STUDY #: NIDA-MDS-ARIPIP-0001

DOUBLE-BLIND, PLACEBO-CONTROLLED ASSESSMENT OF POTENTIAL INTERACTIONS BETWEEN INTRAVENOUS METHAMPHETAMINE AND ARIPIPRAZOLE

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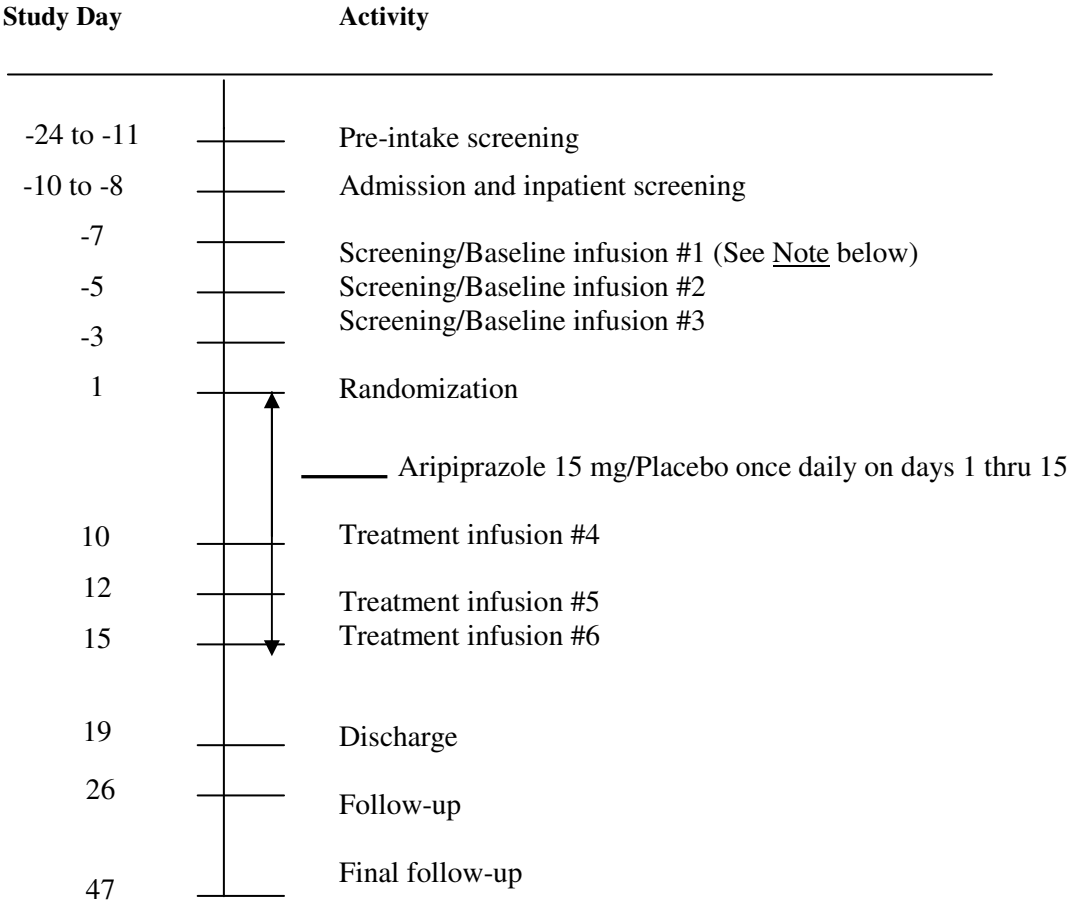
1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADD/ADHD	attention deficit disorder/attention deficit hyperactivity disorder
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
$alpha_1$	$alpha_1$-adrenergic
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ANOVA	analysis of variance
ARCI	Addiction Research Center Inventory
ASI-Lite	Addiction Severity Index-Lite
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	area under the blood concentration-time curve
BDI	Beck Depression Inventory
BP	blood pressure
bpm	beats per minute
BPRS	Brief Psychiatric Rating Scale
BSCS	Brief Substance Craving Scale
BSI	Brief Symptom Inventory
BUN	blood urea nitrogen
CAP	College of American Pathologists
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendment of 1988
CRF	Case Report Form
CPK	creatinine phosphokinase
CYP2C9	cytochrome P450 2C9 isoform
CYP2C19	cytochrome P450 2C19 isoform
CYP2D6	cytochrome P450 2D6 isoform
CYP3A4	cytochrome P450 3A4 isoform
DBP	diastolic blood pressure
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DTR&D	Division of Treatment Research and Development
ECG	electrocardiogram
EM	extensive metabolizers
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
GGT	gamma-glutamyl transferase
H	histamine
HIV	human immunodeficiency virus
HR	heart rate

Abbreviation	Definition
HRBS	HIV Risk-Taking Behavior Scale
5-HT	5-hydroxytryptamine (serotonin)
IND	Investigational New Drug
IRB	Institutional Review Board
i.v.	intravenous(ly)
LDH	lactate dehydrogenase
mg	milligrams
mL	milliliter
M	muscarinic
MAO	monoamine oxidase
MHA-TP	microhemagglutinin assay - *Treponema pallidum*
NDA	New Drug Application
NIDA	National Institute on Drug Abuse
OTC	over-the-counter
PK	pharmacokinetic
PM	poor metabolizers
POMS	Profile of Moods States
PPD	purified protein derivative (test for tuberculosis)
RPR	rapid plasma reagin (test for syphilis)
SAE	serious adverse event
SAS-EPS	Simpson-Angus Scale for Extrapyramidal Symptoms
SCID	Structured Clinical Interview for DSM-IV
VAS	visual analog scale

2 STUDY SCHEMA



Note: Randomization Schema for Methamphetamine/Saline Infusion Sessions. The infusions will be administered in a double blind, randomized fashion; 15 mg methamphetamine infusions will always precede 30 mg methamphetamine infusions.

Sessions #1 & #4	Sessions #2 & #5	Sessions #3 & #6
Saline	15 mg methamphetamine	30 mg methamphetamine
15 mg methamphetamine	30 mg methamphetamine	saline
15 mg methamphetamine	saline	30 mg methamphetamine

This study will be conducted at two sites, UCLA School of Medicine and New York University (NYU) School of Medicine.

3 ABSTRACT

STUDY OBJECTIVES: This is a human laboratory clinical pharmacology study to assess potential interactions between intravenous *d*-methamphetamine* infusion and treatment with oral aripiprazole.

Primary: The primary objective of this study is to determine if there are significant interactions between aripiprazole treatment concurrent with i.v. methamphetamine infusions of 15 mg and 30 mg by measuring adverse events and changes in cardiovascular responses from baseline [heart rate (HR), blood pressure (BP), and electrocardiogram (ECG)].

Secondary:

1. To evaluate whether administration of aripiprazole alters the pharmacokinetics (PK) of methamphetamine or its metabolites.
2. To determine PK of aripiprazole during chronic treatment at 15 mg once a day dose.
3. To evaluate whether aripiprazole treatment alters the subjective effects of methamphetamine measured by Visual Analog Scales (VAS) and Brief Substance Craving Scale (BSCS) and craving for methamphetamine measured by BSCS and by cue-induced arousal and craving for methamphetamine.
4. To assess the effects of aripiprazole on mood and personality using Brief Symptom Inventory (BSI), Beck Depression Inventory (BDI), Profile of Mood States (POMS) and the abuse liability of aripiprazole by Addiction Research Center Inventory (ARCI).

STUDY DESIGN: This is a double-blind inpatient study in which subjects' eligibility, including cardiovascular responses to screening/baseline methamphetamine infusions of 15 mg and 30 mg i.v. administered over 5 days (sessions #1 - 3), will be established. Three days after infusion session #3 and with urine methamphetamine level proven to be lower than 1,000 ng/mL, subjects will be randomized into one of two treatment groups and on the same day will initiate treatment with 15 mg aripiprazole (N=8) or matched placebo (N=8) for 15 days. That same day (day 1) before administration of the first dose of study agent, a methamphetamine cue reactivity test will take place. Eight days after initiation of daily treatment with either 15 mg aripiprazole or placebo, another methamphetamine cue reactivity test will take place. Nine days after initiation of daily treatment with either 15 mg aripiprazole or placebo, subjects will receive treatment methamphetamine infusions of 15 mg and 30 mg i.v. over 6 days (sessions #4 - 6). For two (2) days after infusion sessions #2, 3, 5, and 6, samples for PK analysis will be collected.

Each series of repeated methamphetamine administrations (screening/baseline and treatment) will consist of 3 infusions; each infusion session will be conducted on a different day with a one-day break between infusions except for a two-day break between infusions #5 and #6. Subjects will be randomized with the order of administration of the saline, 15 mg methamphetamine and 30 mg methamphetamine infusions (see Study Schema); the 15 mg methamphetamine infusions will always precede 30 mg methamphetamine infusions.

* *Referred to as methamphetamine throughout the protocol.*

The subjects will be discharged from the hospital 4 days after the last dose of aripiprazole and treatment infusion. The subjects will be asked to return twice for safety follow-up 1 and 4 weeks after clinic discharge. Note: Some flexibility in the precise timing of follow-up visits is suggested with first follow-up visit to take place in the week following discharge and the second in the week 4 weeks after discharge.

STUDY DURATION: Subjects will have up to 2 weeks for outpatient screening. The inpatient period will include three days allotted to complete screening assessments (days -10 to -8), five days for screening/baseline methamphetamine infusions (days -7 to -3), three days between screening/baseline methamphetamine infusions and the first dose of aripiprazole (days -2 to 1), fifteen days of treatment with 15 mg of aripiprazole or placebo (days 1 to 15) and four days of inpatient washout and follow-up (days 16-19). Clinic discharge is on day 19. Subjects will be requested to return for safety follow-up 1 and 4 weeks after the day of discharge.

SAMPLE SIZE: 16 subjects total, 8 subjects will receive aripiprazole and 8 will receive placebo. Subjects dropping out before completion of study procedures up to midnight of study day 15 (after discussion with the NIDA Investigator) will be replaced.

POPULATION: Volunteer experienced methamphetamine users, 18 to 45 years of age who have used methamphetamine within 2 weeks of entering the study, as assessed by self-report and a positive urine test for methamphetamine.

TREATMENTS: Subjects will be randomized on study day 1 to one of the following arms:

Aripiprazole: Subjects will take 15 mg aripiprazole on study days 1 through 15.

Placebo: Subjects will take matched placebo on study days 1 through 15.

ASSESSMENTS: The primary study endpoint is safety. Safety of methamphetamine administration in aripiprazole treated subjects will be determined by recording adverse events (AE), blood pressure (BP), heart rate (HR), and by performing ECG monitoring. Secondary outcome measures include pharmacokinetic parameters and psychometric assessments. The effect of aripiprazole on the PK of methamphetamine will be assessed by collecting blood and determining PK parameters for methamphetamine using a between- and within-subjects design. The PK of aripiprazole will be assessed at steady state. The effect of aripiprazole on methamphetamine craving will be assessed by BSCS and by cue-induced arousal and craving for methamphetamine; other psychometric assessments include POMS, BSI, BDI, VAS, and ARCI.

4 INTRODUCTION AND RATIONALE

4.1 Therapeutic Strategies for Treating Methamphetamine Abuse

A variety of neuropharmacological strategies are being pursued in the search for an effective treatment for methamphetamine abuse. One approach has been to target the dopaminergic neurotransmitter system involved in the reward mechanism to interrupt the reinforcing action of

methamphetamine and thus reduce its use and prevent relapse (Hyman and Nestler, 1995; Mendelson and Mello, 1996). Methamphetamine is known to produce its major effects through dopaminergic mechanisms in the midbrain, specifically, via a direct action at dopaminergic neurons in ventral tegmental area or their target neurons in nucleus accumbens. Methamphetamine causes dopamine release and blocks the reuptake of dopamine; the consequent excess of dopamine stimulates the midbrain reward centers. With the exception of D5 receptor, all other D1-like and D2-like dopamine receptor subtypes are reported to be present in these areas. The D1-like subfamily includes D1 and D5 dopamine receptor subtypes and D2-like subfamily includes D2-, D3- and D4- receptor subtypes (Seeman and Van Tol, 1994). One therapeutic strategy is to develop and test dopamine antagonists, to see if blocking dopamine can reduce methamphetamine abuse. Another, and diametrically opposed therapeutic strategy, is to develop and test dopamine agonists - agents that increase dopamine release or dopaminergic activity to determine whether methamphetamine abuse can be reduced. This second strategy is based on a combination of theory and data suggesting that chronic methamphetamine use depletes brain dopamine and that this depletion is experienced as methamphetamine craving; the aim is to reduce craving for and use of methamphetamine by restoring the depleted dopamine system to normality. Recently, a new therapeutic strategy based on a dual-deficit model of stimulant addiction has emerged (Rothman *et al.,* 2000). According to this model, withdrawal from prolonged exposure to stimulants (cocaine, methamphetamine) results in synaptic deficits of dopamine and serotonin with dopamine dysfunction underlying anhedonia and psychomotor retardation whereas serotonin dysfunction gives rise to depressed mood, obsessive thoughts and lack of impulse control. That model predicts that only pharmacotherapies that correct both neurochemical deficits will be effective in treating stimulant dependence. From this point of view, aripiprazole (Abilify®), the first representative of a new class of antipsychotic agents referred to as 'dopamine-serotonin system stabilizers', may have a potential for the treatment of methamphetamine dependence.

4.2 Aripiprazole as a Potential Medication to Treat Methamphetamine Dependence

This study will evaluate the safety of aripiprazole (Abilify®), a dopamine-serotonin system stabilizer, compared to placebo, concurrent with i.v. methamphetamine infusions.

Aripiprazole is FDA-approved and marketed for the treatment of schizophrenia. Aripiprazole is a quinoline derivative that appears to have a mechanism of action differing from currently marketed typical and atypical antipsychotics. Aripiprazole is a partial agonist of dopamine D2 and serotonin 5-HT_{1A} receptors, and is also an antagonist at 5-HT_{2A} receptors. Thus, like other atypical antipsychotics (risperidone, olanzapine, quetiapine, and ziprasidone), aripiprazole blocks both D2 dopamine and 5-HT_{2A} receptors, but unlike its predecessors, aripiprazole is a partial dopamine D2 agonist, i.e. it has a potent agonist activity at D2 dopamine autoreceptors and also displays the properties of a postsynaptic D2 receptor antagonist (Ozdemir *et al*., 2002; Tamminga, 2002). Theoretically, this unique mechanism of action should lead to dopamine antagonist-like actions in areas where dopamine activity is high (e.g., the mesolimbic pathway) and to dopamine agonist-like actions in areas where dopamine activity is low (e.g., the mesocortical pathway, tuberoinfundibular pathway). Taken in the context of the importance of D2 dopamine receptor in the addictive process (loss of control and compulsive drug intake) (Volkow *et al.,* 2001) and the usefulness of partial dopamine receptor agonists as treatments for

the addictive behavior (Pulvirenti and Koob, 1994; Pilla *et al*., 1999), the potential of aripiprazole for the treatment of methamphetamine dependence seems predictable. In therapeutic applications, the partial D2 dopamine agonist activity of aripiprazole should be particularly beneficial to such symptoms of methamphetamine dependence as craving and psychomotor retardation, including amotivation, apathy, and asociality, while correction of serotonin system would benefit another set of symptoms of methamphetamine dependence, such as depressed mood, lack of impulse control, obsessional thoughts, and hallucinations.

Prior to a randomized outpatient clinical trial of aripiprazole as a potential medication to treat methamphetamine dependence it is necessary to gather phase 1 data to demonstrate that aripiprazole can be used safely in a population likely to use methamphetamine concurrently with aripiprazole and to explore whether and how aripiprazole might affect methamphetamine pharmacokinetics and pharmacodynamics.

4.3 Methamphetamine

Pharmacology. Methamphetamine inhibits the reuptake and causes release of norepinephrine, serotonin, and dopamine. The dopaminergic activity is thought to contribute to the reinforcing effects of methamphetamine, and actions at dopamine and norepinephrine terminals may contribute to its sympathomimetic effects.

Pharmacokinetics. Following i.v. administration, methamphetamine is eliminated with a $t_{1/2}$ of 12 ± 3.2 hours.

Metabolism. Methamphetamine is metabolized by N-demethylation to amphetamine (Lin *et al.,* 1997) and by hydroxylation to 4-OH methamphetamine (Lin *et al.,* 1995). Both of these reactions are catalyzed by cytochrome P450 2D6 (CYP2D6). Approximately 38% of the administered dose is excreted in the urine unchanged (Mendelson *et al.,* 1995). Methamphetamine and amphetamine also inhibit CYP2D6 with an apparent K*i* of 25 μM and 26.5 μM, respectively (Wu *et al.,* 1997). This could shift metabolism during chronic administration towards urinary excretion of the parent compound.

Methamphetamine Dose Justification. Peak plasma concentrations of 140 ng/mL are observed after i.v. administration of 30 mg doses of methamphetamine in humans (Mendelson, *et al.,* 1995). These 30 mg doses of methamphetamine translate into an effective dose of 21 mg when delivered by the smoked route (Cook*,* 1991). A peak plasma concentration of 44 ng/mL was observed after 30 mg of methamphetamine was administered by smoking (Cook*,* 1991). Logan *et al.* (1998) quantitated methamphetamine levels in the postmortem blood of individuals involved in traffic fatalities that had detectable levels of methamphetamine. Levels ranged from 50 to 2,600 ng/mL (median 350 ng/mL). Thus, the highest dose of methamphetamine to be used in this study is representative of the levels in blood of methamphetamine users while at the same time being a safe dose to administer in the human laboratory setting.

4.4 Aripiprazole

4.4.1 Chemistry

Aripiprazole (Abilify®) has a chemical name of 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butyloxy]-3,4-dihydro-2(1H)-quinolinone, a molecular formula of $C_{23}H_{27}Cl_2N_3O_2$ and a molecular weight of 448.38.

4.4.2 Pharmacology

Aripiprazole is a partial agonist of dopamine D2 and serotonin 5-HT_{1A} receptors, and is also an antagonist at 5-HT_{2A} receptors. Thus, like other atypical antipsychotics (risperidone, olanzapine, quetiapine, and ziprasidone), aripiprazole blocks both D2 dopamine and 5-HT_{2A} receptors, but unlike its predecessors, aripiprazole is a partial dopamine D2 agonist, i.e. it has a potent agonist activity at D2 dopamine autoreceptors and also displays the properties of a postsynaptic D2 receptor antagonist. In theory, a partial agonist should decrease excessive levels and increase low levels of dopamine, avoiding both overactivity (hallucinations, delusions) and underactivity (anhedonia, lack of motivation). Pharmacologically, aripiprazole's partial agonism at D2 dopamine receptors means activation at low dopaminergic tone and inhibition at high dopaminergic tone, thus stabilizing dopamine output from either direction, which in combination with its ability to act as an agonist at serotonin 5-HT_{1A} receptors and an antagonist at 5-HT_{2A} receptors, indicates that overall aripiprazole acts as a dopamine-serotonin system stabilizer (Burris *et al.,* 2002; Jordan *et al.,* 2002). Affinity of aripiprazole to various receptors including dopamine (D), serotonin (5-HT), $alpha_1$-adrenergic ($alpha_1$), histamine (H1) and muscarinic (M1) is summarized in Table 1 (Bailey, 2003; Burris *et al.,* 2002; Jordan *et al.,* 2002, Lawler *et al*., 1999; McQuade *et al*., 2002; Porras *et al*., 2002).

Table 1. Aripiprazole Receptor Affinities

Receptor	High Affinity	Moderate Affinity	Low Affinity
D2	√*		
D3	√		
5-HT_{1a}	√*		
5-HT_{2a}	√{		
D4		√	
5-HT_{2c}		√	
5-HT_7		√	
$alpha_1$		√	
H1		√	
5-HT transporter		√	
D1			√
D5			√
5-HT_6			√
M1			√

* Partial agonist

{ Antagonist

Aripiprazole has a pharmacological profile that is different from any of the other typical or atypical antipsychotic agents currently available. Affinity of aripiprazole to dopamine D2, serotonin ($5\text{-}HT_{2a}$, $5\text{-}HT_{2c}$, $5\text{-}HT_{1a}$), $alpha_1$, H1 and M1 receptors is compared to that of other antipsychotics in Table 2 (Goodnick and Jerry, 2002).

Table 2. Comparative Pharmacology of Antipsychotics*

Receptor	Aripiprazole	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Clozapine	Haloperidol
D2	0.45	3.1	2.2	20	180	130	1.4
$5\text{-}HT_{2a}$	3.4	0.39	0.29	3.3	220	8.9	120
$5\text{-}HT_{2c}$	15	0.72	10	10	1400	17	4700
$5\text{-}HT_{1a}$	4.4	2.5	210	2100	230	140	3600
$alpha_1$	47	13	1.4	54	15	4.0	4.7
H1	67	47	19	2.8	8.7	1.8	440
M1	>10,000	5100	2800	4.7	100	1.8	1600

*Note: Affinity to different receptors is expressed as K*i* (inhibition constant) values in nM.

Comparative pharmacology of antipsycotics confirms a unique receptor binding profile of aripiprazole (Table 2). Among the atypical antipsychotics, aripiprazole displays the highest activity to D2 dopamine receptors and the lowest affinity for alpha1, H1 and M1 receptors. This combination of effects may be responsible for aripiprazole's efficacy in treatment of schizophrenia's both positive/psychotic symptoms, such as hallucinations and delusions, and negative/deficit symptoms, such as amotivation, apathy and asociality. Similarly, this pharamacological profile may be also the reason for low rates of reported side effects associated with aripiprazole administration, including low incidence of weight gain and a low liability for inducing movement disorders.

Recently certain concerns have been raised about the effect of antipsychotic agents on the QTc interval that measures ventricular depolarization and repolarization period. Prolonged QTc interval, an ECG abnormality, is in indicator of an increased risk of cardiac complications, including potentially dangerous cardiac arrythmias. The FDA has prevented the release of the antipsychotic, sertindole and placed a 'black box' warning on the use of thioridazine based on risks regarding lengthening of this interval. When prolonged beyond 500 ms, QTc is indicative of conduction disturbance and has been associated with an increased possibility of torsades des pointes and sudden death. Both animal and human studies have been conducted to check the effect of aripiprazole on QTc. In canine models, effects of aripiprazole on the QTc were not significant at a dose of 0.3-3 mg/kg, while PR and QT intervals were shortened (Sugiyama *et al.*, 2001). Data on the effect of aripiprazole on the QTc level in humans are available from short-term, long-term and switch studies and indicate that aripiprazole may lead to reductions in QTc interval (Goodnick and Jerry, 2002). In a human safety study, the mean changes in QTc values reported during 4-week treatment with aripiprazole at 15 mg/day or 30 mg/day doses were not statistically different from placebo (Kane *et al.,* 2002). No patient experienced a clinically meaningful change in QTc interval indicating that aripiprazole does not carry the risk of potentially dangerous ECG changes; the highest recorded QTc intervals at any time point were

454 ms and 453 ms for the15 mg and 30 mg aripiprazole treatment groups, respectively. Meta-analysis of safety data from five double-blind studies indicates that aripiprazole reduces QTc interval (-1 ms) in contrast to risperidone (+6 ms) and halopridol (<+1 ms) (Carson *et al*., 2002).

Another potential side effect associated with nearly all antipsychotic agents is hyperprolactinemia, which is caused by blockade of D2 dopamine receptors in the tuberoinfundibular pathway. From a clinical standpoint, prolactin elevation may result in galactorrhea, amenorrhea, gynecomastia and impotence. Theoretically, partial agonism at D2 dopamine receptor displayed by aripiprazole should prevent the release of prolactin. Indeed, data from the clinical trials indicate that, compared to placebo, treatment with aripiprazole reduced serum prolactin levels both in short term, 4- and 6-week ($p<0.01$) and long term, 26- and 52-week ($p<0.05$) studies (Goodnick and Jerry, 2002).

Aripiprazole appears to have positive effect on cognitive function (McGavin and Goa, 2002; Ozdemir *et al.,* 2002)). Long-term (26 weeks) treatment with aripipraziole at the dose of 30 mg/day improved verbal learning; it also improved working memory, compared with baseline at week 8 ($p<0.05$), but did not have effect on problem solving.

Neuroimaging studies indicate that aripiprazole passes through blood brain barrier (Ozdemir *et al.,* 2002; Yokoi *et al*., 2002). A preliminary neuroimaging study in healthy volunteers suggested that aripiprazole treatment for 2 weeks (30 mg/day, N=4; 10 mg/day, N=1)) results in a 92 an 87% D2 dopamine receptor occupancy in caudate and putamen measured by [^{11}C]-raclopride positron emission tomograhy (PET) imaging, respectively (Ozdemir *et al.,* 2002). These results were confirmed in another PET study that also used [^{11}C]-raclopride to measure the D2 receptor occupancy of aripiprazole in the corpus striatum of 15 male normal volunteers at baseline and after the administration of 5 different oral doses of aripiprazole for 14 days (Yokoi *et al*., 2002). Administration of aripiprazole resulted in a dose-dependent receptor occupancy between 40-95%; thus, treatment with 0.5 mg (N=3), 1 mg (N=3), 2 mg (N=3), 10 mg (N=2), and 30 mg (N=4) of aripiprazole for 14 days led to D2 dopamine receptor occupancy of 40%, 50%, 75%, 85%, and 95%, respectively. These results suggest that an adequate receptor occupancy may be achieved and may be useful to predict an appropriate therapeutic dose of aripiprazole for an individual patient. Interestingly, even at striatal D2 receptor occupancy values of above 90%, which occurred with the 30 mg doses of aripiprazole, extrapyramidal side effects were not observed. This fact indicates that the current opinion that schizophrenic patients treated with neuroleptics develop acute extrapyramidal side effects when occupancy of D2 receptors is about 80% or higher does not hold for aripiprazole and can be attributed to unique pharmacological properties of this compound.

Aripiprazole has not been tested in animal models of psychostimulant addiction; it is not known whether aripiprazole has reinforcing properties, and its potential for abuse and physical dependence in humans has not been systematically studied either (Package Information, 2002). However, literature data on a partial agonist of D3 dopamine receptor, which, as D2 dopamine receptor, is a member of D2-like subfamily of dopamine receptors, are encouraging and indicate that this compound, BP 897, changes cocaine-seeking behavior in animals in a way that may be useful in the treatment of addiction (Pilla *et al.,* 1999). Thus, BP 897 significantly inhibits cocaine-seeking behavior elicited by drug-associated environmental cues without having any

intrinsic, primary rewarding effects, e.g., it is neither self-administered nor able to change self-administration of cocaine in rats (Pilla *et al.,* 1999). BP 897 does not reduce self-administration of cocaine in monkeys (Preti, 2000). These results indicate a dissociation in the effects of this partial agonist on drug-cue-controlled cocaine-seeking behavior and on the reinforcing effects of cocaine. Partial agonist character of this compound seems to be essential for its dissociated actions by conferring a 'buffering' (stabilizing) capacity to BP 897, allowing it to oppose, as an antagonist, a chain of neural events initiated by a conditioned increase in dopamine release, while maintaining, as an agonist, a moderate degree of D3 receptor stimulation. This ability of BP 897 to reduce the motivational effects of drug-related cues without exhibiting reinforcing properties indicates that partial dopamine agonists of D2 subfamily of dopamine receptors may be used for reducing craving and vulnerability to relapse that are elicited by drug-associated environmental stimuli.

In summary, the rationale for studying aripiprazole as a potential medication to treat methamphetamine dependence is based on its mechanism of action. First of all, as a dopamine-serotonin system stabilizer, aripiprazole may act as a weak substitutive stimulant providing mild reinforcement and thus decreasing craving and methamphetamine-seeking and at the same time contribute to the stabilization of emotional status by reducing apathy, amotivation and asociality and thus promote abstinence and engagement in psychosocial therapy. Secondly, the dopamine-serotonin system buffering ability of aripiprazole, in combination with its favorable safety profile (low incidence of endocrine side effects and extrapyramidal symptoms and low effect on weight) and positive effects on cognitive functions (verbal learning and working memory), may facilitate adherence to both pharmacotherapy and psychosocial therapy in methamphetamine-dependent subjects. Aripiprazole is of particular interest because it does not seem to produce sensitization or tolerance; it is of importance that discontinuation of treatment with aripiprazole is not accompanied by withdrawal symptoms and thus will not hamper the consolidation of abstinence.

However, prior to a randomized outpatient clinical trial of aripiprazole as a potential medication to treat methamphetamine dependence it is necessary to gather phase 1 data to demonstrate that aripiprazole can be used safely in a population likely to use methamphetamine concurrently with aripiprazole and to explore whether and how aripiprazole might affect methamphetamine pharmacokinetics and pharmacodynamics.

4.4.3 Pharmacokinetics

Aripiprazole (Abilify®) activity is primarily due to the parent drug, aripiprazole, and to a lesser degree, to its major metabolite, dehydro-aripiprazole, which has been shown to have affinity to D2 dopamine receptors similar to the parent molecule. The mean elimination half-lifes are about 75 hours and 94 hours for aripiprazole and its active metabolite dehydro-aripiprazole, respectively, which allows once daily dosing and also confers a practical benefit in that a single missed dose should not interrupt therapeutic benefit once steady state is established. Steady state concentrations are attained within 14 days of dosing for both active moieties, aripiprazole and dehydro-aripiprazole; at steady state, dehydro-aripiprazole represents about 40% of aripiprazole AUC in plasma (Package Information, 2002). Meta-analysis of 4 premarketing studies of aripiprazole for the treatment of schizophrenia lasting 6-8 weeks (N>1000) indicates that at the daily doses of $\exists$15 mg, the clinical effect, compared to placebo ($p<0.05$), is noticeable by the end of week 1 rather than week 2 (assessed by improvements in positive, negative and total scores on

the Positive and Negative Syndrome Scale) (Goodnick and Jerry, 2002). Aripiprazole accumulation is predictable from single-dose pharmacokinetics; at steady-state, the PK of aripiprazole are dose-proportional at doses 5-30 mg (Package Information, 2002).

Aripiprazole is well absorbed after oral administration with peak plasma concentrations occurring within 3 to 5 hours (Package Information, 2002). The absolute oral bioavailability of the tablet formulation is 87%. At therapeutic doses (10-30 mg) aripiprazole and dehydro-aripiprazole are greater than 90% bound to serum proteins, predominantly to albumin. Aripiprazole can be administered with or without food. Administration of a 15 mg of aripiprazole with a standard high-fat meal did not significantly affect the C_{max} or AUC of aripiprazole or dehydro-aripiprazole but delayed T_{max} by 3 hours for aripiprazole and 12 hours for dehydro-aripiprazole. Pharamacokinetics of aripiprazole does not seem to be influenced by age or gender (Taylor, 2003). Aripiprazole passes through blood brain barrier, and neuroimaging studies indicate its accumulation in caudate and putamen of healthy volunteers upon 14 day-long administration at oral doses of 0.5-30 mg/day (Ozdemir *et al.,* 2002; Yokoi *et al*., 2002).

4.4.4 Metabolism

About 25% of single oral dose of aripiprazole is excreted in urine and 55% in feces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the feces. Aripiprazole is metabolized mainly by cytochrome P450 (CYP)-mediated oxidative pathways. Based on *in vitro* studies, CYP450 isoforms CYP3A4 and CYP2D6 are responsible for dehydrogenation and hydroxylation of aripiprazole while N-dealkylation of aripiprazole is catalyzed by CYP3A4 (Package Information, 2002). Approximately 8% of Caucasians lack the capacity to metabolize CYP2D substrates and are classified as poor metabolizers (PM), whereas the rest are extensive metabolizers (EM). PMs have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite compared to EMs, resulting in about 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to EMs. The mean elimination half-lives for aripiprazole are about 75 hours and 146 hours in EMs and PMs, respectively. Coadministration of aripiprazole with inhibitors of CYP2D6, like quinidine, in EMs, results in a 112% increase in aripiprazole plasma exposure, and requires dosing adjustment. Aripiprazole does not inhibit or induce the CYP2D6 pathway.

As aripiprazole may be administered with other medications, the potential for metabolic drug-drug interactions has been examined both *in vitro* and *in vivo* (Package Information, 2002). *In vitro* studies indicate that aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes is unlikely. Due to the involvement of CYP3A4 and CYP2D6 in the metabolism of aripiprazole, coadministration of potent inducers of CYP3A4 (e.g., carbamazepine, phenobarbital, rifampin), inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole) or inhibitors of CYP2D6 (e.g., quinidine, fluoxetine, paroxetine), could alter the plasma levels of aripiprazole.

Aripiprazole is unlikely to cause clinically significant interactions with drugs metabolized by CYP450 enzymes. *In vivo* studies indicate that 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin),

CYP2C19 (omeprazole, warfarin) and CYP3A4 (dextromethorphan) substrates (Package Information, 2002).

4.4.5 Previous Human Experience

Aripiprazole has been proved to be effective for the treatment of schizophrenia and is FDA-approved and marketed for this indication. Aripiprazole is the most recent addition to the new class of antipsychotiic medications, following the release of clozapine, risperidone, olanzapine, quetiapine, and ziprasidone. Aripiprazole has been tested in clinical studies for the treatment of acute relapsing and stable chronic schizophrenia. The results of several multicenter, randomized, placebo-controlled short-term (4- and 6-week) and long term (26- and 52-week) trials in patients with schizophrenia indicate efficacy and safety of aripiprazole (Aripiprazole, 2002; Aripiprazole (Abilify) for schizophrenia, 2003; Bailey, 2003; Goodnick and Perry, 2002; Kane *et al*., 2002; Package Information, 2002; Stahl, 2001; Taylor, 2003). Aripiprazole proved to be effective for the treatment of schizophrenia's both positive/psychotic symptoms, such as hallucinations and delusions, and negative/deficit symptoms, such as amotivation, apathy and asociality.

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance and physical dependence (Package Information, 2002). Patients with a history of drug abuse should be observed closely for signs of aripiprazole misuse or abuse (e.g., increases in doses, drug-seeking behavior). Aripiprazole has not been investigated for the treatment of methamphetamine, cocaine or any other psychostimulant dependence.

4.4.6 Dose Justification

The 15 mg daily doses of aripiprazole to be used in this study are commonly prescribed as a single daily dose in clinical practice for the treatment of schizophrenia (Package Information, 2002). Long-term administration of the 15 mg daily doses of aripiprazole was well tolerated, without being associated with clinically significant adverse events and without evidence of physical dependence in several large-scale, placebo-controlled, double-blind, clinical studies involving patients with schizophrenia (Package Information, 2002).

4.5 Safety Considerations

4.5.1 Aripiprazole Safety

Aripiprazole is a new psychotropic agent for oral administration that was approved by FDA for the treatment of schizophrenia in 2002. The safety and tolerability of aripiprazole has been established in premarketing clinical studies involving more than 5,500 patients, including more than 1,250 patients who were treated for at least one year (Package Information, 2002). In general, aripiprazole has been used as a once-daily oral tablet at 10 to 30 mg doses. At these doses, aripiprazole is well tolerated and AEs possibly associated with aripiprazole are short-lived, mild or moderate in severity and do not include dystonia, parkinsonism, ECG changes (QTc prolongation) or increased levels of plasma prolactin and cholesterol.

The AEs reported during treatment with aripiprazole can be broadly divided into effects on the nervous system and gastrointestinal tract. The nervous system AEs include (in addition to movement disorders below) agitation, headache, insomnia, somnolence, lightheadedness, anxiety and tremor. The risk of induction of movement disorders (extrapyramidal symptoms, akathisia

and tardive dyskinesia) by aripiprazole appears to be minimal. Gastrointestinal symptoms include nausea, vomiting, dyspepsia and constipation. In short-term (4- and 6-week) placebo-controlled trials, there was no difference in the incidence of discontinuation due to AEs between patients treated with aripiprazole (7%) and placebo (9%). The most commonly reported AEs associated with the use of aripiprazole with an incidence greater than 15% and greater than placebo in short-term clinical trials were headache (32% *versus* 25% with placebo), anxiety (25% *versus* 24% with placebo) and insomnia (24% *versus* 19% with placebo). Other, less common AEs associated with aripiprazole use in short-term placebo-controlled trials include somnolence (11% *versus* 8% with placebo) and orthostatic hypotension (1.9% *versus* 1% with placebo); however, the incidence of significant orthostatic change in blood pressure defined as a decrease of at least 30 mm Hg in systolic BP when changing from supine to standing position for aripiprazole was not statistically different from placebo (14% *versus* 12% with placebo). Two possible cases of neuroleptic malignant syndrome and one case of seizures were reported in the premarketing studies of aripiprazole.

Acute overdose of aripiprazole, accidental or intentional, was reported in seven patients (Package Information, 2002). The only symptoms reported with the largest identified amount, 180 mg of aripiprazole, were somnolence and vomiting in one of the two patients. In the patients evaluated for the overdose in the hospital settings, including the two patients that took 180 mg of aripiprazole, there were no observations indicating an adverse change in vital signs, laboratory assessments, or ECG. An uneventful, accidental overdose (15 mg) occurred in a non-patient, an 18-month-old child, with concomitant ingestion of Ativan (2 mg). The treatment of overdose is symptomatic as there is no specific antidote and should include cardiovascular monitoring.

Aripiprazole, as other antipsychotics, may impair judgment, thinking and motor skills. Although the risk of induction of movement disorders (extrapyramidal symptoms, akathisia and tardive dyskinesia) by aripiprazole appears to be minimal, the Simpson-Angus Scale for Extrapyramidal Symptoms (SAS-EPS) and Barnes Akathizia scales will be administered on days 1, 5, and 12 to monitor the status of participants' motor system.

Subjects will not be allowed to take concomitant medications, whether prescription or over the counter (OTC), during the study without the approval by the site principal investigator/study physician.

4.5.2 Methamphetamine Safety

Intravenous methamphetamine administration spanning the doses proposed for use in this study has been previously investigated in human laboratory clinical trials. Mendelson and colleagues (personal communication) have employed i.v. methamphetamine doses from 15 mg to 0.5 mg/kg (about 45 mg maximally). These doses were administered safely over 1 to 10 minutes in subjects with prior experience with i.v. methamphetamine use. In these studies, the immediate subjective effects of a 15 mg dose were minimal and almost indistinguishable from placebo. However, after about 10 minutes all subjects were able to distinguish when methamphetamine was administered as compared to placebo. The cardiovascular effects of the 15 mg dose were also minimal.

In a pharmacokinetic and interaction study with alcohol, Mendelson *et al.,* (1995) reported the cardiovascular effects in 8 subjects following i.v. administration of 30 mg of methamphetamine.

Blood pressure peaked at 2 minutes and heart rate peaked at 10 minutes. Both measures returned from peak values to a plateau level (20 mm Hg above and about 15 bpm above pre-methamphetamine baseline) 15 minutes following i.v. administration. The plateau levels slowly returned to baseline levels over the rest of the day. Heart rate and blood pressure responses were dramatic in some individuals (50 mm Hg elevations in systolic blood pressure occurred). A few subjects exhibited a baroreceptor reflex response with a brief, relative bradycardia with heart rates of 55 to 60. All subjects had a robust, predictable response to the 30 mg dose with immediate intoxication ratings of about 50 (0=none, 100=max). In the interaction part of this study, methamphetamine (30 mg i.v.) was administered in combination with ethanol (1 gm/kg). Methamphetamine pharmacokinetics were not altered by the concurrent administration of ethanol, with the exception of lowering the apparent volume of distribution at steady state for methamphetamine. Based on these data, Mendelson concluded that doses around 30 mg produced at least half maximal acute subjective and cardiovascular responses.

4.5.3 Potential Aripiprazole-Methamphetamine Interactions

Methamphetamine would not be expected to alter the PK of aripiprazole. Metabolism of aripiprazole occurs largely through CYP3A4 and CYP2D6. Methamphetamine is neither metabolized by CYP3A4 nor affects the activity of CYP3A4. Although methamphetamine is a substrate for CYP2D6 (Lin *et al.,* 1997), and preclinical studies indicate that inhibition of CYP2D6 may affect the PK of methamphetamine and may be behaviorally relevant (Tomkins *et al.,* 1997), aripiprazole does not inhibit CYP2D6. Thus, treatment with aripiprazole would not result in higher methamphetamine plasma concentrations and would not be expected to have meaningful effects on cardiovascular and subjective effects of experimentally administered methamphetamine.

However, it is necessary to examine the potential for aripiprazole interactions with methamphetamine in human laboratory studies. Thus, a phase 1 placebo-controlled study to demonstrate that aripiprazole can be used safely in a population likely to use methamphetamine by i.v. route concurrently with aripiprazole is warranted.

5 STUDY OBJECTIVES

5.1 Primary

The primary objective of this study is to determine if there are significant interactions between aripiprazole treatment concurrent with methamphetamine infusions of 15 mg and 30 mg i.v. by measuring adverse events and cardiovascular responses [heart rate (HR), blood pressure (BP), and electrocardiogram (ECG)].

5.2 Secondary

1. To evaluate whether administration of aripiprazole alters the pharmacokinetics (PK) of methamphetamine or its metabolites.
2. To determine PK of aripiprazole during chronic treatment at 15 mg once a day dose.
3. To evaluate whether aripiprazole treatment alters the subjective effects of methamphetamine measured by Visual Analog Scales (VAS) and Brief Substance Craving Scale (BSCS) and

craving for methamphetamine measured by BSCS and by cue-induced arousal and craving for methamphetamine.

4. To assess the effects of aripiprazole on mood and personality using BSI, BDI, POMS and the abuse liability of aripiprazole by ARCI.

6 STUDY DESIGN

This is a double-blind inpatient study in which subjects' eligibility, including cardiovascular responses to screening/baseline methamphetamine infusions of 15 mg and 30 mg i.v. administered over 5 days (sessions #1 - 3), will be established. Three days after infusion session #3 and with urine methamphetamine level proven to be lower than 1,000 ng/mL, subjects will be randomized into one of two treatment groups and on the same day will initiate treatment with 15 mg aripiprazole (N=8) or matched placebo (N=8) for 15 days. That same day (day 1) before administration of the first dose of study agent, a methamphetamine cue reactivity test will take place. Eight days after initiation of daily treatment with either 15 mg aripiprazole or placebo, another methamphetamine cue reactivity test will take place. Nine days after initiation of daily treatment with either 15 mg aripiprazole or placebo, subjects will receive treatment methamphetamine infusions of 15 mg and 30 mg i.v. over 6 days (sessions #4 - 6). For two (2) days after infusion session #2, 3, 5, and 6, samples for PK analysis will be collected.

Each series of repeated methamphetamine administrations (screening/baseline and treatment) will consist of 3 infusions; each infusion session will be conducted on a different day with a one-day break between infusions except for a two-day break between infusions #5 and #6. Subjects will be randomized with the order of administration of the saline, 15 mg methamphetamine and 30 mg methamphetamine infusions (see Study Schema and Table 3); the 15 mg methamphetamine infusions will always precede 30 mg methamphetamine infusions.

The subjects will be discharged from the hospital 4 days after the last dose of aripiprazole and treatment infusion. The subjects will be asked to return twice for safety follow-up 1 and 4 weeks after clinic discharge. Note: Some flexibility in the precise timing of follow-up visits is suggested with first follow-up visit to take place in the week following discharge and the second in the week 4 weeks after discharge.

The study will assess the subjective and physiological response to methamphetamine, the pharmacokinetics of methamphetamine and its major metabolite, and the blood levels of aripiprazole and its major metabolite. A combination between-subjects and within-subjects analysis will be performed. A between-subjects analysis will be used to assess the effects of aripiprazole pretreatment on subjective effects of two doses of methamphetamine. A combined between-subjects and within-subjects analysis will allow for a pharmacodynamic assessment of methamphetamine's effects before and after initiating treatment with aripiprazole.

7 STUDY SITES

This study will be conducted at two sites, UCLA School of Medicine and New York University (NYU) School of Medicine.

Study participants will be methamphetamine abusing or dependent subjects who are not seeking treatment for drug abuse. Subjects at the NYU site will be recruited primarily by advertising in the *Village Voice*, fliers and cards, as well as referrals from NYU affiliated medical centers, the community, and word of mouth. All advertising will be approved by the IRBs.

8 SUBJECT IDENTIFICATION

8.1 Inclusion Criteria

In order to participate in the study, subjects must:

1. Be volunteers who meet DSM-IV criteria for methamphetamine abuse or dependence and are non-treatment seeking at time of study enrollment.

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

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

4. Have used methamphetamine, as assessed by self-report and a positive urine test for methamphetamine, within 2 weeks of inpatient screening.

5. Have a history and physical examination that demonstrate no clinically significant contraindication for participating in the study, in the judgment of the admitting physician and the site investigator.

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

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

7. Have vital signs as follows: resting heart rate between 50 and 90 bpm, systolic BP below 150 mm Hg and diastolic BP below 90 mm Hg.

8 Have electrolytes (Na, K, Cl, HCO_3) and hematocrit that are clinically normal (+/- 10% of laboratory limits).

9. Have liver function tests (total bilirubin, ALT, AST, GGT and alkaline phosphatase) within

normal limits.

10. Have kidney function tests (creatinine and BUN) within normal limits.

11. Have an ECG performed that demonstrates normal sinus rhythm, normal conductivity, and no clinically significant abnormalities.

NOTE: Recent intermittent alcohol or other illicit drug use without physical dependence is allowable (however, an opiate and benzodiazepine-free urine should be produced to document absence of recent use).

8.2 Exclusion criteria

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

1. Meet DSM-IV criteria for dependence on drugs or alcohol (aside from methamphetamine or nicotine).

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

3. According to DSM-IV criteria as determined by structured clinical interview (SCID), have any history of major psychiatric illness other than methamphetamine dependence or disorders secondary to drug use including Axis I psychiatric disorders, such as psychosis, bipolar illness, organic brain disease, dementia, major depression, schizoaffective disorder or schizophrenia which require ongoing treatment or which would make medication compliance difficult.

4. Have any evidence of clinically significant heart disease, hypertension or significant medical illness, condition, and/or use of medications that in the opinion of the site investigator and the admitting physician, would preclude safe and/or successful completion of the study.

5. Be pregnant or nursing.

6. Have a significant family history of early cardiovascular morbidity or mortality.

7. Have a diagnosis of adult onset asthma (i.e., 21 years or older), or chronic obstructive pulmonary disease (COPD), including those with a history of acute asthma within the past two years, and those with current or recent (past 2 years) treatment with inhaled or oral beta-agonist or steroid therapy (due to potential serious adverse interactions with methamphetamine).

8. Have active syphilis that has not been treated or refuse treatment for syphilis (see note).

9. Be undergoing HIV treatment with antiviral and non-antiviral therapy or treatment for HIV-related opportunistic infection.

10. Have AIDS according to the current CDC criteria for AIDS - MMWR 1999; 48 (no. RR-13:29-31).

11. Have received investigational drug in the last 30 days prior to informed consent.

12. Be using aripiprazole or any medication that could interact adversely with aripiprazole, within the following times of beginning of administration of aripiprazole based on the longest time interval of A, B, or C, below or as otherwise specified:

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

Notes on inclusion/exclusion criterion: Although AIDS is an exclusion criterion, a positive antibody titer to HIV is not. Prospective subjects will be offered HIV testing during screening but may not have the test performed until after inpatient admission. This test is offered as a courtesy to the prospective subject along with HIV education.

Prospective subjects who are positive for syphilis by the RPR test will have a fluorescent treponemal antibody absorbant assay (FTP-abs) or microhemagglutinin assay-*Treponema pallidum* (MHA-TP) confirmatory test performed. If this test is positive, prospective subjects must be treated for syphilis to be enrolled on the study or provide evidence of previous successful treatment for syphilis.

The infectious disease panel for hepatitis is performed as an aid to determine if the prospective subject has been exposed to a hepatitis virus. Positive hepatitis test results do not exclude a prospective subject from participation unless there is an indication of active liver disease. Similarly, a positive tuberculin (PPD) result does not exclude a prospective subject from participation, but if the diagnostic tests (e.g., chest x-ray) indicate that active disease is present, subjects may be excluded from participation.

If any test results are positive subject will be notified of positive and confirmatory test results and will be referred for treatment.

Methamphetamine is known to produce paranoia and occasionally other symptoms of psychosis when taken in large doses over extended periods of time. Occasionally, methamphetamine induced psychosis may last longer than acute drug intoxication. Subjects with a history of methamphetamine induced psychosis that does not last longer than acute drug intoxication will not be excluded; however, a history of methamphetamine-induced psychosis lasting longer than acute drug intoxication will be exclusionary. In addition, the presence of current methamphetamine-induced psychosis will be exclusionary.

9 INVESTIGATIONAL AGENTS

9.1 Aripiprazole

Aripiprazole (Abilify®) has a chemical name of 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butyloxy]-3,4-dihydro-2(1H)-quinolinone, a molecular formula of $C_{23}H_{27}Cl_2N_3O_2$ and a molecular weight of 448.38.

Aripiprazole is available in 10 mg, 15 mg, 20 mg and 30 mg tablets. Aripiprazole tablets contain the following inactive ingredients: lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate. Colorants include ferric oxide (yellow or red).

Aripiprazole is manufactured jointly by Brystol-Myers Squibb Company and Otsuka America Pharmaceuticals, Inc. Aripiprazole will be supplied by Brystol-Myers Squibb Company and Otsuka America Pharmaceuticals, Inc. as 15 mg tablets for oral administration. It will be administered in the morning 1.5 hours before breakfast.

Aripiprazole should be stored away from heat, sunlight, and moist areas such as the bathroom where the wetness may cause it to break down.

Placebo will be supplied by Brystol-Myers Squibb Company and Otsuka America Pharmaceuticals, Inc. as an exact match of aripiprazole.

9.2 Methamphetamine

Sterile human use methamphetamine HCl at 10 mg/mL in 1 mL ampules will be provided by NIDA. The compound will be stored in the pharmacy vault. Standard narcotics control procedures will govern access to the drug. Aliquots of 0, 15 or 30 mg will be drawn into a syringe for i.v. administration. Methamphetamine will be administered by i.v. infusion over 2 minutes by the study physician. Any unused drug will be disposed according to standard practices.

10 TREATMENT PLAN

Aripiprazole Arm: Subjects will take 15 mg aripiprazole on study days 1 through 15.

Placebo Arm: Subjects will take matched placebo on study days 1 through 15.

Subjects will take 15 mg aripiprazole or matched placebo as a once daily morning dose with a glass of water at approximately 7:00 a.m. about 1.5 hours before breakfast. Note: On Day 1 subjects will take aripiprazole or matched placebo around 1:00 p.m., after administration of SAS-EPS and Barnes Akathizia assessments and cue reactivity test.

Methamphetamine or Saline (All Subjects): Methamphetamine/saline infusions will be administered in a double-blind randomized fashion (Table 3). The 15 mg methamphetamine infusions will always precede 30 mg methamphetamine infusions.

Table 3. Randomization Schema for Methamphetamine/Saline Infusion Sessions

Sessions #1 & #4	Sessions #2 & #5	Sessions #3 & #6
Saline	15 mg methamphetamine	30 mg methamphetamine
15 mg methamphetamine	30 mg methamphetamine	saline
15 mg methamphetamine	Saline	30 mg methamphetamine

Saline or 15 mg methamphetamine i.v.: Study days -7 and 10.

Saline or 15 mg methamphetamine or 30 mg methamphetamine i.v.: Study days -5 and 12.

Saline or 30 mg methamphetamine i.v.: Study days -3 and 15.

Methamphetamine (15 mg or 30 mg) will be administered by i.v. infusion over 2 minutes by the study physician approximately at 11:00 a.m. During treatment infusions (sessions #4-6), subjects will take aripiprazole at approximately 7:00 a.m., have breakfast at 8:30 a.m. and get infusion at 11:00 a.m.

11 STUDY PROCEDURES

Appendix I provides a detailed table of the timing of study activities.

11.1 Pre-intake Screening (Study Days -24 to -11)

Interested candidates between the ages of 18 and 45 who have been determined to have used methamphetamine within 2 weeks of entering the study, are not seeking treatment, and are available to participate in an inpatient medication study for approximately 45 days will meet with the investigator and receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the site's IRB. Non-treatment seeking subjects will be counseled by the site investigator regarding the option of receiving treatment before and at the conclusion of the study.

Screening of subjects to establish eligibility will occur initially before clinic intake; some assessments will be completed after intake. Assessments performed before intake include collection of demographic information and completion of a subject intake form, subject locator form, a timeline follow back for methamphetamine use for the prior 6 weeks, drug use and treatment history, urine test for methamphetamine (will be repeated until a positive test is obtained within 14 days prior to intake), medical history, a physical exam, laboratory analyses including hematology, blood chemistries, and urinalysis, a 12-lead ECG, and vital signs (HR and BP). For women of reproductive potential a urine pregnancy test will be performed. Adverse events will be recorded at each visit starting the day of the completion of informed consent process. Note: Some of those assessments may be performed during the inpatient screening.

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

11.2 Inpatient Screening (Study Days -10 to -8)

Potential candidates whose results of screening assessments conducted prior to intake do not exclude them from study participation, will complete intake procedures and reside full-time as inpatients until discharge or completion of the study. The remaining screening procedures must be conducted during study days -10, -9 and -8 before the first methamphetamine infusion (study day -7). These screening assessments include 12-lead ECG, family history of drug or alcohol abuse/dependence, an HIV antibody test (optional), infectious disease panel including PPD test, urine drug toxicology tests, a pregnancy test for women of reproductive potential, SCID for DSM-IV diagnosis of methamphetamine dependence and Axis I Disorders, BSCS, BDI, BSI, POMS, HRBS, Attention Deficit Disorder (ADD) interview, and ASI-Lite assessment.

To ensure abstinence, qualitative testing for methamphetamine will be performed on days -10, -9 and -8 on subjects with urine test positive for methamphetamine upon hospital admission until urine is negative for methamphetamine. Note: For subjects admitted to the hospital on Monday, Tuesday, Wednesday and Thursday, the intake procedures may take longer than 3 days as the first infusion should be always scheduled on Mondays.

11.3 Enrollment and Randomization

If the prospective subject meets all of the study inclusion and does not meet any of the exclusion criteria, then the subject can be enrolled into the study*. Four randomizations will be performed. The first will be for the schedule of administration of the saline and 15 mg or 30 mg doses of methamphetamine for the infusion sessions and will take place before infusion #1 (see Table 4). The second randomization will be performed on day 1 to determine the sequence of cues for methamphetamine cue-reactivity test, i.e. neutral cue followed by methamphetamine-related cue or vice versa. The third randomization will apply to the assignment to the aripiprazole or placebo arm and will also take place on study day 1. The fourth randomization will be performed on day 9 to determine the sequence of cues for methamphetamine cue-reactivity test, i.e. neutral cue followed by methamphetamine-related cue or vice versa.

The data-coordinating center (Technical Resources International, Inc.) will supply the Research Pharmacist with pre-coded envelopes with treatment assignments. On study day 1, the investigator or study coordinator will obtain the treatment assignment from the Research Pharmacist. The Research Pharmacist will dispense the coded bottle of investigational agent for

** Enrollment refers to admission and inpatient screening occurring between days -10 and -8 throughout the protocol.*

the subject to the investigator. If a subject is terminated before completing all of the methamphetamine infusion sessions, a replacement subject will be randomized until 16 subjects have completed the study.

11.4 Aripiprazole Treatment

Subjects will take 15 mg aripiprazole or matched placebo on study days 1 to 15 as a once daily morning dose with a glass of water at approximately 7:00 a.m. about 1.5 hours before breakfast. Note: On Day 1 subjects will take aripiprazole or matched placebo around 1:00 p.m., after administration of SAS-EPS and Barnes Akathizia assessments and cue reactivity test.

11.5 Methamphetamine Infusion Sessions

11.5.1 Schedule

Intravenous methamphetamine infusions will be conducted according to the schedule shown in Table 4. Each series of repeated administrations (screening/baseline and treatment) will consist of three infusion sessions performed in a double-blind randomized fashion (Randomization schema of methamphetamine/saline infusions is presented in Table 3). Each infusion session will be conducted on different day and there will be a one-day break between each infusion except for a two-day break between infusions #5 and #6. The 15 mg methamphetamine infusions will always precede 30 mg methamphetamine infusions. The fixed ascending sequence of methamphetamine infusions each week is a safety precaution.

During the screening/baseline infusion sessions, the subject's responses to methamphetamine without concomitant aripiprazole or placebo administration will be assessed. During the treatment infusion sessions, the subject's responses to methamphetamine with concomitant aripiprazole or placebo administration will be assessed.

Table 4. Methamphetamine Infusion Session Schedule

Study Phase	Session Number	Study Day	Infusion
Screening/Baseline	Session 1	-7	saline or 15 mg methamphetamine
Screening/Baseline	Session 2	-5	saline or 15 mg methamphetamine or 30 mg methamphetamine
Screening/Baseline	Session 3	-3	saline or 30 mg methamphetamine
Treatment	Session 4	10	Aripiprazole 15 mg or placebo followed by saline or 15 mg methamphetamine 4 hrs later
Treatment	Session 5	12	Aripiprazole 15 mg or placebo followed by saline or 15 mg methamphetamine or 30 mg methamphetamine 4 hrs later
Treatment	Session 6	15	Aripiprazole 15 mg or placebo followed by saline or 30 mg methamphetamine 4 hrs later

11.5.2 Conduct of Methamphetamine/Saline Infusion Sessions

Each intravenous infusion dose will be administered over a 2-minute duration by a study physician. The methamphetamine or saline infusion will occur between 11 a.m. and noon, depending on scheduling constraints.

For a subject to receive the first screening/baseline i.v. methamphetamine/saline infusion, s/he must have a drug toxicology screening that shows negative urine drug/metabolite levels for drugs of abuse (except marijuana) before conduct of methamphetamine/saline infusion session. Subjects with positive urine drug toxicologies will be discharged and replaced. The screening/baseline infusions (sessions #1-3) are to ensure that volunteers are responsive to and safely tolerate the 15 mg and 30 mg doses of methamphetamine; they also provide cardiovascular and psychometric response data in the absence of the investigational agent and serve for training and adaptation purposes. Only subjects responsive to and safely tolerating both doses of methamphetamine (15 mg and 30 mg) will continue in the study. Note: Prior to each methamphetamine administration subject's blood pressure must be at 150/90 mm Hg or below and heart rate <130.

Subjects will have breakfast prior to infusion session initiation, but will not be allowed to eat within the hour prior to the infusion until after the entire session. Cigarette-smoking subjects may not smoke from 1-hour prior to infusion session initiation until 90-minutes after the infusion. Smoking is not permitted within 15 minutes of scheduled vital sign measurements.

Before and after each i.v. infusion, the subject's physiologic responses will be closely monitored using repeated HR, BP, and ECG readings. BP and HR will be taken at -25 and -15 minutes before, and 3, 6, 9, 12, 15, 20, 30, 45, 60, 90, 180, 210, 240, 300, 360, 420, 480 minutes and 10 and 12 hours following methamphetamine/saline administration. Continuous telemetry of ECG and HR will start 15 minutes before and will be conducted until 60 minutes after each methamphetamine/saline infusion; 12-lead ECG readings will be performed at the following time points: 15 minutes before and 15, 30, 45 and 60 minutes after infusion.

11.5.3 Safety Precautions

A physician will perform the infusions and will be present at least 60 minutes after the infusion and will remain until vital signs have returned to normal. The physician may leave the room, if the subject's vital signs are approaching baseline, but will remain nearby and available by pager for prompt response, if needed, for at least four hours post-injection. If a subject demonstrates a significant adverse reaction to methamphetamine, the methamphetamine administration will be halted, appropriate medical response will be implemented (see Appendix III), and the subject will be discontinued from the remainder of the study.

11.5.4 Stopping Criteria for Further Methamphetamine Infusion

Methamphetamine i.v. administration will be discontinued if any of the following events occurs:

1. Systolic BP > 165 mm Hg;
2. Diastolic BP > 100 mm Hg;

3. Heart rate > 130 bpm;
4. Behavioral manifestation of methamphetamine toxicity, e.g., agitation, psychosis, inability to comply with study procedures.

11.5.5 Stopping Criteria for Further Study Participation

Subject participation will be terminated if any of the following events occur:

1. Stopping criteria for further methamphetamine infusion do not return to acceptable limits within appropriate time frames (e.g., 30 minutes);
2. Stopping criteria for further methamphetamine infusion are met for a second time within the protocol;
3. Systolic BP > 180 mm Hg sustained for 5 minutes or more;
4. Diastolic BP > 120 mm Hg sustained for 5 minutes or more;
5. Heart rate > (220 – age x 0.85) bpm sustained for 5 minutes or more.
6. A clinically significant ECG abnormality, such as:
    - ST segment elevations in two or more continuous leads of greater than 0.1 mV.
    - ST segment depression of greater than 1 mm that are flat or down-sloping at 80 msec after the J point.
    - New bundle branch block.
    - Mobitz II 2^0 or 3^0 heart block.
    - Atrial fibrillation or atrial flutter or activation of any tachyarrhythmia for greater than 10 seconds.
    - Three or more consecutive ectopic ventricular complexes at a rate of greater than 100 per minute.
7. Any condition that in the clinical judgment of the investigator is of sufficient magnitude to present a danger to the subject.

11.5.6 Aripiprazole Safety Concerns

The most commonly reported AEs associated with the use of aripiprazole with an incidence greater than placebo in short-term clinical trials were headache (32% *versus* 25% with placebo), anxiety (25% *versus* 24% with placebo), insomnia (24% *versus* 19% with placebo), somnolence (11% *versus* 8% with placebo) and orthostatic hypotension (1.9% *versus* 1% with placebo). Other, less common AEs associated with the use of aripiprazole include agitation, tremor, nausea, vomiting, dyspepsia and constipation.

Although the risk of induction of movement disorders (extrapyramidal symptoms, akathisia and tardive dyskinesia) by aripiprazole appears to be minimal, the SAS-EPS and Barnes Akathizia scales will be administered on day 1 (before cue procedure and first dose of study agent), on day 5, and on day 12 (in the morning before the second treatment methamphetamine infusion).

Subjects will not be allowed to take concomitant medications, whether prescription or over the counter (OTC), during the study without the approval by the site principal investigator/study physician.

11.5.7 Subjective Responses

During and after infusions, subject's subjective responses will be closely monitored. Computerized VAS will be administered 15 minutes before and 3, 6, 10, 15, 30, 45, 60, 90, 180, 210, 240, 300, 360, 420, and 480 minutes after each infusion.

11.5.8 Volunteer Discontinuation

Subjects will be excluded or discharged if their behavior is disruptive, non-compliant with study procedures, or otherwise not consistent with remaining in the hospital. Subjects will be excluded if urine toxicology indicates illicit use of illegal or legal drugs that are not allowed on this study during participation in this protocol, such as cocaine, marijuana or opiates.

11.5.9 Off-Unit Passes

Subjects will normally reside full-time in the clinic throughout their study participation. In extraordinary cases, subjects may be allowed a pass for the shortest period feasible at the site investigator's discretion. Subjects must agree to provide urine for toxicology upon return. Subjects will be excluded from the remainder of the study, if there is evidence that they used drugs during the off-unit period.

11.5.10 Subject Payment

Subject payment will be determined by the local IRB requirements at two sites, UCLA School of Medicine and New York University Veteran's Affairs Medical Center. A completion bonus is suggested to encourage subjects to complete the study and to remain for the full duration of safety monitoring follow-up. Subjects who drop out or are excluded after initiating the protocol will be paid on a prorated basis according to the number of days that they participated, but will not receive the completion bonus. Subjects will not receive the entire payment at once but in increments paid after discharge. These follow-up visits will permit monitoring of safety outcomes and provide therapeutic support that should reduce the likelihood of immediate relapse to methamphetamine abuse.

Compensation for New York University Study Site Participants. The costs for participating in this research include the loss of time and the inconvenience related to outpatient visits and a stay in an inpatient ward at Bellevue Hospital. Subjects will not be liable for any research related costs in terms of the necessary medical evaluations, stay at the hospital, and the testing procedures.

Subjects will receive $80 for each inpatient test day payable after they are discharged, plus a bonus of $30 for each inpatient test day if they complete the inpatient testing schedule through discharge.

Reimbursements for New York University Study Site Participants. Subjects will be paid for visits according to the following schedule:

	Payment	Frequency	Total
Outpatient screening visits	$25	2	$50
Inpatient stay (per day)	$80	36	$2,880
Bonus payment (per day) for completing inpatient phase	$30	36	$1,080
Outpatient follow-up visit	$25	2	$50
Total possible compensation			$4,060

*Subject must complete each visit and/or study phase to receive the compensation listed for that visit.

Subjects will receive the funds for outpatient screening visits as soon as they have completed all assessments. The remaining funds for the inpatient stay, follow-up visits, and bonus will not be paid at once, but in 3 separate increments beginning approximately one week after their discharge from Bellevue Hospital. Subjects who drop out, or are excluded, after starting the inpatient phase of the study will be paid on a prorated basis according to the number of days that they participated, but will not receive the completion bonus. Payments for the inpatient and follow-up phases of the study will be provided to subjects in the form of a check. Subjects will also receive referral for substance abuse treatment services.

12 CLINICAL AND LABORATORY EVALUATIONS

A table summarizing the timing of the clinical and laboratory assessments to be conducted over the entire study period is shown in Appendix I.

12.1 Screening

Screening evaluations will be performed initially before clinic intake with some assessments conducted after intake in the inpatient setting.

Screening Assessments before Intake: The following evaluations will be performed before clinic intake and must be conducted within 14 days prior to intake.

1. Informed consent;
2. Locator form;
3. Demographics information;
4. Timeline follow-back for methamphetamine use for prior 6 weeks;
5. Drug use and treatment history;
6. Physical exam and medical history;
7. Vital signs (BP and HR);
8. Hematology;
9. Blood chemistries;
10. Urinalysis;
11. Qualitative urine drug toxicology (this test will be repeated until a methamphetamine positive test is obtained within 14 days prior to intake);
12. 12-lead ECG and vital signs (HR and BP);
13. Pregnancy test for women of reproductive potential;

14. Adverse events.

Inpatient Screening Assessments: The following evaluations will be performed once, unless otherwise specified, following intake on study days -10 to -8 before the first methamphetamine infusion:

1. SCID for DSM-IV Axis I Disorders and methamphetamine abuse/dependence;
2. Family history of drug/alcohol abuse;
3. Qualitative urine drug toxicology (daily).
4. 12-lead ECG;
5. Pregnancy test for women of reproductive potential;
6. BDI, BSI, and POMS;
7. ADD interview;
8. HRBS;
9. ASI-Lite;
10. Adverse events (daily);
11. Timeline follow-back for methamphetamine use for the interval between first assessment and study start;
12. HIV test (optional);
13. Infectious disease panel and PPD test;
14. Concomitant medications.

Note: To ensure abstinence, qualitative testing for methamphetamine will be performed on days -10, -9 and -8 on subjects with urine test positive for methamphetamine upon hospital admission until urine is negative for methamphetamine

12.2 Evaluations Performed While Inpatient

1. Illicit drug use will be monitored once daily (8 a.m.), as documented by a daily qualitative urine test;
2. Vital signs (daily);
3. Adverse events (daily);
4. BSI, BDI, POMS will be conducted on day 10 (before the first treatment infusion) and at discharge;
5. BSCS will be conducted every other day.
6. Cue-induced arousal and craving for methamphetamine will be performed on day 1 and day 9.
7. SAS-EPS and Barnes Akathizia scales will be performed on days 1, 5 and 12.

12.3 Evaluations Performed During Infusion Sessions

Table 5 shows the series of activities that occur during methamphetamine infusion sessions. Refer to Table 4 for the timing of the infusion sessions according to the study day. All activities occur at each infusion session, unless otherwise noted.

Table 5. Methamphetamine Infusion Sessions Daily Schedule

Time-point	Activity (occurs at all sessions unless otherwise noted)
6:55 a.m.	Draw blood for trough aripiprazole assay (sessions #4-6)
7:00 a.m.	**Administer aripiprazole or placebo (sessions #4-6)**
8:00 a.m.	Urine Drug Toxicology
8:30 a.m.	Breakfast
9:15 a.m.	SAS-EPS and Barnes Akathizia scales (session #4)
The following should start at approximately 10:30 a.m.	
-30 min	Insert catheters (catheter for blood may already be in place)
-25 min	BP, HR
-15 min (10:45 a.m.)	**Start continuous telemetry of ECG and HR until 60 min after infusion; 12-lead ECG readings will be performed at the following time points: 15 minutes before and 15, 30, 45 and 60 minutes after infusion.** VAS, ARCI, BP, HR
- 5 min	Draw blood for peak aripiprazole assay (sessions #4-6) (Note: Timing of the blood collection should be 4 hours after aripiprazole administration) Draw blood for baseline methamphetamine assay (sessions #2, 3, 5 & 6)
Time 0 (11:00 a.m.)	**Inject methamphetamine or saline 2 min i.v. infusion**
3 min	VAS, BP, HR
5 min	Draw blood for methamphetamine assay (sessions #2, 3, 5 & 6)
6 min	VAS, BP, HR
9 min	BP, HR
10 min	VAS
12 min	BP, HR
15 min	VAS, BP, HR Draw blood for methamphetamine assay (sessions #2, 3, 5 & 6)
20 min	BP, HR
30 min	Draw blood for methamphetamine assay (sessions #2, 3, 5 & 6) VAS, ARCI, BP, HR
45 min	VAS, BP, HR
60 min	**Stop continuous telemetry of ECG and HR** VAS, BP, HR Draw blood for methamphetamine assay (sessions #2, 3, 5 & 6) BPRS
90 min	VAS, BP, HR Draw blood for methamphetamine assay (sessions #2, 3, 5 & 6)
120 min	Draw blood for methamphetamine assay (sessions #2, 3, 5 & 6) Draw blood for aripiprazole assay (sessions #4-6)
180 min	VAS, BP, HR
210 min	VAS, BP, HR
240 min	VAS, BP, HR Draw blood for methamphetamine assay (sessions #2, 3, 5 & 6)
300 min	VAS, BP, HR
360 min	VAS, BP, HR

Time-point	Activity (occurs at all sessions unless otherwise noted)
	Draw blood for methamphetamine assay (sessions #2, 3, 5 & 6)
420 min	VAS, BP, HR
480 min	VAS, BP, HR Draw blood for methamphetamine (sessions #2, 3, 5 & 6)
10 hr	BP, HR
12 hr	BP, HR Draw blood for methamphetamine assay (sessions #2, 3, 5 & 6)
20 hr	Draw blood for methamphetamine assay (sessions #2, 3, 5 & 6)
24 hr	Draw blood for methamphetamine assay (sessions #2, 3, 5 & 6)
36 hr	Draw blood for methamphetamine assay (sessions #2, 3, 5 & 6)
48 hr	Draw blood for methamphetamine assay (sessions #2, 3, 5 & 6)

Table 6. Schedule for Collection of Urine Specimens for Methamphetamine Elimination Pharmacokinetics

Sample #	Time Relative to Infusion
1	-2 to 0 hours
2	0 to 6 hours
3	6 to 12 hours
4	12 to 21 hours
5	21 to 24 hours
6	24 to 30 hours
7	30 to 36 hours
8	36 to 48 hours
9	48 to 54 hours
10	54 to 60 hours
11	60 to 72 hours
12	72 to 84 hours
13	84 to 96 hours

*Urine is collected for 48 hours after infusion sessions #2 and #5 and for 96 hours after infusion sessions #3 and #6.

12.4 Evaluations at Discharge and Follow-up

The subjects will be discharged from the hospital 4 days after the last doses of aripiprazole and methamphetamine. The following evaluations will be performed at time of discharge. The same evaluations will be performed in the case of early study discontinuation.

1. Vital signs;
2. Hematology;
3. Blood chemistries;
4. 12-lead ECG;
5. Qualitative urine drug toxicology;
6. BSI, BDI, POMS, BSCS;
7. AEs;

8. Pregnancy test for women of reproductive potential.

The following evaluations will be performed during the follow-up visits:

1. AEs (days 26 and 47);
2. Pregnancy test for women of reproductive potential (day 47).

Note: Some flexibility in the precise timing of follow-up visits is suggested with first follow-up visit to take place in the week following discharge and the second in the week 4 weeks after discharge.

12.5 Clinical and Laboratory Assessment Methods

12.5.1 Screening Assessments

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

12.5.1.1 Follow-up Locator Form

A locator form will be used to assist in finding participants at follow-up. This form asks participants to give consent for follow-up and to provide names, addresses, and phone numbers of several friends and family members. This information is essential and will be collected at enrollment, and will be updated throughout the study as necessary.

12.5.1.2 Addiction Severity Index (ASI)-Lite CF Version

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

12.5.1.3 Timeline Follow-back

Detailed histories of methamphetamine use over the past 6 weeks prior to screening will be obtained using the timeline follow-back method. The timeline follow-back method was described and validated by Sobell *et al.,* (1986) for reporting alcohol use. It has also been found to be a reliable method for assessing the history of psychoactive substance use in drug-abusing populations (Fals-Stewart *et al.,* 2000).

12.5.1.4 Structured Clinical Interview for the DSM-IV (SCID)

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

12.5.1.5 Attention Deficit Disorder (ADD) Interview

An interview from the DSM-IV criteria for childhood attention deficit hyperactivity disorder (ADHD) has been adapted to diagnose adult ADD. This interview assesses the subject's inattention, hyperactivity, and impulsivity both as the childhood history and as current adult behaviors. This interview will be conducted during screening.

12.5.1.6 HIV Risk-Taking Behavior Scale (HRBS)

The HRBS is a brief 11-item interviewer-administered scale (Darke *et al.,* 1991), to which 12th item ("Have you ever been diagnosed with AIDS?") was added by NIDA. It measures two distinct HIV risk factors in the behavior of intravenous drug users: one related to injecting behaviors and the other to sexual behaviors.

12.5.2 Medical Assessments

12.5.2.1 Physical Exam

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

12.5.2.2 Medical History

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

12.5.2.3 Vital Signs

Vital signs to be assessed during screening and discharge include oral temperature, sitting blood pressure, heart rate, and respiratory rate. In addition, vital signs will be taken daily after clinic intake.

12.5.3 Eligibility Checklist

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

12.5.4 Laboratory Tests

12.5.4.1 Hematology

Blood will be collected in anticoagulant containing vacutainer tubes for hematological assessments. Analysis of hemoglobin, hematocrit, mean corpuscular volume, white blood cell count, differential white blood cell count and platelets count will be performed. Analyses will be performed in the institutions clinical laboratory. The laboratory performing these assessments should be either directly regulated by the College of Pathologists (CAP) or the Clinical Laboratory Improvement Act of 1988 (CLIA) or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

12.5.4.2 Blood Chemistries

Blood will be collected in serum separation vacutainer tubes and serum separated according to standard procedures. Quantitative analysis will be performed for the following analytes: creatinine, blood urea nitrogen (BUN), glucose, creatinine phosphokinase (CPK), lactate dehyrodrogenase (LDH), electrolytes (Na, K, Cl, HCO_3), and liver function tests [total bilirubin, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), gamma-glutamyl transferase (GGT) and alkaline phosphatase]. The laboratory performing these assessments should 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.

12.5.4.3 Pregnancy Test

A urine-based pregnancy test designed to measure human chorionic gonadotropin will be used during outpatient screening, during inpatient screening, within 72 hours prior to the first dose of aripiprazole, at discharge and during final follow-up.

12.5.4.4 HIV Test

All subjects will be offered the opportunity to have an HIV test performed during inpatient screening. This test is not requisite for study participation. Subjects may be tested at the clinical site or may be referred to another clinic for testing and education on HIV risk-behaviors. If the test is to be performed by the clinical site, a separate HIV test informed consent must be obtained before collecting blood for this test.

12.5.4.5 Infectious Disease Panel and PPD Test

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 B surface antibody, Hepatitis B core antibody, and Hepatitis C virus antibody. A rapid plasma reagin test (RPR) for syphilis will be performed.

A purified protein derivative (PPD) skin test for tuberculosis will be performed and, if positive, a chest x-ray is required to assess active tuberculosis. If the subject reports that they have been previously positive for the PPD test, the PPD test will not be performed and only a chest x-ray will be required.

12.5.4.6 Urine Drug Toxicology

Qualitative analysis for urine toxicology will be performed daily (8 a.m.) starting at intake for the duration of the inpatient phase of the study. Urine toxicology for marijuana, opiates, cocaine, and methamphetamine will be monitored by a qualitative urine test that detects these substances. If the qualitative urine test indicates the presence of cocaine, THC or opiates, subjects will be disqualified. A quantitative test may be performed to monitor the level of methamphetamine, if there is any indication that the subject has used methamphetamine outside of infusion sessions. Quantitative tests for methamphetamine will not be performed routinely as the subjects are receiving methamphetamine as one of the investigational agents.

12.5.4.7 Medical Urinalysis

Urine will be collected and analyzed for specific gravity, pH, blood, protein, glucose, ketones, leukocytes, and nitrite at a local laboratory.

12.5.5 Methods for Assessment of Primary Outcome Measures

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

12.5.5.1 Adverse Events (AEs)

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

12.5.5.2 Cardiovascular Assessments

Before and after each i.v. infusion, the subject's physiologic response will be closely monitored using repeated HR, BP, and ECG readings. BP, HR, and ECG will be measured using a telemetry unit. BP and HR will be taken at -25 and -15 minutes before, and 3, 6, 9, 12, 15, 20, 30, 45, 60, 90, 180, 210, 240, 300, 360, 420, 480 minutes, and 10 and 12 hours following the methamphetamine/saline administration. Continuous telemetry of ECG and HR will start 15 minutes before and will be conducted until 60 minutes after each methamphetamine/saline infusion; 12-lead ECG readings will be performed at the following time points: 15 minutes before and 15, 30, 45 and 60 minutes after infusion.

12.5.6 Methods for Assessment of Secondary Outcome Measures

The secondary outcome measures include PK of aripiprazole, PK of methamphetamine and metabolite, craving for methamphetamine assessed using BSCS and cue-induced craving for methamphetamine procedure, psychometric and mood and personality tests including BSI, BDI, POMS, and VAS, and abuse liability of the study agent using ARCI.

12.5.6.1 Blood Sample Collections for Pharmacokinetic Determinations

A schedule of blood collections and volumes is provided in Appendix II including collection of samples for methamphetamine pharmacokinetics, aripiprazole blood levels, and hematology and blood chemistry assays. Blood samples collected for methamphetamine and aripiprazole pharmacokinetic analysis will be prepared and shipped according to the instructions in Appendix IV.

An intravenous catheter will be inserted for each infusion session, and maintained in place for the duration of the entire test, if the subject wishes. Two intravenous catheters will be placed for infusion sessions that involve repeated blood draws (days -7, -5, -3, 10, 12 and 15): one will be for methamphetamine or saline administration, the other for blood sample collection.

In order to limit the amount of blood drawn, samples will be collected during the 30 mg, but not the 15 mg methamphetamine infusion sessions. However, to maintain the study blind, mock blood draws will be conducted during the 15 mg methamphetamine or saline infusion sessions

(sessions: #1 and #4); mock blood draw is achieved by blocking the subject's view of the i.v. sampling line with a sheet, curtain or other material. Samples will be collected for assessment of methamphetamine pharmacokinetics on days -5, -3, 12 and 15 (sessions: #2, #3, #5 and #6) in 10 cc green-stoppered Vacutainer™ tubes. In order to assess aripiprazole pharmacokinetics, peak and trough levels, blood will be collected in heparin-containing green-stoppered Vacutainers™ on days 10, 12 and 15. Total blood loss during the study will be approximately 420 mL.

12.5.6.2 Urine Collections for Methamphetamine Elimination Pharmacokinetics

All of the urine output from each subject will be collected after methamphetamine infusion sessions #2, 3, 5, and 6 at the intervals shown in Table 6. Urine will be collected and pooled for each time interval and the total volume recorded. At the end of each time period the subject will be asked to void into collection bottles. Two 20 mL aliquots from each timed specimen will be frozen at -20ºC until analyzed. Note: To maintain the study blind, mock urine collections will be conducted during the 15 mg methamphetamine or saline infusion sessions (sessions: #1 and #4).

12.5.6.3 Subjective Responses (VAS and ARCI)

During and after the infusions, subject's subjective response to the methamphetamine will be closely monitored. Computerized VAS will be administered 15 minutes before, and 3, 6, 10, 15, 30, 45, 60, 90, 180, 210, 240, 300, 360, 420, and 480 minutes after each infusion. For the VAS scales, subjects will report the degree to which they feel "any drug effect", "high", "good effects", "bad effects", "like methamphetamine", "desire for methamphetamine", "depressed", "anxious", "stimulated", and "likely to use" on a continuous scale digitized between 0 to 100 for computing a score. In addition, they will be asked to answer the question: How much do you think this is worth in dollars?

An ARCI will be administered 15 minutes before and at 30 minutes after infusions. The ARCI consists of 49 statements in a true/false format.

12.5.6.4 Brief Substance Craving Scale (BSCS)

The BSCS is a self-administered assessment that asks the subject to rate his or her craving for methamphetamine. 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 to complete this questionnaire on an every other day basis, until the end of the study.

12.5.6.5 Beck Depression Inventory (BDI)

The BDI is a 22-item self-report inventory that focuses on the subject's subjective feelings of depression and is sensitive to changes in feeling status. This assessment will be conducted at baseline before first screening/baseline methamphetamine infusion and then on day 10 (before the first treatment infusion) and at discharge.

12.5.6.6 Brief Symptom Inventory (BSI)

The BSI is a 53-item self-report clinical rating scale used to assess psychological distress. This assessment will be conducted at baseline before first screening/baseline methamphetamine infusion and then on day 10 (before the first treatment infusion) and at discharge.

12.5.6.7 Profile of Mood States (POMS)

The POMS is a questionnaire that measures dimensions of affect or mood. It consists of 65 adjectives to which the client responds according to a 5-point scale ranging from "not at all" to "extremely". This assessment will be conducted at baseline before first screening/baseline methamphetamine infusion and then on day 10 (before the first treatment infusion) and at discharge.

12.5.6.8 Brief Psychiatric Rating Scale (BPRS)

The BPRS is a psychiatrist-administered interview that may be conducted either by remote video or in face-to-face format to evaluate the severity of subject's psychopathology, including anxiety, depression and symptoms of schizophrenia. The BPRS may be dichotomized into subjective items based on patients' verbal reports and objective items based on visual observation of patients' behavior. The BPRS total score ratings serve as indicators of psychiatric co-morbidity in drug-dependent subjects and as predictors of mental health services utilization. This assessment will be conducted 60-minutes after all methamphetamine/saline infusions, i.e. on days -7, -5, -3, 10, 12 and 15.

12.5.6.9 Cue-induction Procedure

The cue-reactive arousal and craving resulting from the presentation of environmental cues related to methamphetamine use will be tested at baseline (day 1, after SAS-EPS and Barnes Akathizia scales but before the first dose of study agent) and after treatment with aripiprazole (day 9). Subjective ratings of methamphetamine craving and euphoria will be assessed using standard VAS measures immediately before and after neutral and methamphetamine cue exposure. The neutral cues consist of pinecones, shells and rocks that are handled and inspected for 5 min followed by viewing a 10 min long audiovisual videotape of landscapes and items found in nature. The methamphetamine-related cues consist of methamphetamine paraphernalia including stems, lighter, and small plastic bags with white powder designed to simulate methamphetamine crystals that are handled and inspected for 5 min followed by viewing a 10 min long audiovisual videotape of actors using methamphetamine and methamphetamine paraphernalia. This procedure will determine "baseline" craving, craving associated with neutral cues and craving associated with environmental cues related to methamphetamine.

The cue procedures will start at 11:00 a.m. and end at approximately 1:00 p.m., beginning with neutral followed by methamphetamine cues, or methamphetamine followed by neutral cues (order is randomly selected on each test day) (Table 7). Each cue procedure starts with baseline VAS and BSCS assessments (-10 min) followed by 10 min of baseline BP and HR recording at 5 min intervals (-10 min, -5 min). Thereafter cues are presented; 5 min of cue viewing and handling followed by 10 min of video viewing. BP and HR are assessed during cue presentation in 5 min intervals (0, +5, +10, +15 min). Immediately after, and 10 min after, the cue procedures are completed VAS will be assessed (+15, +25 min). BP and HR are assessed for 15 min after

the cue procedures are completed in 5 min intervals (+20, +25, +30 min). There is a 20 min rest period between the neutral and methamphetamine cue sessions.

Table 7. Methamphetamine Cue Reactivity Test Schedule

Time-point	**Activity (occurs at both day 1 and day 9 unless otherwise noted)**
7:00 a.m.	**Administer aripiprazole or placebo (day 9)**
8:00 a.m.	Urine Drug Toxicology
8:30 a.m.	Breakfast
9:15 a.m.	SAS-EPS and Barnes Akathizia scales (day 1)
The following should start at approximately 10:45 a.m.	
-10 min	VAS, BSCS BP, HR
-5 min	BP, HR
Time 0 (11:00 a.m.)	**Cue presentation (neutral or methamphetamine): min 0-15**
0 min	BP, HR
5 min	BP, HR
10 min	BP, HR
15 min	BP, HR VAS
20 min	BP, HR
25 min	BP, HR VAS
30 min	BP, HR
30 – 50 min	**Subject is resting**
55 min	VAS, BSCS BP, HR
60 min	BP, HR
65 min (12:10 p.m.)	**Cue presentation (methamphetamine or neutral): min 65-80**
65 min	BP, HR
70 min	BP, HR
75 min	BP, HR
80 min	BP, HR VAS
85 min	BP, HR
90 min	BP, HR VAS
95 min (12:35 p.m.)	BP, HR

12.5.7 Simpson-Angus Scale for Extrapyramidal Symptoms (SAS-EPS)

The Simpson-Angus Scale is a clinician-rated, 10-item scale used to measure extrapyramidal symptoms (EPS), such as tremor, rigidity, eye blink and salivation, which can result from treatment with antipsychotic medication. The EPS items are rated from 0 to 4. The SAS-EPS will be administered on day 1 (before cue procedure and first dose of study agent), on day 5, and on day 12 (in the morning before the second treatment methamphetamine infusion).

12.5.8 Barnes Akathisia Scale

The Barnes Akathisia Scale is a clinician-rated 4-item scale used to measure motor restlessness, which can result from treatment with antipsychotic medication. It comprises of 3 items rated on a 0-3 scale for observable restless movements, the subjective awareness of restlessness, and any distress associated with restlessness. A global severity item rates the akathisia symptoms on a 0-5 scale. The Barnes Akathisia Scale will be administered on day 1 (before cue procedure and first dose of study agent), on day 5, and on day 12 (in the morning before the second treatment methamphetamine infusion).

12.5.9 Concomitant Medications

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

12.5.10 Discharge Form

The Discharge CRF will document all data relevant to subject discharge: reason for discharge, date of discharge and study day of discharge.

13 REGULATORY AND REPORTING REQUIREMENTS

13.1 Good Clinical Practices

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

13.2 FDA Form 1572

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

13.3 IRB Approval

Prior to initiating the study, the site investigator will obtain written Institutional Review Board (IRB) approval to conduct the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to the IRB by the investigator for IRB approval prior to implementation. In addition, IRBs will approve all advertising materials used for subject recruitment and any educational materials given to the subject. Annual reports and progress reports will be submitted to the IRB annually or at a frequency requested by the IRB.

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

study, its risks and benefits, to each subject and ensure that each subject understands the study prior to obtaining the subject's signature. A copy of the consent form will be given to the subject.

13.4 Informed Consent

All potential candidates for the study will be given a current copy of the Informed Consent Form to read. The investigator or other study physician will explain all aspects of the study in lay language and answer all of the candidate's questions regarding the study. If the candidate desires to participate in the study, s/he will be asked to sign the Informed Consent. No study procedure will be performed prior to signing Informed Consent. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

13.5 Risks and Benefit Assessment

The primary risks of this study are those of possible adverse reactions to the investigational agents, methamphetamine and aripiprazole. The procedures have been safely performed many times without significant adverse effects. The doses of methamphetamine used are modest, the safety screening and monitoring are careful, and there have been no significant prior adverse events with these procedures.

Aripiprazole (Abilify®) is approved by the FDA for the treatment of schizophrenia. Aripiprazole is a product with extensive level of clinical experience and little indication of significant risk. However, it is possible that the dopaminergic activities of methamphetamine and aripiprazole might be additive or greater when they are given together. The ascending order of methamphetamine doses (the 15 mg dose will always precede the 30 mg dose) during the treatment infusions is one protection against this risk. Although the risk of induction of movement disorders by aripiprazole appears to be minimal, the SAS-EPS and Barnes Akathizia scales will be administered on days 1, 5, and 12 to monitor the status of participants' motor system.

There is the risk of a breach of confidentiality regarding study records, but this is unlikely, since staff is well trained and experienced in this area.

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

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

13.6 Drug Accountability

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

13.7 Outside Monitoring

Data and Safety Monitoring Board: Safety data will be reviewed by a data and safety monitoring board that will meet quarterly during the first year of study recruitment. Additional meetings after that will be held on an *ad hoc* basis. The board will be blinded to subjects' actual treatment assignments for the safety data. Reports from the DSMB will be sent to the site investigator for transmission to the appropriate IRB, in accordance with NIH policy.

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

Clinical Monitors: All investigators will allow representatives of the sponsor to periodically audit, at mutually convenient times during and after the study, all source documents for each subject. The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that investigational agents are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by GCP guidelines are appropriately filed.

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

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

13.8 Adverse Events Reporting.

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the principal investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and Appendix V.

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

arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. All AEs must be recorded on the AE Form.

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

13.9 Serious Adverse Events

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

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

An unexpected event is one that is not described with respect to nature, severity, or frequency in the current Investigator's Brochure 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 Study Medical Monitor, the NIDA Project Officer, and the investigator-sponsor (IND holder) as follows:

NIDA Medical Monitor: Ahmed Elkashef, M.D., 301/443-5055

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

Investigator-Sponsor: Tom Newton, M.D., 310/267-0159

The telephone report is to be followed by submission of a completed SAE Form with demographic information and a narrative explanation of the event. Attached to the SAE Form should be photocopies of the AE Form, the Concomitant Medication Form, and the Medical History Form from the subject's CRFs. All serious medical events are also to be reported to the responsible IRB according to local regulatory requirements. All participating investigators will be notified of any serious and unexpected AE requiring submission to the FDA in an IND safety report from the sponsor.

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

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

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

14 ANALYTICAL PLAN

14.1 Outcome Measures

14.1.1 Primary Outcome Measures

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

14.1.2 Secondary Outcome Measures

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

1. PK parameters of methamphetamine and its metabolite including:

AUC_{0-4}	Area under the plasma concentration time-curve
C_{max}	Maximum observed concentration
T_{max}	Time for maximum concentration
k_e	Elimination rate constant (if data permit)
$t_{1/2}$	Elimination half-life (0.693/(z))
CL/F	Clearance of the study agent determined by the formula CL=Dose/AUC_{0-4} (if data permit)
V_d/F	Volume of distribution (if data permit)

2. PK of aripiprazole (peak and trough)
3. Craving for methamphetamine, assessed using BSCS and cue-induced craving procedure
4. Mood and personality assessments (BSI, BDI, and POMS)
5. Psychometric measure (VAS)
6. Abuse liability of aripiprazole using ARCI

14.2 Analysis Plan

14.2.1 Primary Outcome Measures

Baseline (pre-methamphetamine) resting HR and BP measures will be compared to HR and BP after each methamphetamine infusion (15 mg and 30 mg doses). Maximal changes (from baseline) in HR and BP, induced by methamphetamine infusion with aripiprazole, will be compared to those with placebo, by methamphetamine dose level (15 mg and 30 mg doses), using ANOVA in a between-subjects analysis. Changes in ECG parameters will be reported as summary statistics. Adverse events data will be compiled and presented as summary statistics.

14.2.2 Secondary Outcome Measures

Plasma concentration-time profiles of methamphetamine after each methamphetamine infusion will be analyzed to obtain pharmacokinetic parameter estimates of methamphetamine (C_{max}, T_{max}, $AUC_{0\text{-}4}$, apparent $t_{½}$, CL/F, V_d/F, and k_e) by individual and means computed by group. Urine elimination pharmacokinetic parameters will also be computed using plasma data in combination with urine data to calculate renal clearance. Blood and urine will be collected according to the following schedule:

Blood collection time points: 5 minutes prior to infusion and 5, 15, 30, 60, 90 minutes and 2, 4, 6, 8, 12, 20, 24, 36, and 48 hours after infusion.

Urine collection time points: -2 to 0 hours prior to infusion and 0 to 6, 6 to 12, 12 to 21, 21 to 24, 24 to 30, 30 to 36, 36 to 48 after infusions #2 and #5; -2 to 0 hours prior to infusion and 0 to 6, 6 to 12, 12 to 21, 21 to 24, 24 to 30, 30 to 36, 36 to 48, 48 to 54, 54 to 60, 60 to 72, 72 to 84, and 84 to 96 hours after infusions #3 and #6.

Comparisons of PK estimates of methamphetamine between the placebo and aripiprazole arms will be performed for the 30 mg dose of methamphetamine using ANOVA. Pharmacokinetic parameters within subjects will be also compared using data collected during the screening/baseline 30 mg methamphetamine infusions as compared to those collected during treatment 30 mg methamphetamine infusions. Confidence intervals (90%) for each parameter will be determined.

Pharmacokinetic (peak and trough plasma levels) of aripiprazole and metabolites will be compared between the saline, 15 mg and 30 mg doses of methamphetamine using repeated measures ANOVA.

Psychometric outcome measures (including VAS) obtained in the control phase will be compared, by methamphetamine dose level, to those in the aripiprazole phase to determine the

extent to which these measures are modified by the administration of aripiprazole using repeated measures ANOVA.

Changes in BSCS, BSI, BDI, and POMS scores will be compared before and after aripiprazole administration using repeated measures ANOVA.

Population demographics will be compiled for both treatment arms and presented in tabular form. The results of SAS-EPS and Barnes Akathizia assessments will be reported in the summary safety tables at the end of the study.

14.3 Sample Size

No formal sample size analysis was performed. The number of subjects (8 will receive aripiprazole and 8 will receive placebo) is hypothesized to provide an indication of the safety and potential interactions between aripiprazole and methamphetamine. The evaluable subject population is defined as the subjects who have completed study procedures up to midnight of study day 15.

14.4 Control of Bias/Randomization

Subjects will be randomized into one of the two treatment arms (aripiprazole or placebo) and with the order of administration of the saline, 15 mg methamphetamine and 30 mg methamphetamine infusions; 15 mg methamphetamine infusions will always precede 30 mg methamphetamine infusions. The sequence of the cues for methamphetamine cue-reactivity test, i.e. neutral cue followed by methamphetamine-related cue or vice versa, will be also randomly assigned.

15 DATA MANAGEMENT AND CASE REPORT FORMS

15.1 Data Collection

Data will be collected at the study sites on source documents that will be entered at the site onto case report forms (CRFs). The CRFs will be supplied by the data coordinating center (Technical Resources International, Inc.). CRFs 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. CRFs should be completed according to the instructions in the study operations manual. The principal investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. The principal investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

15.2 Data Editing and Control

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

Participating investigators agree to routine data audits by the sponsor's designated staff. Monitors will routinely visit the site to assure that data submitted on the appropriate forms are in agreement with source documents. They will also verify that study agents have been properly stored and accounted for, subject informed consent for study participation has been obtained and documented, all essential documents required by GCP regulations are on file, and the site is conducting the study according to the research protocol. Any inconsistencies will be resolved, and any changes to the data forms will be made using the established procedures specified in the Study Operations Manual.

15.3 Data Entry, Processing, and Analyses

Data will be collected at the study sites on source documents that will be entered into CRFs. When the study is completed and all data have been entered into the clinical database and the database has been checked by Quality Assurance and is locked, statistical analysis of the data will be performed by the data coordinating center's statisticians in accordance with the analytical plan section of this protocol.

15.4 Study Documentation and Records Retention

Study documentation includes all 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 IRB correspondence and approved consent form and signed subject consent forms, Statement of Investigator (FDA Form 1572), and clinical supplies receipt and distribution records).

Source documents include <u>all</u> 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 new Drug Application (NDA).

15.5 Confidentiality

15.5.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that proprietary

information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

15.5.2 Confidentiality of Patient Records

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

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

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

16 PUBLICATIONS OF THE STUDY RESULTS

A publication committee will be formed and comprised of representatives from NIDA and principal investigators to review and approve all documents to be submitted for publication.

NIDA and the investigative group agree that the study database will be made available to individual investigators to encourage other publications, either by a group or by an individual investigator provided that: manuscripts based on the use of aripiprazole for the treatment for methamphetamine dependence may not be submitted for publication until the main findings of the study have been published and this study has been accepted by the FDA for filing to the IND or NDA.

17 SIGNATURES

NIDA REPRESENTATIVES

Typed Name	Signature	Date
Jurij Mojsiak, M.S. Project Manager	_____	_____
Ahmed Elkashef, M.D. NIDA Investigator	_____	_____
Nora Chiang, Ph.D. NIDA Investigator	_____	_____
Ann Anderson, M.D. Medical Monitor	_____	_____

INVESTIGATOR (S)

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in section 13.8 of this protocol.

Typed Name	Signature	Date
Tom Newton, M.D. Lead Investigator	_____	_____
Malcolm S. Reid, Ph.D. Principal Investigator	_____	_____

18 LITERATURE CITED

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Appendix I: Time and Events Schedule

Study Phase	**Pre-intake Screening**	**Intake Screening**	**Screening/ Baseline Infusions**					**Treatment Infusions**			**Discharge**	**Follow-up***	
Study day	**-24 to -11**	**-10 to -8**	**-7**	**-5**	**-3**		**1-9**	**10**	**12**	**15**	**19**	**26**	**47**
Informed consent	X												
Locator form/Demographics	X												
Methamphetamine use by timeline follow back	X	X											
12-lead ECG	X	X									X		
SCID		X											
Medical History/Physical Exam	X												
ASI-Lite, HRBS, ADD		X											
Vital Signs	X	X	X	X	X		X	X	X	X	X		
Blood chemistries	X										X		
Hematology	X										X		
Urinalysis	X												
Pregnancy Test	X[a]	X									X		X
HIV Test (optional)		X											
Infectious disease panel		X											
Urine Toxicology Screen	X[b]	X	X	X	X		X	X	X	X	X		
BSI, BDI, POMS		X[c]					X[c]				X[c]		
BSCS		X[d]									X		
Cue-induction procedure							X[f]						
Aripiprazole or placebo administration							X[e]	X	X	X			
Adverse Events	X	X	X	X	X		X	X	X	X	X	X	X
SAS-EPS and Akathizia scales							X[g]						
Concomitant medications		X	X	X	X		X	X	X	X			
Methamphetamine session #			**1**	**2**	**3**			**4**	**5**	**6**			
Saline or 15 mg methamphetamine i.v.			X					X					
Saline or 15 mg or 30 methamphetamine i.v.				X					X				
Saline or 30 mg methamphetamine i.v.					X					X			
VAS			X	X	X			X	X	X			
Continuous BP, HR, ECG monitoring			X	X	X			X	X	X			
ARCI, BPRS			X	X	X			X	X	X			
Methamphetamine Urine PK				X[h]	X				X	X			
Methamphetamine Blood PK				X[h]	X				X	X			

Randomization

*Note: Some flexibility in the precise timing of follow-up visits is suggested with first follow-up visit to take place in the week following discharge and the second in the week 4 weeks after discharge.

X^a - pregnancy test will be performed during outpatient screening, during inpatient screening, within 72 hours prior to the first dose of aripiprazole, at discharge and during final follow-up.
X^b - urine is collected during pre-intake screening visit for a qualitative drug screen and, if tested positive, will be analyzed for methamphetamine levels quantitatively.
X^c - BSI, BDI and POMS will be administered before the first screening/baseline methamphetamine infusion, on day 10 (before first treatment methamphetamine infusion) and at discharge.
X^d - BSCS will be administered every other day after intake and at discharge.
X^e - 15 mg aripiprazole will be administered once a day on days 1 thru 15.
X^f **-** cue-induction procedure will be conducted on days 1 and 9.
X^g - SAS-EPS and Barnes Akathizia Scales will be administered on day 1 (before cue procedure and first dose of study agent), on day 5, and on day 12 (in the morning before the second treatment methamphetamine infusion).
X^h - blood methamphetamine PK analysis times are specified in Table 5 and Appendix II; urine methamphetamine PK analysis times are specified in Table 6.

APPENDIX II: Schedule of Blood Collections

Analysis	**Volume per Sample**[a]	**7-8 a.m.**	**Minutes Relative to Methamphetamine Infusion**								**Hours Relative to Methamphetamine Infusion**							**Total Volume**
			-5	5	15	30	60	90	120	240	6	8	12	20	24	36	48	
Days -8, 14, 19																		
Hematology	10 mL	X																30 mL
Blood Chemistry	10 mL	X																30 mL
Day -8																		
Infectious Diseases	10 mL																	10 mL
Days 10, 12, 15																		
Aripiprazole Blood Level	5 mL	X	X						X									45 mL
Days -5, -3, 12, 15																		
Methamphetamine PK	5 mL		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	300 mL
Anytime on Days -10 to -8																		
HIV Test (optional)	5 mL																	5 mL
Total Volume of Blood Collected																		**420 mL**

[a]Samples are plasma with the exception of blood chemistry, which is serum, and hematology, which is whole blood with anticoagulant.

APPENDIX III: Standard Operating Procedure for the Detection and Treatment of Cardiac Emergencies

CARDIAC MONITORING:

A: Equipment - Medications

1) Equipment availability - the Infusion Unit shall have available one resuscitation bag, suction apparatus, two oxygen outlets, one compressed air outlets, humidifiers, heated nebulizers and one bedside monitor for ECG, Respiratory efforts, Blood Pressure (by Finger Plethysmography or FinaPress), and pulse oximetry.

2) In addition, the Unit will have an intubation tray and crash cart with ECG, defibrillator and pacemaker.

3) Medications will be located in the locked medication cabinets and crash cart.

4) Procurement of equipment and medications will be handled by the nurse through Research Pharmacy Service, Bio Medical Engineering, SPD (crash cart) and Respiratory Therapy.

5) The integrity of the emergency drug system will be maintained by the Nursing Staff every 24 hours. In addition, Pharmacy Service will check expiration dates on all medications in the Unit on a monthly basis.

B: Safety and Maintenance

1) General safety rules throughout the hospital shall apply in the Unit.

2) Electrical preventive maintenance and safety program and medical equipment maintenance will be conducted according to the Hospital Acute Care Unit Policy and Procedure Manual.

CRITERIA FOR INTERVENTION AND METHODS

(i) Change in Heart Rhythm

1) Ventricular Fibrillation
   a) Recognition: Clinical cardiac arrest with ventricular fibrillation on ECG and absence of carotid pulse.
   b) Procedure: stop study drug/methamphetamine infusion.

   1) If arrest witnessed, apply a precordial thump then check pulse and ECG rhythm.
   2) If no pulse, begin CPR.
   3) Defibrillate (unsynchronized) at 200 joules and check pulse and ECG rhythm. If no change, repeat defibrillation at 300 joules. Check pulse rhythm. If still no change, defibrillate at 360 joules. Check pulse and rhythm.
   4) If above not successful in generating pulse, continue CPR
   5) Give Epinephrine 1 mg I.V. push.
   6) Repeat defibrillation at 360 joules. Check pulse and rhythm.
   7) Give Lidocaine 1 mg/kg I.V. push.

8) Draw arterial blood gases.

2) Sustained Ventricular Tachycardia

a) Recognition:

1) Ventricular tachycardia on ECG associated with stable B/P > 90/60 = Stable V-tach
2) Ventricular tachycardia on ECG associated with a fall in B/P < 90/60, change in mental status, chest pain, or CHF = unstable V-tach.

b) Procedure: stop study drug/ methamphetamine infusion.

For Stable Ventricular Tachycardia*:
1) Apply oxygen at 100%
2) Apply synchronized cardioversion, start with 50 joules (J). If no response go to 100 J, if still no response go to 200 J.
3) Give Lidocaine 1 mg/kg I.V. bolus, followed by Lidocaine drip 2 mg/min

*if patient pulseless treat as ventricular fibrillation.

To effectively deliver a synchronized or synchronous electrical current to the myocardium to terminate lethal arrhythmias using R2 Cath-Pads.

EQUIPMENT AND SUPPLIES

1. LifePak 4
2. R2 Cath-Pads
3. R2 cable adapter

PROCEDURE:

ACTION	**RATIONALE**
A. Expose patient's upper torso	
B. Clean and dry skin sites, preferably with a coarse, dry towel. Shave as needed--remove lotions with alcohol and let dry.	
C. Apply R2 Cath-Pads Tm	
1. Remove pads from package and pull apart lead wires to desired length.	
2. Remove protective cover to expose gel and adhesive area. DO NOT use if gel area is dry.	2. Store R2 pads flat in a cool dry place.

3. Apply large posterior pad just below scapula and the smaller anterior pad over the cardiac apex with the flat edge of half circle toward head. To apply pad, adhere one edge of the pad, then tightly roll pad into place, pressing over adhesive area only.	3. For countershock to be effective the current between two electrodes must depolarize a critical mass of the myocardium. The blue half circle on the apex pad is an area of radio opacity.
D. Plug pad connector into the R2 cable Adapter attached to the Life Pak 4.	D. Check 4 prong connector of patient cable before use. Do not use if damaged.
E. Turn Life Pak 4 on and set ordered parameters, i.e., synchronized or unsynchronized cardioversion and energy level.	
F. Depress charge button on Life Pak 4 after desired energy lever is selected.	F. Charge switch allows capacitor to charge.
G. To deliver countershock, depress 4 red buttons on R2 cable simultaneously.	G. Prior to delivery of countershock ensure that all personnel are CLEAR of the patient area.
H. Document the following on the code arrest form and progress notes: 1. Time of countershock 2. Watt/sec (joules) used in each attempt 3. Effect-include ECG rhythm strip, BP/P 4. Complications, if any	
I. Remove pads by peeling back parallel to the patient's skin.	I. Do not remove pads by pulling directly away from skin as bruising may result.

3) Ventricular Extrasystoles

a) Recognition: Ventricular extrasystoles, single or multiple, unifocal or multifocal

b) Procedure: Discontinue study drug/ methamphetamine infusion if frequent or repeated (three or more in 1 minute). If extrasystoles remain frequent or repeated, give lidocaine 100 mg IV followed by infusion of 2 mg/min.

4) Bradycardia-Severe

a) Recognition: Pulse rate and ventricular rate under 40 associated with fall in B/P below 90/60, change in mental status, chest pain, or dyspnea.

b) Procedure: stop study drug/ methamphetamine infusion. Give Atropine 1 mg I.V. push and obtain ECG rhythm strip.

5) Ventricular Asystole

a) Recognition: Clinical cardiac arrest by ECG in two leads and absence of carotid pulse.

b) Procedure: stop study drug/ methamphetamine infusion.

1) Begin cardiopulmonary resuscitation (CPR)
2) Give Epinephrine 1 mg I.V. push.
3) Continue resuscitation until effective heart action returns.
4) Draw arterial blood gases.

6) Sinus Tachycardia

a) Recognition: From continuous pulse monitoring, pulse elevated over 160 BPM.

b) Procedure: immediately stop study drug/ methamphetamine infusion, monitor rate. If patient symptomatic or if rate does not lower below 160 after 1 minute, treat as hypertensive crisis, below.

(ii) Hypertensive Crises--

a) Recognition: From continuous blood pressure monitoring by FinaPress: elevated BP levels (Diastolic > 120, Systolic > 180) or elevated BP associated with encephalopathy, acute aortic dissection, acute left ventricular failure, stroke or myocardial ischemia will be deemed hypertensive emergencies. These parameters were selected based on the clinical experience of Dr. Williams and are also those used by Dr. Tom Kosten.

b) Procedure: Stop study drug/ methamphetamine infusion. Give Lorazepam 2 mg I.V. Push followed by reduction of BP with combined alpha and beta adrenergic receptor antagonist, labetolol, 20 mg IV over 5 minutes with repeat infusions every 20 minutes if necessary. Subsequent doses should be calculated on the basis of the diastolic response.

(iii) Seizures

a) Recognition: Tonic or clonic seizure activity observed by staff

b) Procedure: Stop study drug/ methamphetamine infusion. Since, benzodiazepines rapidly enter the brain and control seizures give: Diazepam 10-15 mg IV at 4 mg/Min or Lorazepam 2 mg at 5 min intervals to 10 mg. If seizures persist establish an airway and maintain adequate oxygenation.

(iv) Chest Pain

a) Recognition: By complaint
b) Procedure: Discontinue study drug/ methamphetamine infusion. Note heart rate and blood pressure and treat with Labetolol if significantly elevated (parameters above). Give sublingual nitroglycerine 0.4 mg and Lorazepam 2 mg IVPush and review 12 lead ECG for evidence of myocardial ischemia. If chest pain persists give Phentolamine 1 mg IV or Verapamil 5 mg IV over 3 minutes.

(v) Hypotension

a) Recognition: Drop in blood pressure to below 90/50 or subjective complaints of dizziness or fatigue associated with drop in blood pressure from baseline.
b) Procedure: Discontinue study drug/ methamphetamine infusion. Maintain patient in supine position. If symptoms and signs continue, give normal saline bolus of 500 cc over 20 minutes, I.V.

APPENDIX IV: Procedure for Collection, Storage, and Shipping of Blood Samples for Methamphetamine/Methamphetamine Metabolite Levels and Aripiprazole/Aripiprazole Metabolite Levels

Blood Drawing Procedure:

Blood drawn from all patients should be considered infectious and extreme caution should be used to avoid needle sticks and direct contact with blood or plasma. The same procedures are used for samples collected for aripiprazole and methamphetamine analyses. Sample labels must differentiate the drug for which analysis is required and samples should be stored and shipped together (separate outer bags) based upon drug for analysis.

Using 5 cc green-stoppered Vacutainer (heparinized) tubes:

(1) draw one tube of blood, filling it as completely as possible;
(2) invert 8-10 times;
(3) centrifuge the blood (3,000 x g for 15 min.) immediately to prevent hemolysis;
(4) using a disposable pipet, immediately transfer the plasma from the tubes to a single plastic plasma storage vial, and secure the cap tightly;
(5) label the vial as described below, and;
(6) freeze sample at -20 degrees C immediately afterwards in an upright position. Keep frozen until shipment.

Labeling Procedure:

Fill out a shipping/specimen inventory form. Use labels to label tubes. Use indelible black ink to write on labels. The label should include:

(1) the clinic's identification or name,
(2) patient identification, and
(3) date and time of collection.
(4) drug for analysis

After affixing the label to the vial, cover it with transparent tape. A record (shipping/specimen inventory form) containing the same information on the plasma samples shall be generated.

Shipping: Remember to only ship on Monday through Wednesday. When ready to ship:

(1) line the cooler with an open plastic bag (12 gallon waste-container size);
(2) place approximately 10 pounds of dry ice (roughly two slabs) in an Igloo ice chest, place the ice in the bottom, and compress with a hammer (Caution: do not touch dry ice with your bare hands);
(3) cover the dry ice with a layer of newspaper (2-3 sheets folded);

(4) put each vial of plasma into a ziplock bag, each of which should contain an absorbent pack;
(5) place the plasma vials in the Igloo ice chest;
(6) then fill the remaining space with crumpled newspaper;
(7) close the chest and place it into the outer cardboard container;
(8) place completed sample I.D. list in envelope and include in cardboard container;
(9) ship to the University of Utah; and
(10) notify personel (Ms. Bobbie Smith or Dr. David Moody) at the Center for Human Toxicology, University of Utah (801) 581-5117 when samples are shipped.

Shipping Address:

Attn: Bobbie Smith
Center for Human Toxicology
20 S 2030 E, Rm. 490
University of Utah
Salt Lake City, UT 84112

Supplies Needed:

- Outer shipping container (Igloo cooler works well)
- Cardboard box to place cooler into
- 5 cc heparinized blood drawing tubes (Venoject or compatable)
- Disposable transfer pipettes
- 5-9 cc plastic vial to store plasma in
- Adhesive labels for vials
- Ziplock bag with absorbent pad for each vial
- Newspaper and dry ice (day of shipping)

APPENDIX V: 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 informed consent.

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

3. Report the relatedness of the event to the study agent administration according to the guidance in section C.

B. DEFINITIONS – SEVERITY OF EVENTS

Mild: Awareness of symptom, but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity.

Severe: Incapacitating with inability to work or do usual activity.

C. DEFINITIONS – RELATEDNESS OF EVENTS

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

- ***Exposure:*** Is there evidence that the subject was actually exposed to the drug/placebo?

- ***Timing of the study drug/placebo:*** Did the AE/SAE follow in a reasonable temporal sequence from administration of the drug test?

- ***Consistency with study drug profile:*** Known pharmacology and toxicology of the study drug in animals and man; reaction of similar nature having been previously described with the study drug.

- ***Alternative explanations*** for the adverse event such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding findings.

- ***Response to discontinuation*** of the study drug/placebo.

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

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

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

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

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

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

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

D. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

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

All laboratory AEs should be specified as an increased or decreased test result (e.g. “increased glucose”, “decreased potassium”) or as a term that implies an abnormality (e.g., hypocalcaemia, azotemia).

E. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24 hour Reporting Requirements

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

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

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

3-day Supporting Documentation Requirements

Written documentation for all SAEs/unexpected AEs must be received by the 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 NIDA Medical Monitor/Alternate

Follow-Up of All Adverse Events/Serious Adverse Events

All adverse medical events must be followed until they are resolved, or until all attempts to determine the resolution of the AE/SAE are exhausted. This may require an extended inpatient period or a change in status from outpatient to inpatient. All treatments, outcomes and information regarding whether or not the subject was referred to their Primary Care Provider for additional follow-up must be recorded in the source document. All serious and unexpected

adverse events occurring 30 days after administration of the last dose of study drug/placebo must be reported.

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

Reporting to the FDA

The Principal Investigator, who is the IND sponsor, is required to report SAEs to the FDA:

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

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

- in an annual report in all other cases.

APPENDIX VI: Procedure for Applying for a Certificate of Confidentiality

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

- if necessary to protect subjects' rights or welfare, or
- if required by law.

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

Applying for a Certificate of Confidentiality

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

Investigators will obtain a certificate to avoid being required to involuntarily disclose personally identifiable research information about individual study subjects. Under this statute:

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

Accordingly, this special privacy protection can be granted only to research (i.e., a systematic

investigation, designed to develop or contribute to generalizable knowledge). It is granted only when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives.

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

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

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

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

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

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

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

or

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

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

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

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