

**DOUBLE-BLIND, PLACEBO-CONTROLLED, SAFETY AND PHARMACOLOGY STUDY WITH 75mg DOSAGE OF GBR 12909 IN COCAINE EXPERIENCED AFRICAN AMERICAN VOLUNTEERS**

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## TABLE OF CONTENTS

<b>1</b>	<b>LIST OF ABBREVIATIONS .....</b>	<b>5</b>
<b>2</b>	<b>SCHEMA .....</b>	<b>6</b>
<b>3</b>	<b>ABSTRACT.....</b>	<b>7</b>
<b>4</b>	<b>INTRODUCTION AND RATIONALE.....</b>	<b>8</b>
4.1	THERAPEUTIC STRATEGIES FOR TREATING COCAINE ABUSE.....	8
4.2	GBR 12909.....	9
4.2.1	Pharmacology.....	9
4.2.2	Pharmacokinetics.....	10
4.2.3	Metabolism.....	10
4.2.4	Previous Human Experience with GBR 12909.....	11
4.3	RATIONALE FOR THE CURRENT STUDY .....	12
4.4	SAFETY OF GBR 12909 .....	13
<b>5</b>	<b>STUDY DESIGN.....</b>	<b>14</b>
<b>6</b>	<b>STUDY OBJECTIVES.....</b>	<b>14</b>
<b>7</b>	<b>STUDY SITE.....</b>	<b>14</b>
<b>8</b>	<b>STUDY SPONSOR.....</b>	<b>15</b>
<b>9</b>	<b>SUBJECT SELECTION .....</b>	<b>15</b>
9.1	INCLUSION CRITERIA .....	15
9.2	EXCLUSION CRITERIA .....	16
<b>10</b>	<b>INVESTIGATIONAL AGENT.....</b>	<b>17</b>
10.1	GBR 12909.....	17
10.2	DISPENSING INVESTIGATIONAL AGENT.....	17
10.3	PACKAGING, LABELING, STORAGE, AND RETURN OF INVESTIGATIONAL AGENT .....	17
<b>11</b>	<b>TREATMENT PLAN.....</b>	<b>18</b>
11.1	GBR 12909.....	18
11.2	PRIOR AND CONCOMITANT MEDICATION(S) .....	18
11.3	DIETARY, ACTIVITY, AND OTHER RESTRICTIONS .....	18
<b>12</b>	<b>STUDY PROCEDURES .....</b>	<b>18</b>
12.1	SCREENING PROCEDURES .....	19
12.2	ADMISSION AND WASHOUT .....	20
12.3	ENROLLMENT.....	21
12.4	INPATIENT TREATMENT (DAYS 1 – 11) .....	21
12.5	CLINIC DISCHARGE (DAY 19) .....	23
12.6	OUTPATIENT FOLLOW-UPS (DAYS 26, 33, 40, 47) .....	23
12.7	DRUG RE-CHALLENGE (RE-EXPOSURE) PHASE.....	23

12.7.2	Post Re-challenge Inpatient Follow-Up (Days R12 through R18)	24
12.7.3	<i>Clinic Discharge Post-Re-challenge (Day R19)</i>	25
12.7.4	OUTPATIENT FOLLOW-UPS (DAYS R26, 33, 40, 47)	25
12.8	SAFETY MANAGEMENT	25
12.9	SUBJECT COMPENSATION	26
<b>13</b>	<b>CLINICAL ASSESSMENT METHODS</b>	<b>26</b>
13.1	SCID	26
13.2	MEDICAL HISTORY	26
13.3	PHYSICAL EXAM	27
13.4	VITAL SIGNS	27
13.5	URINE TOXICOLOGY	27
13.6	BLOOD AND URINE COLLECTION FOR PHARMACOKINETIC ANALYSIS	27
13.7	HEMATOLOGY	28
13.8	CHEMISTRIES	28
13.9	INFECTIOUS DISEASE PANEL	28
13.10	ROUTINE URINALYSIS	29
13.11	PSYCHOMETRIC ASSESSMENTS	29
13.11.1	<i>Addiction Research Center Inventory (ARCI)</i>	29
13.11.2	<i>Brief Substance Craving Scale (BSCS)</i>	29
13.11.3	<i>Systematic Assessment for Treatment Emergent Effects (SAFTEE)</i>	29
13.11.4	<i>Change in Sexual Function Questionnaire (CSFQ)</i>	29
13.11.5	<i>McClean Hospital Event Overt Aggression Checklist (MOASCL)</i>	29
13.12	ADVERSE EVENTS	30
<b>14</b>	<b>ANALYTICAL PLAN</b>	<b>30</b>
14.1	PHARMACOKINETIC ANALYSIS	30
14.2	STATISTICAL METHODS	30
14.3	SAMPLE SIZE ESTIMATION	31
<b>15</b>	<b>REGULATORY AND REPORTING REQUIREMENTS</b>	<b>31</b>
15.1	FDA FORM 1572	31
15.2	IRB APPROVAL	31
15.3	INFORMED CONSENT	32
15.4	DRUG ACCOUNTABILITY	32
15.5	OUTSIDE MONITORING	32
15.6	ADVERSE EVENTS REPORTING	33
15.7	SERIOUS ADVERSE EVENTS	33
<b>16</b>	<b>DATA MANAGEMENT AND CASE REPORT FORMS</b>	<b>35</b>
16.1	DATA COLLECTION	35
16.2	DATA EDITING AND CONTROL	35
16.3	DATA ENTRY, PROCESSING, AND ANALYSES	35
16.4	STUDY DOCUMENTATION AND RECORDS RETENTION	35
16.5	CONFIDENTIALITY	36
16.5.6	<i>Confidentiality of Data</i>	36
16.5.7	<i>Confidentiality of Patient Records</i>	36

**17 PUBLICATIONS OF THE STUDY RESULTS ..... 37**  
**SIGNATURES..... 37**  
**18 REFERENCES..... 39**

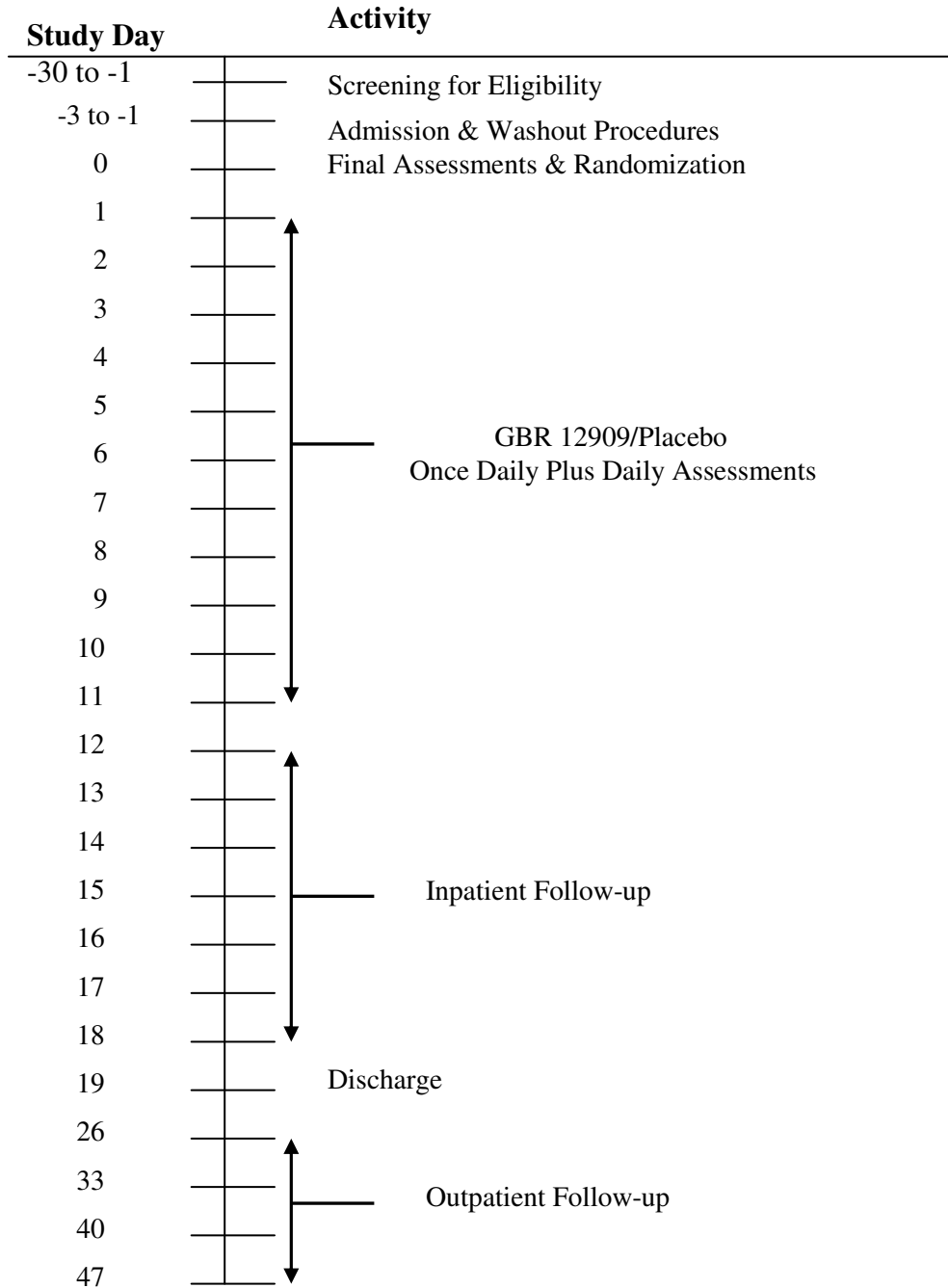
**APPENDICES**

**APPENDIX I: TIME AND EVENTS SCHEDULE**  
**APPENDIX II: RE-CHALLENGE PHASE TIME AND EVENTS SCHEDULE**  
**APPENDIX III: SCHEDULE OF BLOOD COLLECTIONS**  
**APPENDIX IV: RECHALLENGE PHASE SCHEDULE OF BLOOD COLLECTIONS**  
**APPENDIX V: INSTRUCTIONS FOR EVALUATING AND REPORTING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS**

## 1 LIST OF ABBREVIATIONS

<b>Abbreviation</b>	<b>Definition</b>
ADME	adsorption, distribution, metabolism, and excretion
AE	adverse event
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ANC	absolute neutrophil count
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	McClellan 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
WBC	total white blood cell count

## 2 SCHEMA



### 3 ABSTRACT

**STUDY OBJECTIVES:** This is a human laboratory study that will assess the clinical pharmacology, safety and tolerance of 75mg oral doses of GBR 12909, which is 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl) piperazine dihydrochloride, in cocaine experienced volunteers. Particular interest is being given to the hematological safety data.

**STUDY DESIGN:** This is a single dose inpatient study in which 10 cocaine experienced, African American volunteers, who meet the protocol eligibility criteria during a 30-day (maximum) screening period, will receive a single daily dosage of 75mg of study agent or placebo for 11 days. Subjects will be followed for seven days as in-patients after last dose of study drug and weekly as outpatients for 4 weeks. Hematology assessments for WBC and ANC will be performed four times during study drug dosing, three times during in-patient follow-up and weekly during outpatient follow-up.

Subjects who demonstrate a significant decrease in WBC or ANC during the initial in-patient phase will not be discharged but followed as in-patients until blood counts return within the normal range. They will then be re-challenged with the same treatment as the one they received during the initial phase, i.e., study drug or placebo. The in-patient treatment period and the in-patient and out-patient follow-up periods in the re-challenge phase would be identical to those of the initial study phase.

**STUDY DURATION:** The total duration of the study for subjects who will not meet the re-challenge criteria is 25 to 28 inpatient days which includes a washout period if the subject is cocaine positive on admission (day -3), 3 days for baseline hematology workups (days -2, -1, and 0), 11 days of treatment (days 1 through 11) with pharmacokinetic (PK) sampling and 7 days of inpatient follow-up PK sampling and safety assessments (hematology and chemistry laboratory tests) 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 57 to 62 study days per subject.

For subjects who will meet the re-challenge criteria, hematology assessments will continue until WBC and/or ANC values return to within the normal range and are stable for one week. They will then initiate the re-challenge phase, consisting of 11 days of treatment and 7 days of inpatient follow-up and safety assessments (hematology and chemistry labs) 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 78 to 93 study days per subject.

**SAMPLE SIZE:** 10 subjects total. 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 African American, male and female healthy volunteers, 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:** Half the subjects will receive 75mg of GBR 12909 by oral administration daily for 11 days and the other half will receive placebo treatment. Subjects meeting criteria for

entering the re-challenge drug treatment phase will receive the same treatment, either study drug or placebo, that they received in the initial study phase.

**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 and urinalyses data and psychometric evaluations. Complete blood counts will be determined on screening; daily for three days after admission once urine screening for drugs of abuse except cannabis tests negative but before onset of study drug administration; on days 3, 5, 8 and 11 during study drug administration; on days 12, 15 and 18 during study drug wash-out; and weekly for 4 weeks during the out-patient follow-up phase. GBR 12909 plasma concentrations will be determined at the following time points for pharmacokinetic (PK) analysis at pre-dose (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. Safety assessments during the re-challenge period will be identical to those above. PK analysis of plasma during the re-challenge phase will occur on Day R11 only at the time points 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours post dose. Urine will not be collected in the re-challenge phase for PK analysis.

## **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 crossover 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 crossover 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.

A current study that is a NIDA-sponsored phase 1, dose-escalating study in cocaine experienced volunteers, 18-45 years of age is ongoing at the USUHS/NIDA CPU. To date six (6) subjects have been treated with 50 mg of GBR12909 in cohort #1 and six (6) subjects with 75 mg in cohort #2 for 11 days per dose. Two (2) subjects in each cohort received placebo treatment. Analysis of data obtained to date has demonstrated no cardiovascular side effects, and a reduction in WBC and/or ANC in several African American subjects between days 1-18, which was not statistically significant from baseline in cohort #1 ( $p=0.5$ ), but was statistically significant from baseline in cohort #2 ( $p=0.04$  for WBC and  $p=0.002$  for ANC). There was no difference in screening WBC and ANC between subjects who were cocaine-positive or cocaine-negative. A hematologist consultant reviewed data on both cohorts and was also unblinded to the treatment given to subjects in cohort #2. It was found that in one subject in cohort #2 WBC and ANC counts followed a pattern not explained by a drug effect and that two (2) of the subjects with the lowest WBC and ANC had received placebo treatments. It was recommended by the DSMB and the outside hematology consultant to perform more frequent blood counts for the next cohort, preferably in two different laboratories.

#### **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.

Presently, a phase 1 clinical investigation study encompassing the expected "therapeutic" dose of 50 & 75mg dosages of GBR 12909 per day for 11 days has been completed. As part of this study it was noted that there was a reduction in the WBC or ANC count in several subjects, which was statistically significant in subjects taking 75 mg but not 50 mg of study drug. It was also noted that two (2) of the subjects in the 75 mg group with the lowest blood counts were on

placebo. Finally, it was noted that all of these changes were observed in African American subjects. The proposed study will be conducted to evaluate (a) effects of 75 mg of GBR 12909 on WBC and ANC in African Americans treated for 11 days (days 1-11) and followed as inpatient for another 7 days (days 12-18) after the last drug dose and (b) whether any decreases in WBC and ANC are due to GBR 12909.

Subjects who do not have any decrease in WBC and ANC that is below the trigger point for initiating more frequent CBC monitoring or for drug discontinuation during in-patient days 1-18 will be followed weekly for four weeks as out-patients until discharged.

Subjects whose WBC and ANC decrease below the trigger point during treatment days 1-18 will be followed as in-patients until their blood counts return within the range of normal and will then be re-challenged with the same treatment as the one they received initially, i.e., either active drug or placebo, for another 11 days (days R1 to R11). They will be followed as inpatient for 7 days (Days R12-18) and as outpatient weekly for 4 weeks.

In this study, an equal number of subjects will be exposed to either 75 mg GBR 12 909 or placebo. The main hypothesis of the study is that there will be no difference of hematology parameters between the treatment groups.

#### **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, co-administration 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).

A current study that is a NIDA sponsored phase 1, dose escalating study in cocaine experienced volunteers, 18-45 years of age is ongoing at the USUHS/NIDA Clinical Pharmacology unit. To date six (6) subjects have been treated with 50 mg of GBR12909 in cohort #1 and six (6) subjects with 75 mg in cohort #2 for 11 days per dose. Two (2) subjects in each cohort received placebo treatment. Analysis of data obtained to date has demonstrated no cardiovascular side effects, and

a reduction in WBC and/or ANC in several African American subjects between days 1-18, which was not statistically significant from baseline in cohort #1 ( $p=0.5$ ), but was statistically significant from baseline in cohort #2 ( $p=0.04$  for WBC and  $p=0.002$  for ANC). There was no difference in screening WBC and ANC between subjects who were cocaine-positive or cocaine-negative. A hematologist consultant reviewed data on both cohorts and was also unblinded to the treatment given to subjects in cohort #2. It was found that in one subject in cohort #2 WBC and ANC counts followed a pattern not explained by a drug effect and that two (2) of the subjects with the lowest WBC and ANC had received placebo treatments. Because of these findings, the present study is undertaken to evaluate if GBR12909 has any effects on WBC and ANC in cocaine-experienced, African Americans.

## **5 STUDY DESIGN**

This is a single dose inpatient study, in which 10 cocaine-experienced volunteers that meet the protocol eligibility criteria during a 30-day (maximum) screening period will be studied. Five subjects will receive a single daily dosage 75mg of study agent for 11 days. 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 of study drug. 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. 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. Hematology assessments for WBC and ANC will be performed four times during study drug dosing, three times during in-patient follow-up and weekly during outpatient follow-up.

Subjects who demonstrate a significant decrease in WBC or ANC during the initial inpatient phase will not be discharged but followed as inpatients until blood counts return within the normal range. They will then be re-challenged with the same treatment as the one they received during the initial phase, i.e., study drug or placebo. The inpatient treatment period and the inpatient and outpatient follow-up periods in the re-challenge phase would be identical to those of the initial study phase.

## **6 STUDY OBJECTIVES**

To assess the safety, tolerance, and pharmacokinetics of multiple dosages of 75mg oral GBR 12909 in cocaine experienced volunteers. Effects on WBC and ANC will be the primary hematology outcome measure.

## **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 African American 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.
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.
11. Have a mean baseline absolute neutrophil count (from Days -2, -1, and 0) of less than 1000 cells/mcL and a mean total white blood cell count of less than  $2 \times 10^3$  cells/mcL.



## 10 INVESTIGATIONAL AGENT

### 10.1 GBR 12909

The chemical name of GBR 12909 is 1-(2[bis(4-fluorophenyl)methoxy[ethyl)-4-(3-phenylpropyl) piperazine dihydrochloride. The National Institute on Drug Abuse (NIDA) will supply the investigational agent GBR 12909, as 25 mg and 50 mg gelatin capsules. 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:

<b>Ingredient</b>	<b>Placebo</b>	<b>25 mg capsule</b>	<b>50 mg capsule</b>
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
Croscarmellose 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 Agent

The investigational agent will be administered under the supervision of research staff. The 75 mg dose will be administered as one 50 mg and one 25 mg capsule. 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 Agent

Investigational agent will be packaged in high-density polyethylene bottles. Bottles will be labeled with the subject's allocation number, treatment day, quantity/container, and instructions for taking the medication. The investigational agent should be stored at room temperature, and exposure to direct light should be avoided. The GBR 12909 is stable for 31 months with long storage at 25°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

Each subject will receive eleven days of 75mg GBR 12909 or placebo 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 that are African American, black, not of hispanic descent, between the ages of 18 and 45, inclusive, who report current use of cocaine, are not seeking treatment, and are available to participate for the required time, 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.

Ten (10) study subjects will be enrolled onto the study. Two (2) study subject alternates 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 is 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**

<b>Screening Procedures to be Conducted from Study Days - 30 to -1</b>	
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 $\beta$ -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 ( $\beta$ -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  $\beta$ -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 -3. Day -3 of the inpatient period is used to complete screening assessments and will include a hematology test. Table 2 shows the inpatient procedures that will be performed on admission (day -3), on days -2, -1, and day 0. For all subjects, a urine test for drugs of abuse will be done on admission prior to any study 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. Washout days will be designated as days -3.1, -3.2, -3.3, etc.

Once a negative urine toxicology for cocaine is received the subject will have blood drawn for hematology test for three consecutive days prior to dosing. For female subjects, a serum  $\beta$ -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 and the hematology test must be normal prior to receiving the study drug during the inpatient period.

**Day -2.** Hematology testing in the morning.

**Day -1.** Hematology testing in the morning.

**Day 0.** Hematology testing in the morning prior to initiating the ECG profile. 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 Procedures (days –3 to day 0)**

Assessment	Time point
Urine drug toxicology screen	Day –3 (Admission)
Breathalyzer	Day –3
Serum $\beta$ -HCG (pregnancy test)	Admission (but within 72 hours of dosing)
Hematology (RBC, Platelet, WBC and WBC Differential count)	Day -3, -2, -1, 0
Abbreviated physical examination	Day –3
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 Enrollment

A prospective subject who meets all of the study inclusion criteria and does not meet any of the exclusion criteria may be enrolled onto the study. Five (5) subjects will receive 75mg GBR 12909 and 5 subjects will receive placebo. On study day 0, the investigator or study coordinator will obtain the 75mg GBR 12909 from the Research Pharmacist. The Research Pharmacist will dispense the coded bottle of investigational agent for the subject to the investigator.

### 12.4 Inpatient Treatment (Days 1 – 11)

Subjects will receive 75mg of GBR12909 on study days 1 through 11. Study day 1 is defined as the first day of GBR 12909 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 doses of GBR 12909 will be observed. Subjects will fast from midnight to 2 hours after each investigational agent dosing. Subjects will also have hematology labs drawn on days 3, 5, 8 and 11. 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
75mg GBR 12909/placebo	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	Once daily
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 hour
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

<b>Procedure</b>	<b>Study Days</b>	<b>Time During Day</b>
Urine collection for GBR 12909 PK	1, 11	Pre-dose collection
	11	8 hour pools for the first 24 hours after dosing
Hematologies	3, 5, 8 and 11	Once in the morning
Chemistries	5, 9	Once in the morning
Adverse Events	1 to 11	Once daily
Concomitant Medications	1 to 11	Once daily

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.

A WBC less than  $2.0 \times 10^3$  cells/mcL and/or an ANC less than 1000 cells/mcL will trigger every-day CBC blood sampling. If the decline occurs during drug treatment and the WBC decreases to less than  $1.5 \times 10^3$  cells/mcL and/or ANC decrease to less than 500 cells/mcL for two consecutive days, then treatment will be discontinued and blood counts will be monitored daily until the WBC is greater than  $2.0 \times 10^3$  cells/mcL and the ANC is greater than 1000 cells/mcL for three consecutive days and every other day until they return to subject's baseline. If the decline occurs after completion of drug dosing on Day +11, and values similar to these above are observed for two consecutive days, then values will also be monitored as above until they return to baseline. Once the CBC parameters return to a level similar to the subject's baseline, and are stable for one week, as shown by every other day measurements, then the subject will continue to the re-challenge phase.

#### **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)**

<b>Procedure</b>	<b>Study Days</b>	<b>Time During Day</b>
Vital signs	12 to 18	At PK time-points
Psychometric determinations: ARCI	12 to 18 13, 15, 18	Once daily Once a week
BSCS	12 to 18	
SAFTEE, CSFQ, MOASCL		
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	12, 15, 18	Once in the morning
Routine Urinalysis	18	Once
Serum $\beta$ -HCG (pregnancy test)	18	Once
Adverse Events	12 to 18	Once daily
Concomitant Medications	12 to 18	Once daily

## 12.5 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.

## 12.6 Outpatient Follow-Ups (Days 26, 33, 40, and 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**

<b>Procedure</b>	<b>Study Day</b>
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	26, 33, 40, 47
Chemistries	47
Routine Urinalysis	47

## 12.7 Drug Re-challenge (re-exposure) Phase

A WBC less than  $2.0 \times 10^3$  cells/mcL and/or an ANC less than 1000 cells/mcL will trigger every-day CBC blood sampling. If the decline occurs during drug treatment and WBC decrease to less than  $1.5 \times 10^3$  cells/mcL and/or ANC decrease to less than 500 cells/mcL for two consecutive days, then treatment will be discontinued and blood counts will be monitored daily until the WBC is greater than  $2.0 \times 10^3$  cells/mcL and the ANC is greater than 1000 cells/mcL for 3 consecutive days and every other day until they return to subject's baseline. If the decline occurs after completion of drug dosing on Day +11, and values similar to these above are observed for two consecutive days, then values will also be monitored as above until they return to baseline. Once the CBC parameters return to a level similar to the subject's baseline, and are stable for one week, as shown by every other day measurements, then the subject will continue to the re-challenge phase.

### 12.7.1. Re-challenge phase, Inpatient Treatment (Days R1 to R11)

Treatment and procedures performed during this period will be identical to those of the initial period, described in section 12.4 above. Table 6 shows the procedures conducted during the re-challenge treatment period (days R1 through R11). However, the ECG 12 hour profile (Day R11) will not be done for the re-challenge phase. Also, neither blood nor urine will be collected during the re-challenge phase for PK analysis.

Subjects will receive 75mg of GBR12909 or placebo on re-challenge study days R1 through R11 and the treatment given will be identical to the treatment given after randomization during the initial phase (study days 1-11). Study day R1 is defined as the first day of GBR 12909 dosing. Subjects will have hematology testing done on days R3, R5, R8 and R11.

All doses of GBR 12909 will be observed. Subjects will fast from midnight to 2 hours after each investigational agent dosing.

**Table 6. Procedures Conducted During Re-Challenge Inpatient Treatment (Days R1 to R11)**

Procedure	Study Days	Time During Day
75mg GBR 12909	R1 to R11	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	R1 to R11 R2, R4, R6, R8, R11 R1 to R11	Within 4-8 hours post dosing Once daily Once a week
12-lead ECG	R1 to R11	Once daily
Hematologies	R3, R5, R8 and R11	Once in the morning
Chemistries	R5, R9	Once in the morning
Urine collection for GBR 12909 PK	R1, R11 R11	Pre-dose collection 8 hour pools for the first 24 hours after dosing
Adverse Events	R1 to R11	Once daily
Concomitant Medications	R1 to R11	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, no further drug will be given and the subject will undergo final study evaluation procedures as listed above.

During the re-challenge phase the same trigger points for daily CBC assessment and for drug discontinuation as those used during the initial dosing phase will be used. That is, a WBC less than  $2.0 \times 10^3$  cells/mcL and/or an ANC less than 1000 cells/mcL will trigger every-day CBC blood sampling. If the decline occurs during drug treatment and WBC decrease to less than  $1.5 \times 10^3$  cells/mcL and/or ANC decrease to less than 500 cells/mcL for two consecutive days, then treatment will be discontinued and subject will proceed to Day R12 per the schema noted above. In such an event, blood counts will be monitored daily until the WBC is greater than  $2.0 \times 10^3$  cells/mcL and the ANC is greater than 1000 cells/mcL for 3 consecutive days and every other day until they return to subject's baseline.

If the decline occurs after completion of drug dosing on Day +R11, and values similar to these above are observed for two consecutive days, then values will also be monitored as above until they return to baseline. The exact time of drug administration will be recorded on a CRF. 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.

### 12.7.2 Post Re-challenge Inpatient Follow-Up (Days R12 through R18)

Procedures to be performed during this inpatient period will be identical to those described in section 12.5. They are summarized in Table 7.



**Table 7. Procedures Conducted During Inpatient Follow-up Post Re-Challenge (Days R12 to R18)**

<b>Procedure</b>	<b>Study Days</b>	<b>Time During Day</b>
Vital signs	R12 to R18	Once daily
Psychometric determinations: ARCI BSCS SAFTEE, CSFQ, MOASCL	R12 to R18 R13, R15, R18 R12 to R18	Once daily Once a week
Digital and 12-lead ECG	R12 to R18	Once daily
Abbreviated Physical Exam	R18	Once
Chemistries	R-18	Once
Hematologies	R12, R15, R18	Once in the morning
Routine Urinalysis	R18	Once
Serum $\beta$ -HCG (pregnancy test)	R18	Once
Adverse Events	R12 to R18	Once daily
Concomitant Medications	R12 to R18	Once daily

### 12.7.3 Clinic Discharge Post-Re-challenge (Day R19)

Subjects will be discharged from the CPU on inpatient Day R19 after laboratory, hematology, physical examinations and ECG are completed and satisfactory as per the principal investigator or his/her designee.

### 12.7.4 Outpatient Follow-Ups (Days R26, R33, R40, and R47)

On days R26, 33, 40, 47 each subject will report to the CPU between 8:00 AM and noon for follow-up evaluations as shown in Table 8.

**Table 8. Outpatient Follow-up Procedures**

<b>Procedure</b>	<b>Study Day R:</b>
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	26, 33, 40, 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 pre-dose, 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. Subjects will have hematology labs on days, -3, -2, -1, 0, 3, 5, 8, 11, 12, 15, 18, 26, 33, 40 and 47. Subjects with WBC or ANC values below acceptable levels will remain in the CPU until these values return within the normal range and remain stable (at or near their baseline) for one week. They will then be treated again (the re-challenge phase). They will remain inpatient for the duration of the re-challenge period (days R1 to R11) and the post re-challenge follow up period (days R12 to R18).

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

Electrocardiographic effects will be determined through daily pre-dose 12-lead throughout the study and digital ECGs on days 0, 11, 12-18, 26, 33, 40, and 47. For pre-dose ECGs, any trough QTc measurement from the morning pre-dose 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 GBR 12909.

An extensive review of hematology parameters by the investigator must be conducted after the last subject completes day 26 visit.

Psychometric determinations will be measured according to the schedule in Tables 2, 3, 4, 5 and 6 by trained nursing staff during each 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. Subjects who would be re-treated with study drugs will have abbreviated physical exams on the day before treatment (R-0) and on day R-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 10mL heparin-containing green-stopper Vacutainers<sup>TM</sup>.

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 (7mL) 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 (342 mL) is approximately 0.75 times the volume of a standard blood bank donation. Total blood loss for subjects who will enter the re-challenge phase and had completed up to day 18 will be 518 mL.

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 that 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. Dose 75mg
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. Blood samples for CBC will be split, and analyses will be performed in two local clinical laboratories. Each 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. Each 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.

### **13.10 Routine Urinalysis**

Routine urinalysis will consist of tests for pH, protein, glucose, specific gravity, color and appearance, 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 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.

Statistical analysis on WBC and ANC will be done after logarithmic transformation of data using repeated measures ANOVA with post-hoc corrections. Data to be used would be from tests performed on screening, upon admission, on days -2, -1 and 0 before drug treatment; on days 3, 5, 8, and 11 on treatment; and on days 12, 15 and 18 during inpatient follow up. A difference between treatment groups more than 1.15 thousand WBC/ mcL or more than 960 ANC /mcL will be determined to be significant.

### **14.3 Sample Size Estimation**

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 18. 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.

Sample size was calculated using power analysis of repeated WBC and ANC measures separately based on estimates of variance and with-in subject correlation of repeated observations obtained from (a) published data on blood counts in African American, (b) statistical evaluation of screening CBC data obtained in the CPU on cocaine-experienced, African American subjects and (c) the two cohorts who have completed the current GBR study (Protocol NIDA-CPU-0002) (Diggle *et al.*, 1994). We have determined that there was not a significant difference between subjects being positive and negative for cocaine metabolites at the time of screening and, therefore, all available measures at the CPU were pooled for calculations. There did not appear to be a significant difference between these observation and observations reported in the literature (Bain, 1996; Haddy et al., 1999).

For WBC, assuming a variance of 2, a correlation of 0.2, 12 repeated measures and a significance level  $\alpha=0.05$ , a study with five (5) subjects in each treatment arm will have 80% power to detect a difference of  $1.15 \times 10^3$  cell/mcL between the active drug and placebo groups.

For ANC, assuming a variance of  $1.4 \times 10^6$ , a correlation of 0.2, 12 repeated measures and a significance level  $\alpha=0.05$ , a study with five (5) subjects in each treatment arm will have 80% power to detect a difference of 960 cell/mcL between the active drug and placebo groups.

## **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, IRB 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 to 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 agent. 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:** a panel of three independent physicians will review the safety data. The panel membership will be: the NIDA medical monitor, an independent physician with clinical trial experience and a physician representative from the current governing Institutional Review Board (IRB).

**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 agent is 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.

Study investigators will follow all AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, until satisfactory resolution. AEs should be reported up to 4 weeks following completion of, or termination from treatment.

### **15.7 Serious Adverse Events**

The study investigator as serious or non-serious will classify each adverse event or reaction. 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 agent has 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.

## SIGNATURES

### NIDA REPRESENTATIVE

Typed name(s)	Signature	Date
<u>Roberta Kahn, MD</u> NIDA Project Officer	_____	_____
<u>Aida Kuhn, MBA</u> NIDA Project Officer	_____	_____
<u>Jurij Mojsiak, M.S.</u> NIDA Investigator	_____	_____
<u>Ahmed Elkashef, M.D.</u>	_____	_____

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

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## APPENDIX I: TIME AND EVENTS SCHEDULE

Activity	Screening	Admission		Treatment												
				Study Day	-30 to -7	-3	0 <sup>a</sup>	1	2	3	4	5	6	7	8	9
Informed Consent	X															
12-lead ECG	X			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			X
Hematologies	X	X <sup>b</sup>	X			X <sup>b</sup>			X <sup>b</sup>			X <sup>b</sup>				X <sup>b</sup>
Routine Urinalysis	X															
Infectious Disease Serology	X															
Vital Signs	X			8X	8X	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/Placebo Administration				X	X	X	X	X	X	X	X	X	X	X	X	X
PK blood sampling			X			X						X	X	X		11X
Urine PK pre-dose				X												X
Urine PK sampling (8 hr pools)																3X
ARCI			X <sup>b</sup>		X		X		X		X		X			X
BSCS			X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAFTEE, CSFQ, MOASCL			X <sup>c</sup>				X									X
Adverse Events			X	X	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	X	X

<sup>a</sup>The inpatient period before treatment may be extended for 5 days to allow for a washout period for other drugs.

<sup>b</sup>Hematology assessment will on day -2, -1 and 0, and will be performed three times a week or more frequently during the inpatient period of the study.

<sup>c</sup>The assessments will be performed once a week during the inpatient period of the study.

**TIME AND EVENTS SCHEDULE CONTINUED**

Activity	Follow-up											
	12	13	14	15	16	17	18	19 Discharge	26	33	40	47
Study Day												
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 <sup>a</sup>			X <sup>a</sup>			X <sup>a</sup>		X	X	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

<sup>a</sup> Hematology testing will be done more frequently per protocol if WBC and/or ANC levels decline during the inpatient follow up( days 12 to 18).

**APPENDIX II: TIME AND EVENTS SCHEDULE RE-CHALLENGE**

Activity	Hematology workup	Re-challenge Treatment										
		1	2	3	4	5	6	7	8	9	10	11
Study Day	R-7											
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
Hematologies	X <sup>a</sup>			X <sup>b</sup>		X <sup>b</sup>			X <sup>b</sup>			X <sup>b</sup>
Vital Signs		8X	8X	8X	8X	8X	8X	8X	8X	8X	8X	8X
GBR 12909/Placebo Administration		X	X	X	X	X	X	X	X	X	X	X
Urine PK pre-dose		X										X
Urine PK sampling (8 hr pools)												3X
ARCI			X		X		X		X			X
BSCS		X	X	X	X	X	X	X	X	X	X	X
SAFTEE, CSFQ, MOASCL					X							X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X

<sup>a</sup> Hematology testing will be done every other day until the WBC and ANC values return to subject's baseline (up to one week)

<sup>b</sup> Hematology testing will be done more frequently as described in the protocol if WBC and ANC levels decline during treatment

**RE-CHALLENGE TIME AND EVENTS SCHEDULE CONTINUED**

<b>Activity</b>	<b>Follow-up</b>												
<b>Study Day</b>	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 <sup>a</sup>			X <sup>a</sup>			X <sup>a</sup>		X	X	X	X	
Routine Urinalysis							X					X	
Pregnancy Test							X						
Vital Signs	X	X	X	X	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	

Hematology testing will be done more frequently as described in the protocol if WBC and ANC levels decline during in-patient follow up (days R12 to R18)

**APPENDIX III: SCHEDULE OF BLOOD COLLECTIONS**

Analysis	Volume Per Sample	Type <sup>a</sup>	Number of Samples per Day												Total Volume
			Study Day	Screening	Day -3 to -1	Day 0	Day 3	Day 5	Day 8	Day 9	Day 10	Day 11	Days 12-17	Day 18	
Chemistries	7 mL	S		1				1		1			1	1	35 mL
Hematologies	10 mL	P		1	3	1	1	1	1		1	2	1	4	160 mL
Infectious Diseases	7 mL	S		1											7 mL
PK Samples	5 mL	P				1	1		1	1	1	11	1 each day	1	120 mL
Pregnancy Test	5 mL	S		1	1								1		15 mL
Alcohol Level	5 mL	P		1											5 mL
<b>Total</b>															<b>342 mL</b>

<sup>a</sup>S = serum, P = plasma

**APPENDIX IV: RE-CHALLENGE SCHEDULE OF BLOOD COLLECTIONS**

Analysis	Volume Per Sample	Type <sup>a</sup>	Number of Samples per Day										Total Volume	
			Study Day	Day -7-1	Day 0	Day 3	Day 5	Day 8	Day 9	Day 10	Day 11	Days 12-17		Day 18
Chemistries	7 mL	S					1		1				1	21 mL
Hematologies	10 mL	P		7*	1	1	1	1		1	2	1	1	150 mL
Pregnancy Test	5 mL	S											1	5 mL
<b>Total</b>														<b>176 mL</b>

## **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. 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:

***Timing of the study drug:*** 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.

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, 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 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 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.

### ***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.