDA). These capsules were manufactured by Murty Pharmaceuticals (Lexington, Kentucky) under a contract with NIDA. GBR 12909 is supplied as white opaque 25 mg and 50 mg capsules, weighing 300 mg. Specifications of other constituents of GBR 12909 capsules are as follows:

Ingredient	Placebo	25 mg capsule	50 mg capsule
GBR 12909	0 mg	25 mg	50 mg
Lactose Monohydrate, NF	210 mg	185 mg	168 mg
Microcrystalline Cellulose, NF	92 mg	82 mg	74 mg
Croscarmelose Sodium, NF	6 mg	6 mg	6 mg
Colloidal Silicon Dioxide, NF	1 mg	1 mg	1 mg
Magnesium Stearate, USP/NF	1 mg	1 mg	1 mg

10.2 Dispensing Investigational Agents

Investigational agents will be administered under the supervision of research staff. The 50 mg dose will be administered as a single 50 mg capsule, the 75 mg dose will be administered as one

50 mg and one 25 mg capsule and the 100 mg dose will be administered as two 50 mg capsules. This same schema will be used for the matched placebo. GBR 12909 will be ingested once every 24 hours in the fasted state (nothing by mouth except water after midnight until two hours after dose) at approximately 8 a.m. The precise time of day when the dose of GBR 12909 is given (t=0) may be individualized within a range from 0600-0800 for each subject. Subjects will be instructed to take each dose of their study medication with approximately 250 mL of water and their oral cavity will be visually examined by the research nurse to ensure the medication has been ingested. Specific instructions for each treatment are as follows: "Take each pill with 250 mL of water, once daily in the morning."

10.3 Packaging, Labeling, Storage, and Return of Investigational Agents

Investigational agents will be packaged in high-density polyethylene bottles. Bottles will be labeled with the subject's allocation number, dose level (for placebo this will be the dose level of the cohort), treatment day, quantity/container, and instructions for taking the medication. The investigational agents should be stored at room temperature, and exposure to direct light should be avoided. The GBR 12909 is stable for 31 months-long storage at 25^{o}C and relative humidity of 60%.

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are to be dispensed/administered as described above. At the end of the study, all unused clinical supplies must be returned to NIDA.

11 TREATMENT PLAN

11.1 GBR 12909 and Placebo

Each subject will receive eleven days of GBR 12909 or matched placebo at the dose assigned to their cohort (50, 75 or 100 mg) starting on study day 1.

11.2 Prior and Concomitant Medication(s)

No prescription medication for 14 days and non-prescription medications (including 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 and intrauterine progesterone contraceptive system 30 days prior to study participation. 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.

11.3 Dietary, Activity, and Other Restrictions

Diet. For all dosages of GBR 12909, subjects must not consume any food or drink except water from midnight to 2 hours following each dose. Each dose must be taken with at least 250 mL of

water. Except for these restrictions around the time of dosing, there will be no other dietary restrictions during the study except all food and drink must be provided by the CPU.

Snacks are permitted any time except after midnight until 2 hours after each dose. Subjects can consume caffeinated beverages, which will be limited to no more than two 12 oz. portions a day except after midnight until 2 hours after each dose.

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

Tobacco Products. Subjects will be allowed to smoke during the study in designated areas and accompanied by CPU staff at scheduled times according to the rules of the CPU. 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.

12 STUDY PROCEDURES

A time and events table summarizing the study procedures and assessments is provided in Appendix I.

12.1 Screening Procedures

Interested candidates between the ages of 18 and 45, inclusive, who report current use of cocaine, are not seeking treatment, and are available to participate in an inpatient study for 25 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 candidates will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the site's Institutional Review Board *(*IRB). After providing informed consent, the subject will participate in screening assessments.

Eight study subjects (2 receiving placebo arm and 6 receiving GBR 12909 arm) will be enrolled onto the study in one cohort at a time. Two study subject alternates for each cohort will be identified at the time the informed consent is obtained. These two alternates will complete the screening assessments and enter into the study if a study subject is dismissed for non-medical reasons.

The list of assessments to be conducted during screening are shown in Table 1. The screening process will be done in stages. The first stage includes a complete physical examination, including vital signs (BP, HR, respiration rate, and temperature), and a 12-lead ECG. Blood will be collected for hematologic, chemistries, alcohol, pregnancy, and infectious disease serology assessments. Urine will be collected for routine urinalysis. A urine drug toxicology screen will

also be conducted for drugs of abuse. The urine drug toxicology screen must be negative with the exception of cocaine, cocaine metabolites, and marijuana to enroll in the study. Candidates deemed eligible based on the screening assessments mentioned above will enter the second stage of screening that will include administering 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.

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. Female subjects will also be instructed to not use oral contraceptives within 30 days prior to study participation. 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.

Table 1. Screening Assessments

Screening Procedures to be Conducted from Study Days - 30 to -1	
Informed Consent	Routine Urinalysis
Physical Exam	Plasma Alcohol
Medical History	Infectious Disease Serology
Vital Signs (HR, BP, RR, temperature)	Urine Drug Toxicology Screen
12-Lead ECG	Serum ß-HCG (pregnancy test)
Hematologies	Prior Medications
Chemistries	SCID

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. Double barrier contraception techniques or abstinence (starting at least 14 days prior to study) must be used until at least 14 days following the last dose of study drug. Appropriate methods include abstinence and the following double-barrier methods: diaphragm and condom (by the partner), intrauterine device and condom, or sponge and condom. 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.

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 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 inpatient phase of 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.

12.2 Admission and Washout

The day of admission to the CPU is designated as day –1. Day –1 of the inpatient period is used to complete screening assessments. Table 2 shows the inpatient procedures that will be performed on admission (day –1) and day 0. For all subjects, a urine test for drugs of abuse will be done on admission prior to any of the day 0 procedures. The results must be negative, except for marijuana and cocaine, before continuing with study procedures. The subjects will remain in the CPU for a washout period, if necessary, to obtain a negative urine cocaine toxicology result to become eligible for enrollment. For female subjects, a serum ß-HCG (pregnancy test) will be done within 72 hours prior to beginning of the dosing (study day 1). The result of this pregnancy test must be negative prior to receiving the study drug during the inpatient period.

Day 0. A digital and 12-lead ECG profile will be performed over a 12 hour period at the following time points commencing at the scheduled time for subsequent GBR dosing (approximately 8:00 AM): 0, 0.5, 1, 2, 3, 4, 6, 8, and 12 hours after the anticipated GBR dosing time.

Table 2. Admission and Day 0 Procedures

Assessment	**Time point**
Urine drug toxicology screen	Day –1 (Admission)
Breathalyzer	Day –1
Serum ß-HCG (pregnancy test)	Admission (but within 72 hours of dosing)
Abbreviated physical examination	Day –1
Baseline blood sample as a PK control	Day 0
Digital/12-lead ECG 12 hr profile	Day 0
Psychometric assessments: ARCI, BSCS, SAFTEE, CSFQ, MOASCL	Day 0

12.3 Randomization and Enrollment

A prospective subject who meets all of the study inclusion criteria and does not meet any of the exclusion criteria may be randomized and enrolled onto the study. Subjects will be randomized within cohorts to receive either placebo (2 subjects) or GBR 12909 (6 subjects). The data-coordinating center will supply the Research Pharmacist with pre-coded envelopes with treatment assignments. On study day 0, the investigator or study coordinator will obtain the treatment assignment from the Research Pharmacist. The Research Pharmacist will dispense the coded bottle of investigational agents for the subject to the investigator.

12.4 Inpatient Treatment (Days 1 – 11)

Patients will receive investigational agents on study days 1 through 11. Study day 1 is defined as the first day of GBR 12909 (or matched placebo) dosing. On study day 11, a more extensive set of PK samples will be collected. Daily PK samples will be continued for the next 7 study days

(days 12 through 18). Subjects will be confined for the duration of the inpatient period. All dosages of GBR 12909 or placebo will be observed. Subjects will fast from midnight to 2 hours after each investigational agent dosing. Table 3 shows the procedures conducted during the treatment period (days 1 through 11).

Table 3. Procedures Conducted During Inpatient Treatment (Days 1 to 11)

Procedure	**Study Days**	**Time During Day**
GBR 12909 or placebo dosing	1 to 11	Approximately 8:00 AM
Vital signs	1 to 11	0, 1, 2, 3, 4, 6, 8, and 12 hours post dosing
Psychometric determinations: ARCI BSCS SAFTEE, CSFQ, MOASCL	1 to 11 2, 4, 6, 8, 11 1 to 11	 Within 4-8 hours post dosing Once daily Once a week
12-lead ECG	1 to 10	0
Digital/12-lead ECG 12 hr profile	11	0, 0.5, 1, 2, 3, 4, 6, 8, and 12 hours after dosing
Blood sample for trough GBR 12909 measurement	3, 8, 9, 10	0
Blood sample for GBR 12909 PK	11	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 hours after dosing
Urine collection for GBR 12909 PK	1, 11	Pre-dose collection
	11	8 hour pools for the first 24 hours after dosing
Chemistries	5, 9	Once daily
Adverse Events	1 to 11	Once daily
Concomitant Medications	1 to 11	Once daily

Adverse events and any concomitant medication use will be assessed daily. If the physician or his/her designee determines that a subject should stop the study because of adverse effects during treatment, a final pharmacokinetic profile will be done at this time. No further drug will be given and the subject will undergo final study evaluation procedures as listed above.

The exact time of drug administration will be recorded on a CRF. Timing of blood collection for PK assays will take precedence over the timing for other procedures. Precise times of blood collections will be noted on the CRFs. Meals and snacks will be provided by hospital services as ordered by CPU staff.

12.5 Inpatient Follow-Up (Days 12 through 18)

Table 4 shows the procedures that will be performed on inpatient days 12 through 18.

Table 4. Procedures Conducted During Inpatient Follow-up (Days 12 to 18)

Procedure	Study Days	Time During Day
Vital signs	12 to 18	At PK time-points
Psychometric determinations: ARCI BSCS SAFTEE, CSFQ, MOASCL	12 to 18 13, 15, 18 12 to 18	 Once daily Once a week
Digital and 12-lead ECG	12 to 18	At PK time-points
Abbreviated Physical Exam	18	Once
Blood sample for GBR 12909 PK	12 to 18	24, 48, 72, 96, 120, 144, and 168 hours after day 11 dosing
Chemistries	18	Once
Hematologies	18	Once
Routine Urinalysis	18	Once
Serum ß-HCG (pregnancy test)	18	Once
Adverse Events	12 to 18	Once daily
Concomitant Medications	12 to 18	Once daily

12.6 Clinic Discharge (Day 19)

Subjects will be discharged from the CPU on inpatient Day 19 after laboratory, physical examinations and ECG are completed and satisfactory as per the principal investigator or his/her designee.

12.7 Outpatient Follow-Ups (Days 26, 33, 40, 47)

On days 26, 33, 40, 47 each subject will report to the CPU between 8:00 AM and noon for follow-up evaluations as shown in Table 5.

Table 5. Outpatient Follow-up Procedures

Procedure	Study Day
Digital and 12-lead ECG	26, 33, 40, 47
Vital Signs	26, 33, 40, 47
Psychometric Tests (ARCI, BSCS, SAFTEE, CSFQ, MOASCL)	26, 33, 40, 47
Adverse Events	26, 33, 40, 47
Concomitant Medications	26, 33, 40, 47
Full physical examination	47
Hematology	47
Chemistries	47
Routine Urinalysis	47

12.8 Safety Management

The decision to dismiss a subject and to replace dropouts for non-medical reasons will be made collaboratively by the research team. A subject stopped on the study for drug related reasons (i.e., toxicity) will not be replaced by an alternate subject. Two volunteers per cohort will be designated as study alternates. Study alternates will proceed through all screening procedures and be paid accordingly.

Subjects will be confined to the CPU during the eleven days of dosage and 7 days after last dose as the inpatient treatment period. Subjects will be monitored for adverse events and signs and symptoms of CNS abnormalities. Blood pressure will be measured in the supine position by either an automatic BP monitor or manually during each inpatient treatment day at predose, 1, 2, 3, 4, 6, 8, and 12 hours post dose. Heart rate, temperature and respiratory rate will be monitored at the same time intervals.

Electrocardiographic effects will be determined through daily predose 12-lead throughout the study and digital ECGs on days 0, 11, 12-18, 26, 33, 40, and 47. For predose ECGs, any trough QTc measurement from the morning predose ECG >25% of subject's respective baseline will be confirmed by the investigator and the subject will be placed on telemetry until QTc is within 25% of subject's baseline and be cause for discontinuation of the subject in the study.

An extensive review by the investigators of the ECG parameters, not limited to prolongation of the QT interval, must be conducted at the completion of each dose level of GBR 12909.

Psychometric determinations will be measured according to the schedule in Tables 2, 3, and 4 by trained nursing staff during each inpatient treatment period.

Subjects will have blood chemistries performed on days 5 and 9 of the inpatient treatment period.

12.9 Subject Compensation

Subject payment will be determined by IRB requirements.

13 CLINICAL ASSESSMENT METHODS

13.1 SCID

A SCID will be administered during screening and serves to determine whether the subject meets the DSM-IV criteria for cocaine abuse/dependence and to rule out any major psychiatric disorders.

13.2 Medical History

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

13.3 Physical Exam

A full 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 at screening and on study day 47. Height and weight will also be recorded. An abbreviated physical exam will be conducted after admission and on study day 18. The abbreviated exam will consist of an evaluation of the cardiovascular system, lungs, neuropsychiatric mental status and sensory/motor status, and skin.

13.4 Vital Signs

Vital signs to be assessed include oral temperature, supine BP, HR, and respiratory rate.

13.5 Urine Toxicology

Urine toxicology screening for cocaine, amphetamines, barbiturates, benzodiazepines, methadone, opiates, PCP, or propoxyphene will be conducted using a qualitative urine test that detects all these compounds at screening to determine subject eligibility and on admission to the CPU.

13.6 Blood and Urine Collection for Pharmacokinetic Analysis

A schedule of blood collections and volumes for pharmacokinetic analysis is provided in Appendix II. This table also includes the volumes and time-points for collection of other blood samples.

An intravenous catheter will be inserted on days when multiple PK samples are collected and can be maintained in place, if the subject wishes. Samples will be collected for PK assessments in 10 mL heparin-containing green-stoppered Vacutainers™.

Blood samples for GBR 12909 pharmacokinetics will be collected on days 0, 3, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, and 18. On days 0, 3, 8, 9, and 10, only one sample at pre-dosing of GBR 12909 will be collected. On day 11, eleven total samples will be collected, one (1) at pre-dosing and ten (10) more at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, and 12.0 hours post dosing. On days 12, 13, 14, 15, 16, 17, and 18, which is 24, 48, 72, 96, 120, 144, and 168 hours after the last (day 11) dose of GBR 12909, respectively, one blood sample per day will be collected. Each sample (7 mL) will be centrifuged within 20 minutes of the blood collection in a non-refrigerated centrifuge for 10 minutes to separate the plasma. The plasma will be transferred to polypropylene tubes and properly labeled as described below. The samples will be stored at -20 °C immediately and transferred to the -80 °C storage unit at the Division of Clinical Pharmacology within 48 hours until analyzed. The plasma samples will be shipped to the UCSF for analyses of GBR12909 blood concentration.

Total blood loss during the study (271 mL) is approximately 0.55 times the volume of a standard blood bank donation.

Urine will be collected at pre-GBR 12909 dosing on days 1 and 11. After the day 11 dosing, urine will be collected continuously over the first 24 hours in fractions for the periods of 0-8, 8-16 and 16-24 hours post dosing, and all the voids during the collection period will be pooled. The volume of urine will be recorded and aliquots will be removed and frozen at -20°C. Urine samples will be shipped to the UCSF for identification of GBR 12909 metabolites.

Labeling of Specimens

Blood, plasma and urine specimens will be labeled with computer-generated labels which have been preprinted. Labels can be used on polypropylene and will survive freezing and thawing. Labels will contain the following information (all to be filled in by the investigator or his designated staff in waterproof ink):

1. Subject number
2. GBR 12909
3. Dosage cohort: 50, 75, or 100 mg (and as appropriate for placebo)
4. Study number
5. Sample time
6. Date

13.7 Hematology

Blood will be collected in anticoagulant containing vacutainer tubes for hematologic assessments. Analysis of hemoglobin, hematocrit, 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.

13.8 Chemistries

Fasting 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, glucose, urea, uric acid, calcium, sodium, potassium, chloride, bicarbonate, total bilirubin, protein, globulin, and albumin, phosphate, 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.

13.9 Infectious Disease Panel

Blood will be collected in a serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) and serum separated according to standard procedures. Qualitative analysis reporting positive/negative results will be performed for the following analytes: hepatitis B surface antigen, hepatitis C virus antibody and HIV types 1 and 2.

13.10 Routine Urinalysis

Routine urinalysis will consist of tests for pH, protein, glucose, specific gravity, color and apprearance, ketones, bilirubin, blood, and microscopic analysis (white blood cells, red blood cells, epithelial cells, and casts).

13.11 Psychometric Assessments

13.11.1 Addiction Research Center Inventory (ARCI)

The ARCI is a questionnaire that measures the abuse liability. It consists of 49 statements in a true/false format. Subjects will start the measure at baseline and continue to complete this questionnaire three times a week during inpatient phase of the study and during all four follow-up outpatient visits.

13.11.2 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. Subjects will start the measure at baseline and continue with this assessment every day during inpatient phase of the study and during all four follow-up outpatient visits.

13.11.3 Systematic Assessment for Treatment Emergent Effects (SAFTEE)

The SAFTEE is a technique for the systematic assessment of side effects in clinical trials developed by National Institute of Mental Health (NIMH). It is a questionnaire that rates the current severity of a wide range of somatic, behavioral and affective symptoms in general or specific inquiry formats. Subjects will start the measure at baseline and continue to complete this questionnaire once a week during inpatient phase of the study and during all four follow-up outpatient visits.

13.11.4 Change in Sexual Function Questionnaire (CSFQ)

The CSFQ is a 36-item questionnaire designed to measure sexual functioning. It is a self-administered assessment that asks the subject to rate changes in his or her sexual function. The CSFQ total score ratings serve as indicators of comorbidity- or medication-related sexual dysfunction. Subjects will start the measure at baseline and continue to complete this questionnaire once a week during inpatient phase of the study and during all four follow-up outpatient visits.

13.11.5 McClean Hospital Event Overt Aggression Checklist (MOASCL)

The MOASCL is a self administered 20-item questionnaire that assesses 5 areas of aggression each represented by 4 items (Teicher *et al.,* 1989; Salzman *et al.,* 1995). Subjects will start the measure at baseline and continue with this assessment of aggressive responding once a week during inpatient phase of the study and during all four follow-up outpatient visits.

13.12 Adverse Events

AEs will be assessed daily by an investigative staff nurse or physician starting as soon as the subject signed the informed consent form. 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.

14 ANALYTICAL PLAN

14.1 Pharmacokinetic Analysis

On day 11, eleven total blood samples will be collected for pharmacokinetic analysis, one at pre-dosing and 10 more samples at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, and 12.0 hours post dosing. The following pharmacokinetic parameters will be obtained by non-compartmental methods using WinNonlin:

$AUC_{(0-24)}$	Area under the plasma concentration-time curve from 0 to 24 hours at steady state.
C_{max}	Maximum observed concentration
C_{min}	At steady state (trough level at 24 hours after dosing)
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	Oral Clearance (if data permit)
Vd/F	Volume of distribution (if data permit)

$AUC_{(0-24)}$, C_{max}, and C_{min} will be the primary criteria for assessment of the pharmacokinetics. Linearity in the pharmacokinetics of GBR 12909 will be assessed from dose normalized $AUC_{(0-24)}$, C_{max}, and C_{min} values. Descriptive statistical evaluation will also be performed. If data permit, a relationship between plasma GBR 12909 concentrations and changes in ECG will be sought. Standard pharmacokinetic-pharmacodynamic (PK/PD) models will be used for this purpose.

14.2 Statistical Methods

Linear regression of $AUC_{(0-24)}$, C_{max}, and C_{min} values versus dose administered will be performed from the pooled data at various dose levels to determine if there is dose dependency in the pharmacokinetics of GBR 12909. Dose dependency will also be evaluated by performing analysis of variance (ANOVA) of body weight normalized clearance values at the various doses. Dose-normalized pharmacokinetic parameters, $AUC_{(0-24)}$, C_{max}, and C_{min}, will be analyzed for for dose-dependency using ANOVA.

The 90% confidence intervals will be calculated for all the pharmacokinetic parameters. At all the dose levels, inter-individual variability in pharmacokinetic parameters will be calculated as percent coefficient of variation (standard deviation * 100 / mean). If the pharmacokinetics of GBR 12909 are linear, the intra-individual variability in clearance, volume of distribution and dose normalized AUC_{0-24}, C_{max}, and C_{min} values will be obtained by standard procedures.

14.3 Sample Size Estimation

No formal sample size estimation was done. The number of subjects selected was based on empirical considerations and the most recently completed NIDA study with GBR 12909 and was considered appropriate based on the current stage of development of the test medication and the knowledge of usual pharmacokinetic and pharmacodynamic variability of extensively

metabolized drugs. The evaluable subject population is defined as the subjects who are randomized, meet all of the inclusion/exclusion criteria, and have completed inpatient study procedures up to midnight of study day 15. Subjects who are discharged from the study for non-medical reasons will be replaced. Subjects who are discharged for medical reasons (e.g.., adverse effects) will not be replaced.

15 REGULATORY AND REPORTING REQUIREMENTS

15.1 FDA Form 1572

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

15.2 IRB Approval

Prior to initiating the study, the investigator will obtain written Institutional Review Board (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.

15.3 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.

15.4 Drug Accountability

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

15.5 Outside Monitoring

Data and Safety Monitoring: Safety data will be reviewed by the NIDA medical monitor, site investigators and if applicable, a physician representative of the governing Institutional Review Board (IRB). Prior to initiating dosing of the next cohort, the safety data (i.e., up to the end of day 18) of the completed cohort including the ECG parameters (not limited to prolongation of the QT interval) will be reviewed by this group for a determination to proceed to dosing of the next cohort.

Medical Monitor: A medical monitor has been 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 good clinical practices guidelines are appropriately filed.

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training 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 NIDA and the FDA.

15.6 Adverse Events Reporting

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the principal investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and Appendix III. The occurrence of AEs will be assessed daily starting after obtaining informed consent.

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 must be recorded on the AE CRF. The AE CRF is also used to record follow-up information for unresolved events reported on previous visits.

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 4 weeks following completion of, or termination from treatment.

15.7 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 or product package insert.

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 Principal Investigator. Upon notification, the Principal Investigator will notify the Study Medical Monitor and the NIDA Project Officers within 24 hours. The telephone to NIDA report is to be followed by submission of a completed SAE Form with demographic information and a narrative explanation of the event. Included with the SAE CRF should be the AE CRF, the Concomitant Medication CRF, and the Medical History CRF 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 Principal Investigator 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 NIDA in order that NIDA, 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.

16 DATA MANAGEMENT AND CASE REPORT FORMS

16.1 Data Collection

Data will be collected at the study sites on source documents which will be entered at the site into electronic case report forms (eCRFs). The eCRFs and source documents will be supplied by the NIDA data coordinating center. 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.

16.2 Data Editing and Control

Data received at the NIDA 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

All corrections and changes to the data will be reviewed prior to being entered into the main study database. NIDA/DTR&D and the participating site will receive reports at least monthly regarding the quality and quantity of data submitted to data coordinating center.

Participating investigators agree to routine data audits by the sponsor's designated staff, audits by the staff of the NIDA data coordinating center and by NIDA's programmatic 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.

16.3 Data Entry, Processing, and Analyses

Data will be collected at the study sites on source documents which will be entered into eCRFs. 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, analysis of the data will be performed by the data coordinating center in accordance with the analytical plan section of this protocol. Periodically, during the investigation, data sets will be submitted to the NIDA DTR&D central data repository according to procedures specified in the study operations manual.

16.4 Study Documentation and Records Retention

Study documentation includes all CRFs, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, 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 all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, 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 the NDA.

16.5 Confidentiality

16.5.6 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.

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

16.5.7 Confidentiality of Patient Records

To maintain subject confidentiality, all laboratory specimens, eCRFs, reports and other records will be identified by a coded study subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff and NIDA program officials will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by the FDA, NIDA monitoring contractor or NIDA. Upon approval of the study by an IRB, an application will be filed with NIDA for a certificate of confidentiality.

By signing the protocol the investigator agrees that within local regulatory restrictions and ethical considerations NIDA or any regulatory agency may consult and/or copy study documents in order to verify case report form data.

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.

Authorization for protection of identity is now available to investigators engaged in research on the use and effect of psychoactive drugs under section 301 (d) of the Public Health Service Act, as amended by Public Law 93-282 (42 U.S.C. 241) (d) 0. "Such authorization affords the person to whom it is given a privilege to protect the privacy of research subjects by withholding the names or other identifying characteristics of such research subjects from all persons not connected with the conduct of the research. Persons so authorized may not be compelled in any federal, state, or local civil, criminal, administrative, legislative, or other procedures to identify such individuals," (Federal Register/Vol. 44, No. 66/Wednesday April 4, 1979/Rules and Regulations/Part VII.) The usual exemptions for audit and evaluation are allowed, but such auditors and evaluators would be bound to the same protections of subjects. The principal investigator has obtained a certificate of confidentiality. The provision of this authorization will be explained to all potential participants. Additional protection will be offered to our subjects in that identifying information will not be part of the data set and will not be available except on a need-to-know basis.

17 PUBLICATIONS OF THE STUDY RESULTS

Publications derived from this study will include input from the principal investigator, his or her colleagues, and NIDA personnel. Such input should be reflected in publication authorship, and agreement regarding order of authors should be established before writing a manuscript.

18 SIGNATURES

NIDA REPRESENTATIVE

Typed name(s)	Signature	Date
Roberta Kahn, MD NIDA Project Officer	_____	_____
Aida Kuhn, MBA NIDA Project Officer	_____	_____
Jurij Mojsiak, M.S. NIDA Investigator	_____	_____
Ahmed Elkashef, M.D. NIDA Investigator	_____	_____
Nora Chiang, Ph.D. NIDA Investigator	_____	_____

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 15.6 of this protocol.

Typed Name(s)	Signature	Date
Louis R. Cantilena, Jr, M.D., Ph.D. Principal Investigator	_____	_____
Mark Haigney, M.D Sub-investigator	_____	_____

19 REFERENCES

Andersen PH. The dopamine uptake inhibitor GBR 12909: selectivity and molecular mechanism of action. *Eur J Pharmacol* 1989; 166:493-504.

Baumann MH, Char GU, deCosta BR, Rice KC, Rothman RB. GBR 12909 attenuates cocaine-induced activation of mesolimbic dopamine neurons in the rat. *J Pharmacol Exp Ther* 1994; 271: 1216-1222.

Cherstniakova S, Bi D, Fuller DR, Mojsiak J, Collins JM, Cantilena L. Metabolism of vanoxerine, 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl] piperazine by human cytochrome P450 enzymes. *Drug Metab Dispos* 2001; 29:1216-1220.

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

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.

Glowa JR, Wojnicki FHE, Matecka D, Bacher JJ, Mansbach RS, Balster RL, Rice KC. Effects of dopamine reuptake inhibitors on food- and cocaine-maintained responding. I. Dependence on dose of cocaine. *Exp Clin Psychopharmacol* 1995a; 3:219-231.

Glowa JR, Wojnicki FHE, Matecka D, Rice KC, Rothman RB. Effects of dopamine reuptake inhibitors on food- and cocaine-maintained responding. II. Comparison with other drugs and repeated administrations. *Exp Clin Psychopharmacol* 1995b; 3:232-239.

Glowa JR, Fantegrossi WE, Lewis DB, Matecka D, Rice KC, Rothman RB. Sustained decrease in cocaine-maintained responding in rhesus monkeys with 1-[2-]bis(4-fluorophenyl)methoxy [ethyl]-4-hydroxy-3-phenylpropyl] piperazinyl decanoate, a long-acting ester derivative of GBR 12909. *J Med Chem* 1996; 39:4689-4691.

Heikkila RE. Differential effects of several dopamine uptake inhibitors and releasing agents on locomotor activity in normal and in reserpinized mice. *Life Sci* 1981; 28:1867-1874.

Heikkila RE, Manzino L. Behavioral properties of GBR 12909, GBR 13069 and GBR 13098: specific inhibitors of dopamine uptake. *Eur J Pharmacol* 1984;103:241-248.

Howell LL, Wilcox KM. The dopamine transporter and cocaine medication development: drug self-administration in non-human primates. *J Pharmacol Exp Ther* 2001; 298:1-6.

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

Ingwersen SH. Pharmacokinetics and Hormonal Effects of GBR 12909 in Human Volunteers. Internal report from NOVO 1987a. File No. Ph-870649.

Ingwersen SH. Single and Repetitive Dose Study of GBR 12909 in Human Volunteers: Pharmacokinetics and Hormonal Effects. Internal report from NOVO 1987b. File No. Ph 871866.

Ingwersen SH. Relative Bioavailability in Human Volunteers of Tablet Dosage Forms of GBR 12909. Internal report from NOVO 1987c. File No. Ph-872800.

Ingwersen SH, Snel S, Mant TG, Edwards D. Nonlinear multiple dose pharmacokinetics of the dopamine reuptake inhibitor vanoxerine. *J Pharm Sci* 1993a; 82:1164-1166.

Ingwersen SH, Mant TG, Larsen JJ. Food intake increases the relative oral bioavailability of vanoxerine. *Br J Clin Pharmacol* 1993b; 35:308-310.

Jansen JA. Bioavailability of GBR 12909. Internal report from NOVO 1986. File No. Ph-861850.

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.

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.

NIDA Communication. A multiple dose, open label, fixed order, dose escalating study with four dosages of GBR 12909 in normal volunteers. (Internal report, 2001).

Rothman RB, Mele A, Reid AA, Akunne HC, Greig N, Thurkauf A, De Costa BR, Rice KC, Pert A. GBR 12909 antagonizes the ability of cocaine to elevate extracellular levels of dopamine. *Pharmacol Biochem Behav* 1991; 40:387-397.

Rothman RB, Greig N, Kim A, Costa BRD, Rice KC, Carroll FI, Pert A. Cocaine and GBR 12909 produce equivalent motoric responses at different occupancy of the dopamine transporter. *Pharmacol Biochem Behav* 1992; 43:1135-1142.

Rothman RB and Glowa JR. A review of the effects of dopaminergic agents on human, animals, and drug-seeking behavior, and its implications for medication development. Focus on GBR 12909. *Mol Neurobiol* 1995; 11:1-19.

Salzman C, Wolfson AN, Schatzberg A, *et al.* Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. *J Clin Psychopharmac* 1995; 15:23-29.

Sogaard U, Micchalow J, Butler B, Lund Laursen A, Ingwersen SH, Skrumsager BK, Rafaelsen OJ. Tolerance study in healthy volunteers of GBR 12909, a selective dopamine uptake inhibitor. (Internal report).

Sogaard U, Micchalow J, Butler B, Lund Laursen A, Ingwersen SH, Skrumsager BK, Rafaelsen OJ. A tolerance study of single and multiple dosing of the selective dopamine uptake inhibitor GBR 12909 in healthy subjects. *Int Clin Psychopharmacol* 1990; 5:237-251.

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.

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

Teicher MH, Glod CA, Aaronson ST *et al.* Open assessment of the safety and efficacy of thioridazine in the treatment of patients with borderline personality disorder. *Psychopharmacol Bull* 1989; 25:535-549.

Tsukada H, Harada N, Nishiyama S, Ohba H, Kakiuchi T. Dose-response and duration effects of acute administration of cocaine and GBR 12909 on dopamine synthesis and transporter in the conscious monkey brain: PET studies combined with microdialysis. *Brain Res* 2000; 860:141-148.

van der Zee P et al. Aryl 1,4-dialk(en)ylpeperazines as selective and very potent inhibitors of dopamine uptake. *Eur J Med Chem* 1980; 15: 363-370.

van der Zee P and Hespe W. Interaction between substituted 1-(2-(diphenylmethoxyethyl) piperazines and dopamine receptors. *Neuropharmacol* 1985; 24:1171-1174.

Villemagne VL, Rothman RB, Yokoi F, Rice KC, Matecka D, Dannals RF, Wong DF. Doses of GBR 12909 that suppress cocaine self-administration in non-human primates substantially occupy dopamine transporters as measured by [^{11}C]WIN35,428 PET scans. *Synapse* 1999a; 32: 44-50.

Villemagne VL, Wong DF, Yokoi F, Stephane M, Rice KC, Matecka D, Clough DJ, Dannals RF, Rothman RB. GBR 12909 attenuates amphetamine-induced striatal dopamine release as measured by [(11)C]raclopride continuous infusion PET scans. *Synapse* 1999b; 33: 268-273.

Wong DF, Cantilena L., Elkashef A, Yokoi F, Dogan S, Stephane M, Gjedde A, Rothman RB, Mojsiak J, Vocci F. *In vivo* human dopamine transporter occupancy of a potential cocaine treatment agent, GBR 12909. *Soc Neurosci Meet Abstr* 1999, 25, p.522.7.

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; 3:465-471.

APPENDIX I: TIME AND EVENTS SCHEDULE

Activity	**Screening**	**Admission**		**Treatment**										
Study Day	-30 to -2	-1	0[a]	1	2	3	4	5	6	7	8	9	10	11
Informed Consent	X													
12-lead ECG	X			X	X	X	X	X	X	X	X	X	X	
Digital/12-lead ECG 12 hr profile			9X											9X
Digital ECG														
Full Physical Exam	X													
Abbreviated Physical Exam		X												
Medical History	X													
Prior Medications	X													
Chemistries	X							X				X		
Hematologies	X													
Routine Urinalysis	X													
Infectious Disease Serology	X													
Vital Signs	X			8X	8X	8X	8X	8X	8X	8X	8X	8X	8X	8X
SCID	X													
Urine Drug Tox Screen	X	X												
Breathalyzer		X												
Plasma Alcohol	X													
Pregnancy Test	X	X												
Randomization			X											
GBR 12909 Administration				X	X	X	X	X	X	X	X	X	X	X
PK blood sampling			X			X					X	X	X	11X
Urine PK predose				X										X
Urine PK sampling (8 hr pools)														3X
ARCI			X[b]		X		X		X		X			X
BSCS			X	X	X	X	X	X	X	X	X	X	X	X
SAFTEE, CSFQ, MOASCL			X[c]				X							X
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications			X	X	X	X	X	X	X	X	X	X	X	X

[a]The inpatient period before treatment may be extended for 5 days to allow for a washout period for other drugs.
[b]The assessment will be performed three times a week during the inpatient period of the study.
[c]The assessments will be performed once a week during the inpatient period of the study.

TIME AND EVENTS SCHEDULE CONTINUED

Activity	**Follow-up**											
Study Day	12	13	14	15	16	17	18	19 **Discharge**	26	33	40	47
12 lead ECG	X	X	X	X	X	X	X		X	X	X	X
Digital ECG	X	X	X	X	X	X	X		X	X	X	X
Full Physical Exam												X
Abbreviated Physical Exam							X					
Chemistries							X					X
Hematologies							X					X
Routine Urinalysis							X					X
Pregnancy Test							X					
Vital Signs	X	X	X	X	X	X	X		X	X	X	X
PK blood sampling	X	X	X	X	X	X	X					
ARCI		X		X			X		X	X	X	X
BSCS	X	X	X	X	X	X	X		X	X	X	X
SAFTEE, CSFQ, MOASCL							X		X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X

APPENDIX II: SCHEDULE OF BLOOD COLLECTIONS

Analysis	**Volume Per Sample**	**Type[a]**	**Number of Samples per Day**												**Total Volume**
Study Day			Scree-ning	Day -1	Day 0	Day 3	Day 5	Day 8	Day 9	Day 10	Day 11	Days 12-17	Day 18	Day 47	
Chemistries	10 mL	S	1				1		1				1	1	50 mL
Hematologies	10 mL	P	1										1	1	30 mL
Infectious Diseases	10 mL	S	1												10 mL
PK Samples	7 mL	P			1	1		1	1	1	11	1 each day	1		161 mL
Pregnancy Test	5 mL	S	1	1									1		15 mL
Alcohol Level	5 mL	P	1												5 mL
Total															**271 mL**

[a]S = serum, P = plasma

APPENDIX III: INSTRUCTIONS FOR EVALUATING AND REPORTING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A. GENERAL INSTRUCTIONS

1. AEs will be reported as soon as the subject signs the informed consent form.

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

3. 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 NIDA Medical Monitor, the NIDA Project Officer, and the Principal Investigator.

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 NIDA 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 follow-up written report in 8 days;

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

- in an annual report in all other cases.