

OPERATIONAL PROTOCOL

Randomized Trial of Ibudilast for Methamphetamine Dependence

(R01 DA035054)

IND 108,996 (Steven Shoptaw PhD, Sponsor)

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Protocol Summary/Aims

Despite numerous clinical trials (Elkashef, Vocci et al. 2008), no medication has been approved to treat methamphetamine (MA) dependence. Public health problems due to MA dependence include HIV infection: HIV prevalence among men who have sex with men (MSM) approaches 20% in California (Shoptaw and Reback 2007). Among MSM, incidence of HIV among MA-users is significantly higher than for MSM who do not use MA (Buchacz, McFarland et al. 2005, Plankey, Ostrow et al. 2007) and MA accounts for between 28% and 33% of new HIV infections in MSM (Koblin, Husnik et al. 2006, Ostrow, Plankey et al. 2009). MA use is associated with neurocognitive deficits especially with HIV infection (Scott, Woods et al. 2007), poor antiretroviral adherence, and worse HIV treatment outcomes (Rajasingham, Mimiaga et al. 2012). Therefore, development of effective medications for MA dependence, especially among HIV infected populations, is a public health priority.

Ibudilast (IBUD) is a macrophage migration inhibitory factor (MIF) and phosphodiesterase (PDE)-4 and -10 inhibitor at peak clinical exposures (Rolan, Hutchinson et al. 2009) that increases glial cell line-derived neurotrophic factor (GDNF) expression (Mizuno, Kurotani et al. 2004) and reduces microglial activation (Suzumura, Ito et al. 1999, Suzumura, Ito et al. 2003), including HIV-induced glial activation (Kieba and Maggirwar 2011). IBUD significantly reduces MA prime- and stress-induced reinstatement of MA seeking in rats (Beardsley, Shelton et al. 2010) and has multiple effects that may make it an effective treatment for MA dependence including amelioration of dopaminergic and neuroinflammatory dysfunction. Multiple studies implicate glial cells in a variety of neurodegenerative diseases (Hirsch and Hunot 2009, Sidoryk-Wegrzynowicz, Wegrzynowicz et al. 2011) including MA dependence and HIV infection (Nath 2010). Activated glial cells secrete pro-inflammatory mediators (Minghetti, Ajmone-Cat et al. 2005) that may exacerbate MA-induced dopaminergic dysfunction. Glial cells also produce neurotrophic factors, including GDNF, which may ameliorate dopaminergic dysfunction (Pascual, Hidalgo-Figueroa et al. 2008). Thus, IBUD may be an effective medication for MA dependence due to its modulation of glial cell activation resulting in amelioration of dopaminergic and neurocognitive dysfunction and improved treatment outcomes in MA dependence. IBUD may also have unique effects in HIV positive MA users as it may additionally block the degradation of neuronal integrity seen in HIV infection (Chana, Everall et al. 2006, Dash, Gorantla et al. 2011).

The proposed study will complete a phase 2 clinical trial to determine the safety and efficacy of IBUD for the treatment of MA dependence. Treatment-seeking MA dependent volunteers (N = 140) will be randomly assigned to IBUD (50 mg BID; N=70) or placebo (BID; N=70), with twice-weekly clinic visits for counseling, urine drug screens, and safety/medication adherence monitoring, for 12 weeks. The study is powered to detect a statistically significant benefit of IBUD over placebo on the primary study outcome: MA abstinence during the final two weeks of treatment (FDA-preferred efficacy outcome). The study will address the following specific aims among 140 MA dependent participants:

Aim 1: To determine whether IBUD reduces MA use more than placebo among MA dependent participants.

Aim 2: To determine whether IBUD results in longer treatment retention than placebo among MA dependent participants.

As ibudilast has putative mechanisms that would have additional benefit in patients with HIV, we will enroll up to 70 HIV positive (as determined by baseline HIV serology and HIV RNA), MA dependent participants in order to address the following exploratory **HIV-specific Aims**:

Aim 3: To determine whether IBUD improves biological (CD4 count; HIV RNA) and neurocognitive outcomes more than placebo among HIV-positive MA dependent participants.

Aim 4: To determine whether IBUD improves behavioral outcomes (sexual transmission behaviors; uptake and/or adherence to HIV medications) relative to placebo among HIV-positive MA dependent participants.

Secondary analyses will examine treatment outcomes and: (1) medication non-adherence, (2) adverse event rates, (3) MA abstinence during a two week lead-in period, a predictor of outcomes in stimulant trials (Bisaga, Aharonovich et al. 2010), (4) polymorphisms in dopaminergic genes and GDNF (Yoshimura, Usui et al. 2011) and (5) plasma and serum levels of inflammatory and neurotrophic markers. IBUD was well tolerated with no serious adverse events in a phase I study of IBUD in MA dependent individuals (clinicaltrials.gov: NCT01217970). These studies are the result of a long-standing collaboration between our research group and MediciNova, Inc. who are fully committed to seeing IBUD

through the regulatory and marketing process for MA dependence. The study has high public health relevance as an effective medication would improve health outcomes and reduce public health harms in MA dependent patients, especially those with HIV infection.

Background

Despite numerous clinical trials (Elkashef, Vocci et al. 2008), no medication has been approved to treat methamphetamine (MA) dependence, although bupropion, a dopamine/norepinephrine re-uptake inhibitor, shows preliminary efficacy in a subgroup with lower pre-treatment frequency of MA use (Elkashef, Rawson et al. 2008, Shoptaw, Heinzerling et al. 2008). Behavioral therapies including contingency management (CM) are effective for MA dependence but response is variable (Roll, Petry et al. 2006, Lee and Rawson 2008, Dean, London et al. 2009). The past decade of research has highlighted the neurotoxic effects of MA, especially for dopaminergic systems in the ventral striatum (Krasnova and Cadet 2009, Lee, London et al. 2009), as well as the clinical consequences of MA-induced neurotoxicity including neurocognitive dysfunction (Scott, Woods et al. 2007) and poor response to behavioral therapies (Wang, Smith et al. 2011). As a result, medications that ameliorate MA-induced neurotoxicity may improve clinical outcomes in MA dependence.

Of the public health problems due to MA dependence, HIV infection is one of the most serious. HIV prevalence among men who have sex with men (MSM) approaches 20% in California (Shoptaw and Reback 2007). Among MSM, incidence of HIV among MA-users is significantly higher than for MSM who do not use MA (Buchacz, McFarland et al. 2005, Plankey, Ostrow et al. 2007) and MA accounts for between 28% and 33% of new HIV infections in MSM (Koblin, Husnik et al. 2006, Ostrow, Plankey et al. 2009). HIV is associated with deficits in neurocognitive functioning (Heaton, Clifford et al. 2010) which are compounded with co-occurring MA use (Rippeth, Heaton et al. 2004, Jernigan, Gamst et al. 2005, Letendre, Cherner et al. 2005, Carey, Woods et al. 2006), and among HIV positive patients, MA use is associated with poor antiretroviral adherence and worse HIV treatment outcomes (Rajasingham, Mimiaga et al. 2012). Therefore, testing of medications for MA dependence among HIV infected populations is a public health priority.

Multiple studies implicate neuroinflammatory processes in the pathophysiology of a variety of neuropsychiatric conditions (Hirsch and Hunot 2009, Sidoryk-Wegrzynowicz, Wegrzynowicz et al. 2011), including MA dependence. Activated glial cells play a central role in neuroinflammation via the secretion of multiple pro-inflammatory mediators (Minghetti, Ajmone-Cat et al. 2005) that may exacerbate MA-induced neurodysfunction. For example, preclinical studies have shown that MA activates microglia and blocking MA-induced glial activation results in attenuated subsequent MA-induced neurodegeneration (Ladenheim, Krasnova et al. 2000; Flora, Lee et al. 2002; Thomas and Kuhn 2005; Fantegrossi, Ciullo et al. 2008; Narita, Suzuki et al. 2008; Thomas, Francescutti-Verbeem et al. 2008). Importantly, MA-induced microglial activation precedes the development of pathological changes in striatal dopamine neurons (LaVoie, Card et al. 2004), suggesting that microglial activation is involved in the development of MA-induced neurochanges and is not merely a reaction to neurodegeneration. In a human imaging study, a marker for activated microglia was significantly increased in abstinent MA users versus non-using controls and binding levels correlated inversely with the duration of MA abstinence (Sekine, Ouchi et al. 2008). Methamphetamine dependent women exhibited severe reductions in glial tricarboxylic acid (TCA) cycle rate compared to healthy control subjects in a magnetic resonance spectroscopy study, providing further evidence of *in vivo* glial cell dysfunction in methamphetamine users (Sailasuta, Abulseoud et al. 2010). Furthermore, emerging research suggests that microglial activation may mediate MA-induced synaptic plasticity (Narita, Miyatake et al. 2006) thereby contributing to the prolonged susceptibility to drug relapse. Among human MA users, increased plasma levels of pro-inflammatory cytokines (IFN- α , IL-1 β , IL-2, IL-6, TNF- α) and chemokines (MCP-1, MIP-1 α , MIP-1 β) were significantly associated with greater neurocognitive dysfunction (Loftis, Choi et al. 2011). Together, these results suggest that medications that counteract MA-induced neuroinflammation and microglial activation may reduce MA-induced neurodegeneration and thereby improve neurocognition and treatment outcomes in MA dependence.

In addition to the potential negative impact of glial-mediated neuroinflammation on MA-related neurodegeneration, glial cells also produce neurotrophic factors that may ameliorate dopaminergic dysfunction in MA dependence. For example, glial cell line-derived neurotrophic factor (GDNF) is a nerve

growth factor important in early neuronal development (Carnicella and Ron 2009) that is critical to the survival and proper functioning of dopaminergic neurons in the adult brain (Pascual, Hidalgo-Figueroa et al. 2008). GDNF selectively protects dopaminergic neurons, but not serotonergic neurons, from MA-induced neurodegeneration (Cass 1996) and increased GDNF expression in the putamen actually regenerates dopaminergic neurons and restores dopaminergic functioning in a non-human primate model of Parkinson's Disease (Kells, Eberling et al. 2010). GDNF is found at high levels in the striatum including the nucleus accumbens and GFR α 1 and Ret, the receptors for GDNF, are highly expressed in dopaminergic neurons in the ventral tegmental area (Carnicella and Ron 2009). Preclinical studies suggest that increased GDNF expression and the activation of the GDNF pathway reduce the biochemical and behavioral response to a variety of drugs of abuse including cocaine, opioids, alcohol, and MA. GDNF expression is increased in the nucleus accumbens in mice following MA administration and treatment with the peptide Leu-Ile, which is a GDNF inducer, blocked the development of MA conditioned place preference and behavioral sensitization in wild type but not heterozygous GDNF knockout (GDNF +/-) mice (Niwa, Nitta et al. 2007). GDNF +/- mice have lower levels of GDNF and exhibit greater MA conditioned place preference (Niwa, Nitta et al. 2007). GDNF +/- mice acquire stable MA self-administration behavior more quickly than wild type mice, exhibit greater motivation to self-administer MA (increased dose-response curve for MA self-administration and higher break point on progressive ratio schedule) and greater re-instatement of prime- and cue-induced drug seeking following extinction, an effect that remained even 6 months after extinction training (Yan, Yamada et al. 2007). In humans, polymorphisms in the GDNF gene have been associated with age of onset of MA dependence and addiction severity in Japanese MA users (Yoshimura, Usui et al. 2011). GDNF serum levels are lower in alcohol dependent volunteers compared to healthy controls and among alcoholics GDNF serum levels were inversely correlated with alcohol tolerance (Heberlein, Muschler et al. 2010). Together, these studies suggest that increasing GDNF is a promising approach to treating MA dependence due to its neurotrophic and neuroprotective effects that may restore dopaminergic functioning (Gramage and Herradon 2011) and reduce the reinforcing effect of MA (Carnicella and Ron 2009, Ghitza, Zhai et al. 2010). Early clinical trials of GDNF in Parkinson's disease have been complicated by difficulties in delivering therapeutic levels of GDNF to the brain (Richardson, Kells et al. 2011) suggesting that alternate approaches to enhancing GDNF function for treatment of MA dependence are needed.

Neuroinflammation and accompanying neurocognitive dysfunction is also a major clinical issue in HIV infection, and is exacerbated by concomitant MA abuse. HIV-associated neurocognitive disorders (HAND) are common even with antiretroviral therapy, with 52% of patients in a recent HIV clinical cohort exhibiting at least some level of neuropsychological impairment (Heaton, Clifford et al. 2010). HIV does not directly infect CNS neurons and HAND is thought to result primarily from the infection and subsequent activation of CNS macrophages and microglia, which then secrete many of the same pro-inflammatory cytokines that are also secreted in response to MA including TNF- α , IL-1 β , IL-6, and MCP-1 (Yadav and Collman 2009). HIV proteins gp120 and Tat are also neurotoxic and combined with MA exhibit synergistic toxicity on striatal dopaminergic neurons and the blood-brain barrier leading to enhanced CNS penetration by HIV (Silverstein, Shah et al. 2011). Not surprisingly, MA abuse increases the risk for neurocognitive impairment among HIV infected persons (Rippeth, Heaton et al. 2004, Carey, Woods et al. 2006), especially with HIV/HCV co-infection (Cherner, Letendre et al. 2005, Letendre, Paulino et al. 2007). Greater cognitive dysfunction is associated with poor HIV clinical outcomes including medication non-adherence (Becker, Thames et al. 2011) and worse quality of life (Parsons, Braaten et al. 2006). Therefore, medications that reduce neuroinflammation in HIV infected MA users may improve HIV and MA-related clinical outcomes via improvements in neurocognitive functioning.

Ibudilast (IBUD; MN-166/AV411) is a non-selective phosphodiesterase inhibitor with preferential inhibition of PDE3A, PDE4, PDE10, and PDE11 (Gibson, Hastings et al. 2006) that also inhibits glial cell activation (Suzumura, Ito et al. 1999) and production of macrophage migration inhibitory factor (Cho, Crichlow et al. 2010). IBUD has been used clinically for over 20 years in Asia for the treatment of bronchial asthma, and more recently for post-stroke dizziness and ocular allergies during which it has proven to be safe and well tolerated (Rolan, Hutchinson et al. 2009). IBUD increases expression of GDNF in *in vitro* studies (Mizuno, Kurotani et al. 2004) suggesting that IBUD may ameliorate dopaminergic dysfunction among MA users via the induction of GDNF expression. IBUD also reduces microglial activation *in vitro* in preclinical studies (Suzumura, Ito et al. 1999, Suzumura, Ito et al. 2003).

IBUD dose-dependently protected against microglial activation and the subsequent cerebrovascular white matter lesions following bilateral ligation of the carotid arteries (an animal model of vascular dementia/cognitive impairment) in rats (Wakita, Tomimoto et al. 2003). IBUD also suppressed activated microglia-induced neuronal cell death *in vitro* via inhibiting production of pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α), reactive oxygen species, and nitric oxide and increasing the secretion of anti-inflammatory mediators (IL-10, nerve growth factor, neurotrophin-4, and GDNF) by microglial cells (Mizuno, Kurotani et al. 2004).

Preclinical studies have found that IBUD has effects in multiple rodent models of MA dependence including reinstatement, locomotor sensitization, and self-administration. Importantly, IBUD demonstrated a dose-dependent effect in all three models with the greatest effect at higher doses. In the MA-reinstatement model, rats were trained to lever press for MA after which MA infusions were discontinued and lever pressing extinguished. IBUD significantly reduced MA prime- and stress-induced reinstatement of active lever pressing (Figure 1) (Beardsley, Shelton et al. 2010) suggesting that IBUD may be effective in reducing relapse during clinical treatment for MA dependence. While both IBUD doses reduced stress-induced reinstatement, only the higher IBUD dose reduced prime-induced reinstatement.

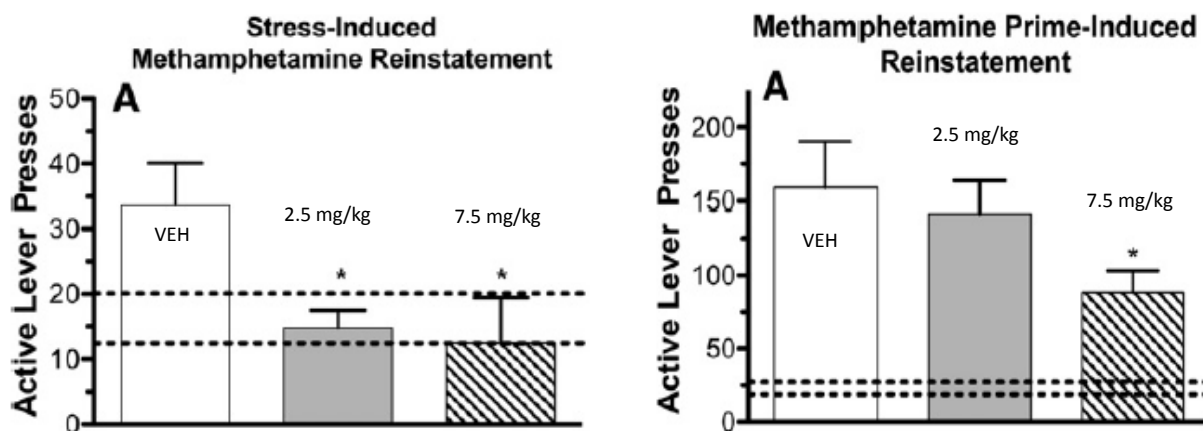


Figure 1: MA-reinstatement in rats under conditions of vehicle (VEH) and IBUD 2.5 mg/kg and IBUD 7.5 mg/kg. * $p < 0.05$ for comparison to vehicle. Taken from (Beardsley, Shelton et al. 2010).

After achieving stable MA self-administration, rats were treated with twice-daily doses of IBUD (1, 7.5, and 10 mg/kg). The highest IBUD dose (10 mg/kg) significantly reduced MA self-administration relative to the control vehicle condition (Figure 2) (Snider, Hendrick et al. 2013) suggesting that IBUD may reduce MA use and facilitate initiation of abstinence in humans during clinical treatment for MA dependence.

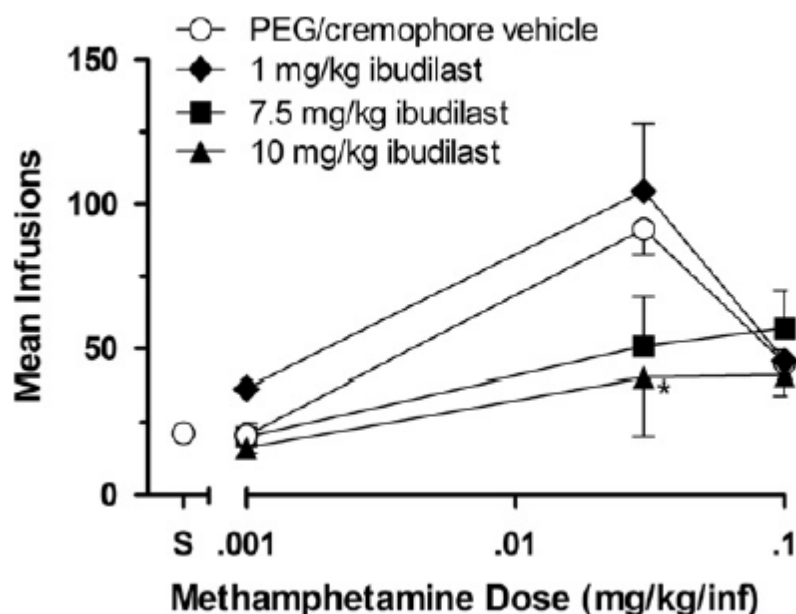


Figure 2: Dose-dependent effect of IBUD on MA self-administration in rats. * $p < 0.05$ for comparison to vehicle. Taken from (Snider, Hendrick et al. 2013).

IBUD also significantly reduced locomotor sensitization to MA in mice (Snider, Vunck et al. 2012). Together these studies provide a strong pre-clinical rationale for testing higher doses of IBUD for the treatment of MA dependence in humans. The mechanism by which IBUD is effective in these multiple preclinical models of MA dependence is not known but may involve induction of GDNF which has been shown to modulate the reinforcing effects of drugs of abuse as described above. Reductions in glial activation may also play a role as IBUD-induced reductions in markers of glial activation following opioid exposure in rats resulted in a reduction in opioid withdrawal symptoms, reduced morphine-induced dopamine release in the nucleus accumbens, and blockade of the development of conditioned place preference to morphine (Hutchinson, Lewis et al. 2008).

Clinically, in addition to its use for asthma in Japan, IBUD has been tested in phase 1 and phase 2 trials among healthy volunteers as well as patients with diabetic neuropathy, multiple sclerosis, chronic headache pain and opioid dependence with approximately 450 study participants treated with IBUD and 160 with matching placebo in these trials to date (Table 1). In a randomized, double-blind, placebo-controlled trial (N = 300) for multiple sclerosis (MS), IBUD 60 mg/day reduced time to MS relapse and the number of CNS lesions that progressed to persistent “black holes” on MRI suggesting a neuroprotective effect for IBUD in MS (Barkhof, Hulst et al. 2010). Of the IBUD clinical trials to date, this multiple sclerosis trial involved the only

Table 1: Safety results from IBUD clinical trials to date.

Phase	Trial No.	Location	Dose Level	Duration	Subjects	# Active	# Placebo	SAEs
1	AV411-016	U.S.	30 mg - 100 mg	Single admin.	Healthy Volunteers	53	18	0
1	AV411-009	Australia	30 mg BID	2 wk	Healthy Volunteers	14	4	0
1/1b	AV411-026	U.S.	20 mg BID to 50 mg BID (100)	2 wk	Healthy Volunteers & Diabetics	18	6	0

			mg/d)					
1b/2a	AV411-010	Australia	20 mg BID, 20 mg TID, 40 mg BID	2 wk (subset ≥ 3 mos)	Diab. Periph. Neuropath. Pain	19	10	0
1b/2a	AV411-OWA MN-166 SA	U.S.	20 mg BID & 40 mg BID	2 wk	Heroin addicts	20	10	0
			50 mg BID	3 wk	Prescription opioid addicts	1 of 24 completed	1 of 24 completed	(ongoing, none yet)
2	MN-166-CL-001	Eastern Europe	10 mg TID, 20 mg TID (60 mg/d)	2 yr	Multiple Sclerosis	192 (+97 2 nd yr via placebo crossover)	100	21; not clearly MN166-related
1b	MN-166-Meth	U.S.	20 mg BID and 50 mg BID	~2 wk	Methamphetamine addicts	11 completed	11 completed	0
2a/2	MOH	Australia	20 and 40 mg BID	2 mos.	Chronic Medication Overuse Headache pain	12 of 20 completed	12 of 20 completed	(ongoing, none yet)

Serious Adverse Event deemed related (possibly) to IBUD which was a participant who developed hepatic steatosis. As a result, a follow-up phase 2 trial of IBUD 100 mg/d in 250 MS patients is planned as part of the NIH-funded NeuroNEXT Network. In trials with IBUD dosing of 80-100 mg/day, adverse events have primarily been GI-related including mild to moderate nausea and diarrhea. Two female participants, one receiving IBUD 60 mg/day and the other 80 mg/day, experienced elevated GGT levels which returned to normal following discontinuation of study medication. In general, these studies have found IBUD to be safe and well tolerated at doses of 100 mg/day for 2 to 3 weeks, 80 mg/day for 2 months, and 60 mg/day for up to 2 years. In a two year trial of IBUD for Multiple Sclerosis, 17.6% (15/99) of patients on IBUD 60 mg/day had a greater than 30 millisecond increase in QTcF during one year compared to baseline, compared to 11.6% (11/95) of patients on 30 mg/day and 7.8% (8/103) patients on placebo. None of these patients experienced a clinical adverse event related to QT changes and only one patient (on IBUD 30 mg/day) had a QTcF > 480 milliseconds.

Our research group recently completed a phase I safety-interaction study of IBUD in MA dependent volunteers (NCT01217970). Eleven non-treatment seeking MA dependent volunteers were admitted to an inpatient research unit for 27 days and nights during which they received infusions with MA (0 mg, 15 mg, and 30 mg) under placebo, IBUD 20 mg BID, and IBUD 50 mg BID conditions using a randomized double-blind, placebo-controlled within-subjects crossover design. Participants were randomly assigned to medication dosing order (placebo, IBUD 20 mg BID, IBUD 50 mg BID versus IBUD 20 mg BID, IBUD 50 mg BID, placebo) in a counter-balanced fashion. In addition to the 11 participants that completed the 27 day admission and experimental procedures, four participants met all eligibility requirements, were admitted to the unit, but did not complete the study and are not included in the analysis. All four of the non-completers voluntarily withdrew from the study stating unwillingness to remain inpatient for the 27 days and none withdrew due to study related adverse events.

There were no Serious Adverse Events during the trial. Adverse events reported by participants by medication treatment are shown in Table 2. These adverse events were mild to moderate in severity, were not significantly more common during IBUD treatment than placebo, and are typical adverse events observed during methamphetamine studies.

Table 2: Proportion of participants (N=11) reporting adverse events during treatment with placebo, ibudilast 20 mg BID, and ibudilast 50 mg BID

Adverse event	Placebo	Ibudilast 20 mg BID	Ibudilast 50 mg BID	<i>p</i> value*
Insomnia	45% (5)	73% (8)	82% (9)	0.236
Nicotine craving	36% (4)	45% (5)	45% (5)	0.368
Gastrointestinal upset	35% (4)	27% (3)	36% (4)	0.819
Headache	45% (5)	55% (6)	27% (3)	0.247
Musculoskeletal pain	0% (0)	18% (2)	18% (2)	0.264
Pain at IV site	27% (3)	18% (2)	18% (2)	0.779
Rash	9% (1)	9% (1)	18% (2)	0.717
Vivid dreams	18% (2)	18% (2)	18% (2)	1.000
Constipation	0% (0)	0% (0)	9% (1)	0.368
Dizziness	0% (0)	0% (0)	9% (1)	0.368
Dysuria	9% (1)	0% (0)	9% (1)	0.607
Ectopic heart beats	0% (0)	0% (0)	9% (1)	0.368
Fever/chills/hot flashes	0% (0)	18% (2)	9% (1)	0.223
Pruritis	0% (0)	18% (2)	9% (1)	0.223
Sore throat	0% (0)	9% (1)	9% (1)	0.368
Tinnitus	0% (0)	0% (0)	9% (1)	0.368
Backache	0% (0)	9% (1)	0% (0)	0.368
Chest congestion	9% (1)	0% (0)	0% (0)	0.368
Sedation	0% (0)	9% (1)	0% (0)	0.368

* Cochran's Q test

One participant had mild anemia (hemoglobin 13.2 with lower limit of normal for lab 13.8) and mild elevation of alanine transaminase (ALT 66 with upper limit of normal for lab of 40) on study termination labs. The participant reported a previous history of mild anemia, especially following plasma donation, and intermittent elevations of liver enzymes and therefore these were not attributed to study medication. No other participants had lab abnormalities.

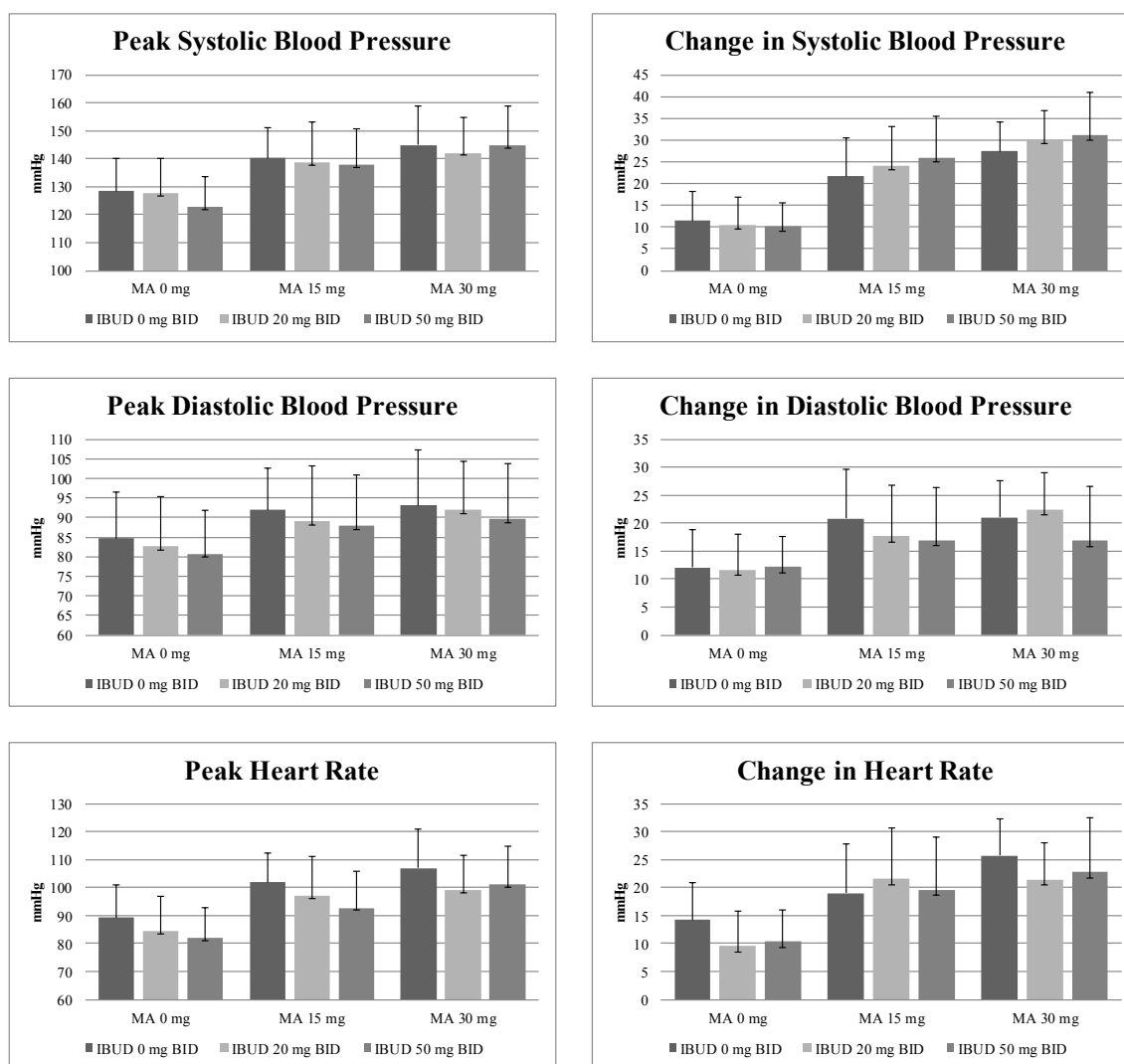
One participant had an episode of ectopic heart beats detected on routine cardiac monitoring. The ectopic beats occurred approximately 240 minutes after a 15 mg methamphetamine infusion while the participant was under the IBUD 50 mg BID condition. The nursing staff notified the study physician that the cardiac monitors showed a brief run of ventricular bigeminy (a pairing of a normal beat with an ectopic beat) running approximately 6 pairs before reverting to normal rhythm. Occasional single premature ventricular contractions (PVCs) were also noted. The participant was in no distress, without complaints, and vital signs were normal throughout. A 12 lead EKG and serial troponin levels were done and were all normal. The participant was kept on the cardiac monitor overnight and no further ectopic beats occurred. Cardiology was consulted and an echocardiogram was performed which was normal. The ectopic beats were attributed to the methamphetamine infusion and the participant completed the remainder of study activities without problems.

Two other participants had EKG abnormalities during the ibudilast 50 mg BID condition; both were determined to be artifact or normal variants. In one case the computer EKG interpretation suggested "septal infarct, age undetermined." Cardiology was consulted, an echocardiogram was done, which showed no evidence of septal wall motion abnormality or previous infarct, and the computer interpretation was attributed to irregular EKG lead placement. The other participant had an EKG that was initially interpreted as having possible ST elevation suggestive of acute pericarditis. The participant was in no distress, vital signs were normal, troponins were negative, and an echocardiogram was normal without evidence of pericarditis. The cardiology consultant attributed the EKG abnormality to early repolarization, a normal variant, which had been present on the participant's EKGs throughout. The participant completed the remainder of study activities without problems.

Ibutilast did not augment or exacerbate the cardiovascular response to methamphetamine. The cardiovascular response to IV methamphetamine (0 mg, 15 mg, and 30 mg) during treatment with IBUD 20 mg BID, IBUD 50 mg BID, and placebo BID and shown in Figure 3. Peak systolic blood pressure, diastolic blood pressure, and heart rate (maximal value observed following IV MA infusion) as well as peak change in systolic blood pressure, diastolic blood pressure, and heart rate (difference between maximal value following MA infusion and -15 minute pre-infusion reading) during IBUD 20 mg BID, IBUD 50 mg BID, and placebo were compared using a repeated measures analysis of variance (ANOVA) model that included IBUD dose, MA dose, order of medication administration, and the interaction between IBUD and MA. As expected, the main effect for MA was significant ($p < 0.05$) in all models demonstrating that MA infusion resulted in a significant increase in blood pressure and heart rate. Results of analyses of IBUD main effects and IBUD-MA interactions are presented below:

- There was a significant main effect for IBUD on peak heart rate ($F = 9.855$, d.f. = 2, $p = 0.001$) but the main effect for IBUD was not significant in models of peak systolic blood pressure ($F = 0.854$, d.f. = 2, $p = 0.442$) and peak diastolic blood pressure ($F = 2.381$, d.f. = 2, $p = 0.121$). The mean peak heart rate for IBUD 20 mg BID was 6.0 (S.E. 2.0) beats per minute lower than the mean peak heart rate for placebo ($p = 0.017$) and the mean peak heart rate for IBUD 50 mg BID was 7.4 (S.E. 1.8) beats per minute lower than the mean peak heart rate for placebo ($p = 0.002$). Although statistically significant, these changes in peak heart rate were not clinically significant and were not associated with any adverse events among participants.
- There were no significant interactions between IBUD and MA in models of peak systolic blood pressure ($F = 1.255$, d.f. = 4, $p = 0.305$ for interaction term), peak diastolic blood pressure ($F = 0.109$, d.f. = 4, $p = 0.978$), or peak heart rate ($F = 0.690$, d.f. = 4, $p = 0.604$).
- There was no significant main effect for IBUD on mean peak change in systolic blood pressure ($F = 0.972$, d.f. = 2, $p = 0.397$), diastolic blood pressure ($F = 1.195$, d.f. = 2, $p = 0.326$), or heart rate ($F = 1.168$, d.f. = 2, $p = 0.333$).
- There were no significant interactions between IBUD and MA in models of peak change in systolic blood pressure ($F = 0.369$, d.f. = 4, $p = 0.829$), diastolic blood pressure ($F = 0.939$, d.f. = 4, $p = 0.452$), or heart rate ($F = 0.857$, d.f. = 4, $p = 0.499$).
- There was no effect of IBUD on daily morning measurements of systolic blood pressure ($F = 0.329$, d.f. = 2, $p = 0.723$), diastolic blood pressure ($F = 1.373$, d.f. = 2, $p = 0.276$), or heart rate ($F = 1.134$, d.f. = 2, $p = 0.342$).

Figure 3: Mean peak and mean peak change in cardiovascular parameters for intravenous methamphetamine (MA 0 mg, 15 mg, and 30 mg) during treatment with ibutilast (IBUD) 20 mg BID, 50 mg BID, or placebo BID in methamphetamine dependent volunteers (N=11). Error bars represent the standard deviation of the mean.



In summary, IBUD was well tolerated in this phase I safety-interaction study among MA dependent volunteers. There were no Serious Adverse Events and adverse events were mild, similar in frequency during IBUD and placebo treatment, and typical of MA clinical trials. IBUD did not affect daily morning blood pressure or heart rate among MA dependent participants nor did it augment or exacerbate the cardiovascular response to MA. IBUD did reduce the peak heart rate following MA infusion although this was not associated with any adverse events among participants. In fact, reductions in the chronotropic effects of MA with IBUD could have beneficial effects in mitigating the cardiovascular risks of MA abuse. Together, results of this phase I clinical trial support the safety and tolerability of IBUD at the 50 mg BID dose used in the current study among MA dependent participants.

Changes in plasma biomarkers during treatment with IBUD were assessed in a phase 1b/2a trial of IBUD in 34 patients with neuropathic pain. There was a significant reduction in plasma MCP-1 with IBUD relative to placebo ($p = 0.015$), but no change was seen in plasma BDNF, ICAM-1, IL-10, IL-1 β , IL-6, TNF- α , VCAM-1, MIP-1 β , VEGF, or PAI-1 (Medicinova 2011). Interestingly, MA users have reduced cerebral perfusion (Iyo, Namba et al. 1997, Alhassoon, Dupont et al. 2001, Chang, Ernst et al. 2002) and IBUD has been shown to increase cerebral perfusion post-stroke (Fukuyama, Kimura et al. 1993) suggesting an additional potential mechanism for IBUD in MA dependence. IBUD's neurotrophic and neuroprotective effects via induction of GDNF and/or reduction in microglial activation/neuroinflammation suggest that IBUD may ameliorate the neurotoxic effects of MA, especially among HIV positive MA users, thereby improve cognition and treatment outcomes in MA dependence. In summary, IBUD has multiple effects that may contribute to ameliorating dopaminergic dysfunction and improving cognition

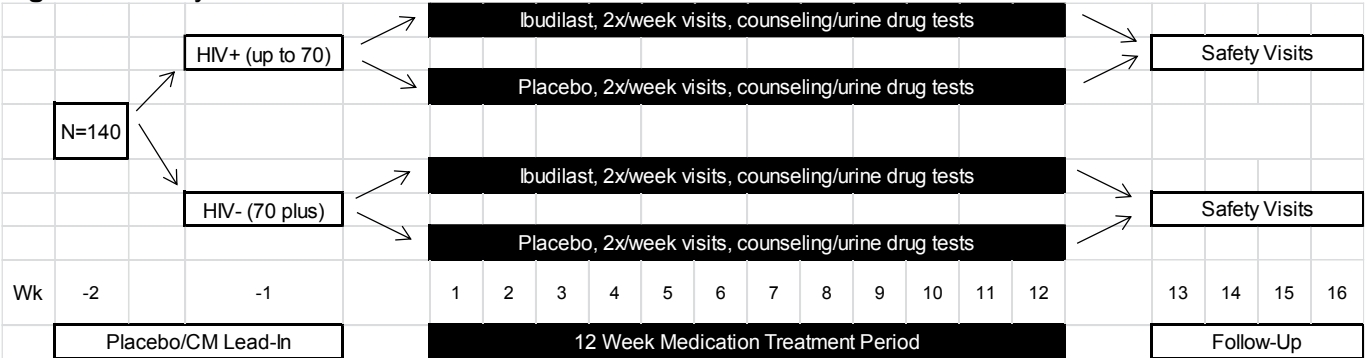
and treatment outcomes in MA dependence including reductions in neuroinflammation and the reinforcing effects of MA, and induction of neurotrophic factors such as GDNF. The clinical development of IBUD for MA dependence is the result of a long-standing collaboration between our research Center and MediciNova, Inc. (San Diego, CA) who are fully committed to seeing IBUD through the regulatory and marketing process for MA dependence.

Drug use disorders commonly follow a history of experiencing high levels of early-life stress (ELS) (Repetti, Taylor et al. 2002, Dube, Felitti et al. 2003, McFarlane, Clark et al. 2005, Cohen, Paul et al. 2006), which have been linked with neural dysfunction (Cohen, Grieve et al. 2006, Seckfort, Paul et al. 2008, Baker, Williams et al. 2013, Philip, Sweet et al. 2013). HIV and high ELS have combined pathological effects on brain morphometry and neurocognitive function in HIV+ patients (Clark, Cohen et al. 2012). MA abuse and high ELS have some common effects, both involving upregulation of neuroinflammatory processes. High levels of ELS also are associated with increases in pro-inflammatory cytokines (Pollitt, Kaufman et al. 2007, Carpenter, Gawuga et al. 2010, Slopen, Lewis et al. 2010). These findings suggest that high ELS may exacerbate MA-related neuropathology in HIV+ patients and therefore we will explore potential effects of ELS on treatment outcomes as well as interactions with ibudilast treatment. As recent stress and/or trauma may confound any associations between ELS and neuroinflammation or cognition, we will assess recent stress and trauma using the Perceived Stress Scale (PSS-14) and the Posttraumatic Stress Disorder Checklist - Civilian (PCL-C) and control for these in our analyses.

Research Plan

The study is a phase 2 clinical trial to determine the safety and efficacy of IBUD for the treatment of MA dependence. The trial will be performed at the UCLA outpatient research clinic in Hollywood, California. Treatment-seeking MA dependent volunteers will undergo screening and eligibility assessments, including determination of HIV serostatus, during a two-week placebo lead-in with a high value contingency management (CM) behavioral intervention aimed at assessing participants' ability to adhere to medication taking and initiate MA abstinence prior to the start of medication, both important predictors of subsequent treatment outcomes (Bisaga, Aharonovich et al. 2005, Anderson, Reid et al. 2009, Bisaga, Aharonovich et al. 2010). Eligible participants (N = 140) will be randomized, stratified by HIV serostatus, to IBUD (50 mg BID) or placebo (BID) treatment for 12 weeks, with twice weekly clinic visits for counseling, urine drug tests, and safety/medication adherence monitoring (Figure 4). An urn randomization procedure will be used to balance the following variables between active and placebo groups: MA use during the two-week placebo/CM lead-in period, gender, ethnicity (Hispanic versus not Hispanic), marijuana dependence, and baseline cognitive function.

Figure 4: Study Schema



The study is powered to detect a statistically significant benefit of IBUD over placebo on the primary study outcome, MA abstinence during the final two weeks of treatment (at least one of the two possible urine drug screens each week is available during weeks 11 and 12 and all available samples are MA negative, the FDA-preferred primary efficacy outcome for phase 2 stimulant trials) in the total sample (N = 140). Treatment retention for participants receiving IBUD versus placebo will also be compared.

Secondary analyses will examine medication tolerability and adverse events, as well as treatment outcomes in pre-specified subgroups defined by level of medication adherence, the ability to achieve initial MA abstinence during the placebo/CM lead-in, and baseline HIV serostatus. Exploratory analyses aimed at probing the mechanism of action for IBUD in MA dependence will examine potential associations between treatment outcomes/medication effects and a panel of inflammatory and neurotrophic markers as well as polymorphisms in dopaminergic and GDNF genes.

As IBUD has putative mechanisms that would have additional benefit in patients with MA dependence and HIV infection, analyses will also assess potential benefits of IBUD over placebo on the following HIV-related outcomes among HIV positive participants (up to n = 70): CD4 count and HIV RNA, neurocognitive performance, sexual HIV transmission behaviors, and uptake/adherence to HIV medications. The study is not powered to detect statistically significant differences in the HIV positive subsample but may provide important data to guide the development of MA medications in this critically important clinical population. Results of the trial, if positive, will be used to pursue eventual FDA approval and marketing of IBUD for MA dependence, in collaboration with MediciNova, Inc.

Recruitment procedures: Using procedures developed by our group we will use a community-wide advertising campaign including advertising in local print, online (facebook, google), and media outlets as well as listing the study on www.clinicaltrials.gov and our own website (<http://www.uclacbam.org/>). We also have a referral network in place to receive referrals of potential participants from community-based clinics and agencies in the area and will utilize a UCLA participant pool (UCLA HIV Research Study Volunteer Project, David Geffen School of Medicine at UCLA, UCLA MIRB # 11-003566). Interested potential participants will call a toll-free number where a staff member will conduct a telephone screen. If the individual appears eligible, an appointment will be made as soon as possible to initiate informed consent and begin the screening process. At that appointment, one of the study clinicians will complete the informed consent process.

Informed Consent: During the informed consent appointment, potential participants are informed of the study purpose, procedures, potential risks, and benefits in a private, confidential setting with a study clinician. Potential participants will read the informed consent document and review the document in detail with a clinician. At this time, and throughout the study period, participants are encouraged to ask questions about study procedures and discuss any concerns they have with a clinician. No information will be withheld from participants regarding purpose or design. The potential participant will be told that his/her participation is completely voluntary. The potential participant will also be informed of his/her right to terminate participation in the study at any time. The potential participant will be asked if he/she has any questions, and all questions will be answered. The clinician performing the informed consent will assess the participant's comprehension by engaging the participant with open ended questions about the study procedures and risks/benefits as a means of prompting further discussion (e.g. "Describe in your own words the purpose of the study.") The clinician performing the consent will clarify any misunderstandings to ensure the participant has comprehended the consent. Potential participants will also be asked if the information they have been given in response to all questions has been adequate and understood. They will then be asked whether they have decided that they would like to participate in the study, whether they would like to have additional time to arrive at a decision, and/or whether they would like to discuss their possible participation in this study with some other person. Referrals to appropriate local treatment resources are offered at any point to those who decide not to participate in the research study and are interested in the referrals. After completion of the informed consent process, participants who remain interested in taking part in the research will sign the consent document, receive a copy of the informed consent form, a copy of the Human Subject's Bill of Rights, in addition to contact information for the study clinicians. The clinician obtaining consent will sign the consent form as a witness.

For informed consent procedures, we will follow the 1991 Code of Federal Regulations (45 CFR 46.102) that defines "research" as a systematic investigation designed to develop or contribute to generalizable knowledge. Guiding principles include respect for persons, beneficence, and just selection of research subjects. The informed consent process will conform to these policies and to UCLA's consent form standards, including the handling and processing of anonymized genetics specimens, and the process will be reviewed and approved by the UCLA IRB.

Two-week Placebo+CM Lead-in Period: After providing written informed consent, participants will begin a two-week (six-visit) outpatient lead-in period during which they will attend the outpatient research clinic thrice-weekly and complete a comprehensive assessment of their baseline drug use and psychological/medical status, including a medical history and physical exam, EKG, labs, HCV and HIV serotyping, and other study measures (see Measures below). An EKG will be repeated if results indicate a corrected QT of > 450 msec in men or > 460 msec in women (see below). Participants will complete a neurocognitive battery on the final week of the lead-in period as described below. All participants will take placebo capsules twice daily during the lead-in period. The placebo capsules will contain riboflavin which will be used to assess participants' ability to adhere to medication taking. Participants will be allowed one urine specimen during the lead-in with a riboflavin concentration less than 900 ng/ml as measured via UV fluorescence, but any participant with more than one of the five (excluding the day of consent) possible urine samples below the 900 ng/ml threshold will be considered medication non-adherent and will not be eligible. In addition, subjects must provide at least one MA positive urine drug screen during the lead-in period. The two-week lead-in period may be extended at the discretion of the PI in limited cases, including telephone consents, holidays, etc.

A high-value CM intervention adapted from (Bisaga, Aharonovich et al. 2010) will be used to characterize participants on their ability to achieve initial MA abstinence during the second week of the lead-in period, a potential confounder of subsequent medication effects. Participants will be instructed at the first study visit that they will have the chance to earn gift cards for providing MA-free urine drug screens during the second week of the lead-in period. Participants will receive \$15 for the first MA-free urine provided during the second week, \$25 for the second MA-free urine provided, and \$40 for the third MA-free urine provided. Participants will be advised that achieving initial MA abstinence during the lead-in may be beneficial to their eventual treatment outcomes, but that failure to achieve abstinence will not affect their subsequent participation and those unable to abstain will be encouraged to complete the screening in order to avoid differential attrition. Participants will be stratified in secondary analyses by their ability to achieve MA abstinence with the CM intervention during the two-week lead-in period. All participants will receive \$25 in gift cards upon completion of the screening measures, regardless of urine drug screen results, to compensate participants for time spent completing screening measures. Participants who complete all baseline/eligibility assessments and meet all eligibility criteria will be randomized and begin study treatments and medication within 1 week of completion of screening measures

Eligibility Requirements: Participants randomized into the study must meet the following eligibility requirements:

Inclusion criteria:

- (1) 18 years of age or older;
- (2) meet DSM-IV-TR criteria for MA dependence (SCID verified);
- (3) a MA-positive urine drug screen at one or more visit during the two week lead-in period;
- (4) seeking treatment for MA problems;
- (5) willing and able to comply with study procedures;
- (6) provide written informed consent;
- (7) English speaking;
- (8) live within 35 miles of the clinical research site; and
- (9) if female of childbearing potential, not pregnant or lactating and willing to use a medically reliable method of birth control during the trial (e.g., birth control pills, Depo-Provera, and/or condoms with spermicide).

Exclusion criteria:

- (1) a medical condition that, in the study physician's judgment, may interfere with safe study participation (e.g., active TB; unstable cardiac, renal, or liver disease; uncontrolled hypertension; unstable diabetes);
- (2) CD4 count < 50 cells/mm³ (suggestive of advanced HIV infection)
- (3) AST, ALT, or GGT > 3 times upper normal limit;
- (4) A corrected QT of > 450 msec in men or > 460 msec in women on at least two ECGs during the baseline period, or clinical risk factors for Torsades de Pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome), or requiring ongoing treatment with

concomitant medication(s) with established risk of Torsades de Pointes (e.g. Amiodarone, Arsenic trioxide, Astemizole, Bepridil, Chloroquine, Chlorpromazine, Cisapride, Citalopram, Clarithromycin, Disopyramide, Dofetilide, Domperidone, Droperidol, Erythromycin, Flecainide, Halofantrine, Haloperidol, Ibutilide, Levomethadyl, Mesoridazine, Methadone, Moxifloxacin, Pentamidine, Pimozide, Probutol, Procainamide, Quinidine, Sotalol, Sparfloxacin, Terfenadine, Thioridazine, Vandetanib);

- (5) current ongoing treatment with psychotropic medications (e.g., antidepressants, antipsychotics, antiepileptics, sedative/hypnotics, narcotic analgesics);
- (6) a neurological disorder (e.g., organic brain disease, dementia) or a medical condition which would make study agent compliance difficult or which would compromise informed consent;
- (7) a major psychiatric disorder not due to substance abuse (e.g., schizophrenia, bipolar disorder) as assessed by the SCID;
- (8) attempted suicide in the past 3 years and/or serious suicidal intention or plan in the past year as assessed by the C-SSRS;
- (9) currently on prescription medication that is contraindicated for use with IBUD including alpha or beta agonists, theophylline, or other sympathomimetics;
- (10) current dependence on cocaine, opiates, alcohol, or benzodiazepines as defined by DSM-IV-TR;
- (11) alcohol dependence within the past year;
- (12) greater than one urine specimens during the lead-in with a riboflavin concentration of < 900 ng/ml as assessed via UV fluorescence;
- (13) a history of sensitivity to IBUD;
- (14) any other circumstances that, in the opinion of the investigators, would compromise participant safety; or
- (15) current participation in another clinical trial.

Comprehensive feedback will be provided to subjects who are judged not suitable for the study for any psychiatric or medical reason. Participants who fail to complete all baseline data collection and procedures within two weeks will not be randomized into the trial. Subjects who are MA abstinent upon entry to the lead-in period are excluded as they are highly likely to remain abstinent regardless of treatment (Hillhouse, Marinelli-Casey et al. 2007).

Randomization Procedures: When participants are determined to be eligible and are cleared by the study physician for participation, they will be randomized to either IBUD 50 mg BID or placebo BID, stratified by baseline HIV serostatus (up to 70 HIV positive). In addition, within each strata an urn randomization procedure (Stout, Wirtz et al. 1994) will be used to provide multivariate balance across conditions along the following variables that may influence treatment outcomes: MA abstinent versus not abstinent as confirmed via urine drug screen during the second week of the lead-in period, (MA abstinence will be confirmed with at least two urine drug screens negative for presence of MA and no urine drug screen positive for MA, while all other urine drug screen results will be considered not abstinent), gender (biologic male versus female), ethnicity (Hispanic versus not Hispanic, marijuana dependence (dependent versus not as assessed by SCID), and baseline cognitive function (greater than 26 on the MoCA versus 25 or less). Participants will be considered to have entered the trial for the intention to treat analysis at the point of randomization. The randomization key will be maintained off-site in the Research office.

Outpatient Treatment Procedures: Participants will attend the outpatient research clinic twice weekly for urine drug screens, counseling, assessment of substance use and other standardized research measures (see below), and safety and medication adherence monitoring for 12 weeks of treatment. During this time repeat safety labs and a repeat EKG will be conducted at weeks 3 and 8. At week 13, a termination assessment will consist of a repeat physical, EKG, safety labs, and other behavioral assessments and cognitive testing, followed by a final brief health check 30 days later for post-medication safety monitoring.

Experimental Drug Procedures: Experimental medication will be obtained from MediciNova. The study drug is Ibudilast (MN-166, previously known as AV411) and the product is delayed-release Pinatos® capsules, the Japanese generic IBUD product produced by Taisho Pharmaceuticals and imported by MediciNova. Matching placebo capsules will also be supplied by MediciNova. The doses

used to date have been 10 mg strength and formulation modification to 20-50 mg dosage strengths are in process. Should this protocol involve dosing at strengths greater than 10 mg, then supportive documents/amendments would be filed in advance of the change. In addition, all participants will also take a daily dose of 25 mg riboflavin for assessment of medication adherence via urinary riboflavin (Herron, Mariani et al. 2010), one capsule in the AM and one capsule in the PM each containing 12.5 mg riboflavin (details under adherence monitoring below). All capsules will be prepared by our research pharmacy. Upon receipt of a prescription signed by the study clinician, the un-blinded pharmacist prepares and sends a supply of study medication in blister packaging to the study clinic. . After randomization, participants will take the first dose of study medication at the research clinic under observation by the study clinician after which study medication will be dispensed to participants for self-administration at home. Participants will then meet with a study clinician and exchange the empty blister package for a new blister package. Participants will be in possession of the current week and next week's medication supply so that they will not run out of medication in the event that they miss one of the medication dispensing visits. Unused medication will be recorded for the pill count and will be sent for incineration after the conclusion of the trial. Additional details concerning medication adherence procedures are detailed below.

Dose Justification: Dosing for IBUD will be 50 mg BID. To minimize nausea, the most common side effect of IBUD, all participants will begin at 20 mg BID for 3 days increasing to 50 mg BID on day 4. Preclinical and clinical pharmacokinetic and pharmacodynamic data from the sponsor suggest that CNS applications such as addiction will require higher doses to achieve clinically significant reductions in glial activation than those currently in clinical use for asthma, dizziness, and allergies (≤ 30 mg a day). The dosage selected for the current study (20 mg BID titrated to 50 mg BID) was selected in consultation with MediciNova scientists and based on preclinical and clinical PK-PD in methamphetamine dependence and other neuropharmacological settings. Reflecting experience in recent MediciNova safety trials, including our group's phase I safety trial of IBUD in MA dependent volunteers, 50 mg BID has been well tolerated, adverse events being easily managed and 50 mg BID representing the upper limit of what the manufacturer believes is the preferable well-tolerated and potentially efficacious dose for an addiction indication. The half-life of IBUD is about 18 hours (Rolan, Gibbons et al. 2008) justifying BID dosing. A large clinical trial of IBUD 50 mg BID for Multiple Sclerosis (N=250; MN-166-NeuroNext) is anticipated to begin enrolling soon in the U.S. and also a phase 2 trial in the U.K. (MS-SMART) is pending (110 SPMS patients in each of 4 treatment arms including placebo and ibudilast) based on a previous trial that found 30 mg and 60 mg IBUD daily to be well tolerated and display dose-dependent effects on surrogate clinical outcomes (Barkhof, Hulst et al. 2010). The study clinician may reduce a participant's dose from 100 mg/day to 80 mg/day (40 mg in AM and 40 mg in PM) , or potentially 30 mg BID, for any potential dose-related side effects but dose increases will not be allowed.

As IBUD is not currently clinically available in the US, information concerning possible adverse events come from results of clinical trials conducted by the US developer (Avigen/MediciNova) ranging from 30-100 mg/day and from experience with clinical use in Asia (typically 30 mg/day). In Avigen/MediciNova trials, ~450 subjects have been treated in the clinical development of IBUD with no SAEs clearly linked to IBUD and one severe AE of hepatic steatosis (possibly-related) at 30 mg/d IBUD and one moderate hepatotoxicity deemed related to IBUD (at 60 mg/d); both at 20-23 months of treatment in a 2-yr MS trial. There were no serious adverse events in any of these trials. Mild-moderate headache and nausea have been the most frequently reported adverse events in trials of IBUD with fatigue, rash, hyperhidrosis, dizziness, hypotension, and tachycardia observed less frequently and more common with placebo than IBUD. According to the package insert for Ketas® (name under which IBUD is marketed in Asia), the most frequently observed adverse reactions are anorexia (weight loss; <1%), nausea (<1%), increased AST (GOT) levels (<1%), increased ALT (GPT; <1%), and thrombocytopenia (<1%). IBUD is metabolized primarily by CYP2B6 and CYP2E1 and weakly inhibits CYP1A2, while MA is primarily metabolized by CYP2D6 suggesting that clinically significant IBUD-MA interactions are not likely (nor observed in our phase Ib trial). There have been no significant drug-drug interactions observed to date in clinical studies of IBUD among patients being treated for diabetes, neuropathic pain, opioid dependence, MOH pain, or multiple sclerosis. There is no evidence to suggest important drug-drug interactions between IBUD and HIV antiretroviral medications. Results of these studies and clinical

experience at the doses proposed here (up to 50 mg BID) suggest that IBUD is likely to be safe and well tolerated in study participants.

Medication Adherence Support/Monitoring: After randomization, participants will visit the clinic and take the first dose of study medication under supervision of a study clinician. A comprehensive medication adherence support program that reinforces the importance of medication adherence at every clinical encounter with participants will be used and will include the following elements:

- **Medication adherence counseling** (Osterberg and Blaschke 2005): Medication adherence counseling is an integral part of the Medical Management Counseling that is provided as part of the trial. At the initial visit when the participant starts study medication, he/she will meet with the study physician/nurse/counselor and review how to take the medication. The use of the blister package (see below) will be reviewed and the critical importance of daily medication adherence will be stressed. Participants will be instructed to take the study medication daily and assisted in developing a practical plan for incorporating medication taking into their daily routine. The need for adherence in order to obtain any potential clinical benefit from the study medication will be emphasized. Participants will also be instructed to report any perceived medication side effects to study clinicians immediately such that they can be promptly addressed and removed as potential barrier to medication adherence (in addition to insuring participant safety). At least weekly, participants will meet with the study clinician to review recent medication adherence. Reasons for any non-adherence will be explored and a plan will be developed to address any non-adherence (including possible dose adjustments in the event of side effects). At each study visit, staff will reinforce adherence counseling by reminding participants to take their medication daily as instructed and any issues regarding non-adherence will be referred to the study clinician. Participants who miss a study visit will receive a telephone call and/or text message to remind them to take their medication daily as instructed and to attend their next scheduled visit. Any non-adherence will be addressed by study clinicians using a non-confrontational approach aimed at bolstering participant self-efficacy and motivation to achieve high adherence.
- Study medication will be dispensed in **blister packages**, which have been shown to be an effective intervention to promote adherence (Haynes et al., 2005). Participants will receive \$5 in gift cards for bringing their medication blister package to the clinic each week for a medication adherence pill count performed by study staff. Any non-adherence will be addressed by the clinician in the weekly medication adherence counseling sessions. Participants will be instructed to leave any unused medication in the blister package such that participants' self-reported pill-taking behaviors can be reconciled with the remainder of pills in the take-home blister packet. In addition to IBUD or placebo capsules, participants will take one capsule containing 12.5 mg **riboflavin** twice daily (total of 25 mg daily if the participant is adherent to both the AM and PM doses). At each study visit, urine specimens will be analyzed via fluorimetry for quantitative measurement of riboflavin as an objective measure of medication adherence during study data analysis. Urine specimens with a riboflavin concentration greater than or equal to 900 ng/ml will be considered positive and indicative of medication adherence (Herron, Mariani et al. 2010). We use 25 mg riboflavin instead of 50 mg as 25 mg is less likely to spill over in the urine past 24 hours and is therefore more accurate in detecting recent medication ingestion (Herron, Mariani et al. 2010). The study clinician will feed back riboflavin results to participants at each visit and counsel participants regarding any negative riboflavin results.
- An aliquot (5 ml) from each of the twice-weekly urine specimens during the 12 week medication period will be collected for measurement of concentrations of IBUD and its primary metabolite (6,7-dihydrodiol-ibudilast) as a "snapshot" **biological assessment of medication adherence** during the trial. One sample will be collected immediately prior to starting study medication (negative control). In addition, one serum sample (10 ml blood) will be collected from participants during week 3 of the study medication period for measurement of serum IBUD and 6,7-dihydrodiol-ibudilast levels. Samples will be frozen and stored until analysis is performed. The study day and time of collection will be recorded. The subject will be asked to provide the time that they took their last dose of study medication before providing the sample.

Drug Accountability: Medical staff at the clinic will keep a dispensing log and drug accountability record for each subject enrolled in the study. Such records will be made available for verification by

relevant regulatory personnel as required. Upon completion of count verification, unused participant-returned medication and expired medication is destroyed or returned to the manufacturer per agreement.

Emergency Unblinding Procedures: The research pharmacist will provide the principal investigator with a set of sealed envelopes containing individual randomization assignment numbers allowing the principal investigator to break the blind in a clinical emergency, should that be necessary.

Counseling Procedures: Participants will attend an initial introductory counseling session (60 minutes) during the baseline period to review the participant's past experience with medication taking, identify any barriers to medication adherence, and explain the adherence monitoring via riboflavin during the lead-in period. A study clinician may follow-up with participants at subsequent lead-in visits if there is any indication of medication non-adherence or if participants have questions regarding the riboflavin adherence monitoring. Participants will then attend a session during week 1 of the study medication treatment period to review medication adherence thus far and explain the study medication regimen (approximately 60 minutes) followed by weekly follow-up counseling sessions (20 minutes) during the remainder of the 12 week medication treatment period. As the study is a medication trial, we will employ a medically-based counseling platform -- Medical Management (MM) counseling -- as used in the COMBINE study of alcohol dependence pharmacotherapy (Pettinati and National Institute on Alcohol Abuse and Alcoholism (U.S.) 2004, Pettinati, Weiss et al. 2005) which we have adapted for stimulant dependence trials. As medication non-adherence is a severe threat to the validity of any medication trial, it is critical that medication adherence is central to the counseling intervention provided. In addition, the use of a medically-based counseling approach that can be implemented by non-specialist clinicians in primary care settings is likely to be more generalizable than a cognitive behavioral therapy platform in light of the national trend towards the integration of addiction treatment into primary care settings. The MM counseling sessions will be delivered by a study physician/nurse or counselor following a manual developed for the trial. A primary focus of MM is to help clinicians provide education, support, and strategies to ensure that participants are medication compliant. Core components of MM include: (1) providing participants strategies for taking their medications and staying in treatment, (2) educating participants about MA dependence and pharmacotherapy, (3) supporting their efforts to reduce or stop MA use, (4) making direct recommendations that participants change their drug use behaviors.

The initial MM session lasts 60 minutes and covers: (1) Review the results from his/her screening evaluation and address any medical concerns, (2) Use the results from the evaluation to support the diagnosis of MA dependence, provide basic information about the disorder (including prognosis), and advise abstinence, (3) Provide a rationale for and information about pharmacotherapy, (4) Provide a rationale for evaluating medication compliance at each session, (5) Use the patient's history of taking medication to establish an individualized plan that will ensure medication compliance, (6) Encourage participation in mutual-support groups (e.g., AA, SMART Recovery), and (7) Answer any questions or concerns about treatment. Follow-up visits last 20 minutes and cover: (1) A medical check on the participant's general functioning, (2) Review results of the participant's urine drug screens, (3) Review the participant's vital signs, (4) Ask about medication side effects and concurrent medications, (5) Perform a brief assessment of the participant's drug use and HIV risk behaviors, (6) Assess his/her medication compliance, and (7) Make recommendations for the participant to follow until the next visit.

To ensure integrity in the delivery of the counseling sessions, Dr. Heinzerling will provide corrective feedback as needed to study clinicians, monitor adherence to the counseling manual through review of audiotaped sessions, and in weekly supervision meetings.

MA Urine Drug Screen Procedures: Participants will have a urine drug screen collected at each clinic visit that will be assessed for MA-metabolites using standard point of care immunoassay drug screen urine cups with a threshold of 300ng/mL. If a participant is unable to attend a clinic visit (e.g. out of town, holiday, etc.), subjects may provide drug screening samples using oral test kits.

"Drop-out" Subject Tracking: Subjects who have not rescinded consent, but are no longer available/interested in attending twice-weekly visits ("drop-outs") will be followed using alternative methods. Every effort will be made for all subjects in the trial to attend a minimum of one clinic visit a week. However, attrition in Phase 2 trials tends to be high. In order to comprehend the reasons for dropping out of the clinical trial, we will arrange to meet the research subject weekly during the course of the medication phase of the trial at a mutually-agreeable location and/or taxi the participant to the clinic to collect a urine drug sample and complete data typically collected on a weekly basis.

Termination and Follow-Up Procedures: Once participants complete the 12-week medication period, they will be asked to return during week 13 for a repeat EKG, labs, and physical exam, and for follow-up assessment. On the final visit (approximately 30 days after completing study medications), participants will complete a brief health check with a study clinician. Every effort will be made to retain all participants through the entire trial. Our group has developed effective procedures for retaining individuals in controlled experimental drug trials (e.g., building strong relationships with study participants, telephone, texting, and letter procedures). Similar strategies will be implemented for this proposed study. However, we recognize that not all participants will complete the trial. Early termination criteria by the principal investigator are defined as two consecutive weeks (or four consecutive visits) of missed study activity or data collection visits. Participants who end the trial early, for whatever reason, will be asked to attend the 4-week follow-up visits.

Safety Procedures: A study clinician will assume primary medical responsibility for each participant and will personally evaluate any significant complaints, clinical adverse events, or abnormal laboratory finding. The observation of the initial dose of study medication at the clinic will provide an added level of safety monitoring that will enable the study clinicians to ensure that participants are able tolerate study medications in the outpatient setting. Participants will be provided with instructions on how to contact the study clinician via a 24 hour phone number. Weekly rounds will be held with the full study team and the status of each participant will be reviewed to assess medical and psychiatric safety, experimental drug compliance, and data completion. Participants assessed at any point to be a danger to self or others or who are judged to be in grave danger due to continued drug use and/or to extreme psychiatric problems will be discontinued from the study and connected with an appropriate treatment facility. All study staff receive training in identifying suicide/homicide risks and/or signs of dangerous intoxication and in the steps needed to appropriately respond to these signs. In the event a participant is a potential risk to harm himself or others, Distress Protocol procedures will be followed to insure that the participant is assessed by a licensed clinician as soon as possible (see Appendix I). There have been rare occurrences of elevations in GGT levels (two participants of IBUD clinical trials to date) and as a result basic lab tests (hematology, chemistry, and hepatic panels including GGT) will be rechecked for each participant during week 3, and week 8 of the medication period, as well as at termination (week 13). Any participant experiencing an SAE will be followed until the resolution of the SAE.

Study Medication Stopping Rules: With respect to medication stopping criteria, mild to moderate symptoms of agitation, hostility, depressed mood, and changes in behavior or thinking are typically observed during the course of methamphetamine treatment due to methamphetamine use and/or withdrawal and will not alone trigger discontinuation of IBUD. Agitation, hostility, depressed mood, and changes in behavior or thinking that are **NOT typical** of methamphetamine use or withdrawal, i.e. severity greater than moderate and/or temporally un-related to methamphetamine use/withdrawal, will trigger immediate discontinuation of IBUD and evaluation by the study clinician.

Pre-specified criteria for discontinuation of study medication include:

- a) Development of agitation, hostility, depressed mood, or changes in behavior or thinking not typical of methamphetamine use or withdrawal (more severe and/or temporally un-related to methamphetamine use/withdrawal)
- b) Development of any psychiatric condition requiring hospitalization or psychiatric intervention
- c) Suicide attempt or active serious suicidal ideation as assessed by the C-SSRS or verbal report
- d) Development of a medical condition that contraindicates treatment using IBUD (e.g., treatment with beta-agonists or phosphodiesterase inhibitors for asthma)
- e) Severe nausea and vomiting that does not respond to a reduction in study medication
- f) Increasing methamphetamine use that requires more intensive care than outpatient treatment
- g) Have a systolic blood pressure greater than 160, or a diastolic blood pressure greater than 100 (i.e. cutoffs for stage 2 hypertension), or a heart rate greater than 70% of the maximum heart rate expected for their age ($0.70(220 - \text{age})$) at any visit
- h) Confirmed QTc > 500 milliseconds on ECG or increase in QTc > 60 milliseconds from baseline (QTc to be determined on at least two ECGs)
- i) Females who become pregnant
- j) Incarceration or mandated court urine testing

- k) Any other circumstances that, in the opinion of the investigators, would compromise participant safety (e.g. onset of alcohol abuse, mania, etc.)

The study clinician may reduce a participant's dose from 100 mg/day to 80 mg/day (40 mg in AM and 40 mg in PM), or potentially 30 mg BID, for any potential dose-related side effects but dose increases will not be allowed. The study physician may temporarily discontinue (hold) study medication for up to two weeks followed by re-initiation of study medication in the event of transient adverse events but if the medication is not re-started within two weeks of holding, the medication will be discontinued. If the medication is discontinued, medication adherence checks and compensation will be discontinued as well. Urine samples will be collected for UV fluorimetry and storage up to 1 week post-medication discontinuation. MM counseling will continue through the remaining study weeks (up to week 12) to support and monitor the participant.

Data and Safety Monitoring Board (DSMB) and Trial Stopping Rules: A Data and Safety Monitoring Plan will be submitted to NIDA and the UCLA Addiction Medicine DSMB and approved prior to enrolling participants. The UCLA Addiction Medicine DSMB will monitor the study and review study progress and adverse events after the first 35 participants have been enrolled and then at least yearly. Any SAEs that occur will be reported to the DSMB, as well as all other regulatory bodies monitoring the trial (e.g. FDA, NIDA, UCLA IRB) at the time of the occurrence of the SAE. In addition, an interim blinded group analysis will be performed once mid-way through the trial when approximately half of the proposed 140 individuals have been enrolled. At this time, the person responsible for randomization will confirm that randomization is proceeding according to the protocol.

While statistical guidelines for stopping the trial are provided below, they are intended as a guide for the DSMB and other regulatory bodies to use in making a determination as to whether the trial should be stopped or continued and will not in isolation trigger discontinuation of the trial. The following statistical guidelines are provided for consideration of stopping the trial:

- If the frequency of SAEs is statistically significantly greater ($p < 0.05$) in the IBUD group compared to the placebo group at interim analysis or anytime during the trial, consider stopping the trial.
- If there is a statistically significant ($p < 0.05$) difference in the primary study outcome (MA abstinence verified by urine drug screens during the final two weeks of the trial) favoring the placebo over the IBUD group (e.g. suggesting significantly worse treatment outcomes and greater MA use during treatment with IBUD), consider stopping the trial.

Following the interim analysis or the occurrence of any severe, unexpected adverse events, the DSMB will review results of blinded group analyses, progress of the trial to date, and revisit the risks versus benefits of the trial for participants and society, and make recommendations regarding the continuation or stopping of the trial. The final decision regarding stopping the trial will be made during consultation between the PI (Dr. Heinzerling), NIDA, the DSMB, and other regulatory bodies (FDA, UCLA IRB) as appropriate.

Collection Procedures and Analysis of DNA and Inflammatory Markers: All participants will have blood (10 ml) collected during the lead-in period for genotyping. DNA will be extracted from samples at the UCLA Biological Samples Processing Core Facility using the Autopure LS[®] (Gentra Systems, Minneapolis, MN) automated DNA purification system. After purification, DNA will be frozen at -20°C until genotyping is performed at the end of the trial. Participants will be genotyped via allelic discrimination with the Taqman 5' –nuclease assay on the ABI PRISM 7700 Sequence Detection System (Applied Biosystems, Foster City, CA) at the UCLA Sequencing and Genotyping Core Facility. Genotyping errors will be checked using the mistyping option in the Mendel version 6.5 statistical software package. To avoid issues of population stratification, analyses will be stratified by ethnicity.

The following SNPs will be genotyped (Table 3): rs2910704 in GDNF which is associated with severity of MA dependence in a Japanese study (Yoshimura, Usui et al. 2011); the A1 allele of the DRD2 Taq1 A polymorphism (rs1800497), actually downstream of DRD2 within the gene for the ANKK1 kinase (Neville, Johnstone et al. 2004), is associated with reduced striatal D2 availability in human autopsy (Thompson, Thomas et al. 1997, Ritchie and Noble 2003) and [¹¹C] raclopride PET studies (Pohjalainen, Rinne et al. 1998, Jonsson, Nothen et al. 1999); C957T in the D2 dopamine receptor gene (DRD2) which is associated with striatal D2 receptor availability on PET (Hirvonen, Laakso et al. 2004, Hirvonen, Laakso et al. 2009) and response inhibition assessed via the stop signal task (Colzato, van den

Wildenberg et al. 2010); rs12364283 within DRD2 which is associated with altered D2 dopamine receptor expression (Zhang, Bertolino et al. 2007); and rs2283265 and rs1076560 in DRD2 which result in alternative splicing of DRD2 RNA and changes in the relative expression of the long (found postsynaptically) and short (found presynaptically) isoforms of the D2 dopamine receptor (Zhang, Bertolino et al. 2007) and are associated with cocaine abuse in Caucasians (Moyer, Wang et al. 2011).

Table 3: SNP Genotyping

SNP	Gene	Rationale	Genotype Frequency ¹			MAF ¹
rs2910704	GDNF	↑ MA dependence in Japanese	CC=0.43	CG=0.46	GG=0.11	0.35
rs1800497 (Taq1 A)	ANKK1	↓ striatal D2 availability	GG=0.67	AG=0.28	AA=0.05	0.20
rs6277 (C957T)	DRD2	↓DRD2 expression/↓D2 availability	GG=0.17	AG=0.59	AA=0.24	0.53
rs12364283	DRD2	DRD2 promoter, ↓D2 expression	AA=0.84	AG=0.15	GG=0.01	0.08
rs2283265	DRD2	Change in ratio D2 _{long} to D2 _{short}	CC=0.71	AC=0.26	AA=0.03	0.16
rs1076560	DRD2	Change in ratio D2 _{long} to D2 _{short}	CC=0.76	AC=0.22	AA=0.02	0.13
rs6265 (Val66Met)	BDNF	Altered BDNF excretion	CC=0.64	CT=0.33	TT=0.03	0.20

¹ from HapMap CEU (Caucasians in Utah) population

Plasma and serum will be collected during the lead-in period and during weeks 3, 8 and 13 to measure inflammatory and neurotrophic markers. Plasma levels of the following inflammatory cytokines and chemokines will be determined via multiplex assay: IFN- α , IL-1 β , IL-2, IL-6, TNF- α , MCP-1, MIP-1 α , MIP-1 β , and MIF. Serum levels of neurotrophic factors, GDNF and BDNF, will be determined via singleplex assays. In addition to the above markers, CRP and uric acid will also be measured from serum at baseline and weeks 3, 8 and 13 via ELISA and Uricase assays, respectively. Potential changes in inflammatory markers with treatment for MA dependence will be assessed.

Neuropsychological Assessment: A battery of neuropsychological (NP) tests will be administered to approximately half of the sample (N = 70) at baseline, week 4, and immediately following discontinuation of study medication (week 13). As acute stimulant use masks neurocognitive deficits in stimulant abusers (Woicik, Moeller et al. 2009), participants will receive gift cards for providing methamphetamine-free urine samples during the second week of the lead-in period when baseline cognitive testing will be done. Any potential confounding effect of MA use on cognitive battery results will be explored in the data analysis.

In addition to the comprehensive pre- and post-medication NP battery, brief serial assessments will be administered during the medication treatment period (weeks 1-12) to examine potential changes in both top-down (Iowa Gambling Task) and bottom up (Stop Signal test) cognitive processing approaches during treatment. The Connors' CPT will be administered on weeks 2, 6 and 10.

Note: Collection of data for the neurocognitive battery was concluded after randomization of 85 participants due to staff and budgetary constraints.

Subject Reimbursement: Subjects will be reimbursed for time spent completing study measures and costs related to transportation to and from the clinic in the form of gift cards only; no cash is provided to subjects (Table 4).

Table 4: Potential Participant Reimbursement with neurocognitive testing (pre- July 2016)

Activity	Amount
CM intervention during lead-in (\$15 for the first MA-free urine, \$25 for second, and \$40 for third)	\$80
Completion of screening measures	\$25
Completion of Medication adherence check (\$5/week x 12 weeks)	\$60
Twice-weekly clinic attendance during weeks 1-10 (\$10/visit x 20 visits)	\$200
Twice-weekly clinic attendance during weeks 11-12 (\$25/visit x 4 visits)	\$100
Iowa Gambling (Half of the participants (n = 70) will receive compensation) task at baseline and weeks 4 and 13 (\$10 per completed task)	\$30
Connors' CPT task at weeks 2, 6, and 10 (\$5/completed task x 3 tasks)	\$15
Cognitive battery at week 4 and termination (\$20/battery x 2)	\$40
Weekly clinic attendance during weeks 13, 14 and 15 (\$10/visit)	\$30

Completion of study close-out visit (week 16)	\$15
Total possible earned by participant	\$565 or \$595

Potential Participant reimbursement without neurocognitive testing (post- July 2016)

Activity	Amount
CM intervention during lead-in (\$15 for the first MA-free urine, \$25 for second, and \$40 for third)	\$80
Completion of screening measures	\$25
Completion of Medication adherence check (\$5/week x 12 weeks)	\$60
Twice-weekly clinic attendance during weeks 1-10 (\$10/visit x 20 visits)	\$200
Twice-weekly clinic attendance during weeks 11-12 (\$25/visit x 4 visits)	\$100
Weekly clinic attendance during weeks 13, 14 and 15 (\$10/visit)	\$30
Completion of study close-out visit (week 16)	\$15
Total possible earned by participant	\$510

Participants may receive compensation for the CM intervention during the second week of the two-week lead-in period as follows: Participants will receive \$15 for the first MA-free urine provided during the second week, \$25 for the second MA-free urine provided, and \$40 for the third MA-free urine provided for a maximum of \$80 for all three clean urine drug screens. All participants will receive \$25 in gift cards upon completion of the screening measures, regardless of urine drug screen results, to compensate participants for time spent completing screening measures. Participants will receive \$5 in gift cards for completing weekly medication pill counts during the 12 week medication period for a total of \$60. During week 1 through week 10 of the medication treatment period, participants will receive \$10 for each of the twice weekly visits attended. During weeks 11 and 12, participants will receive \$25 for each of the twice weekly visits attended. Participants who miss a clinic visit will not receive compensation for that visit. During baseline, and weeks 4 and 13, half of the subjects (n = 70) will be compensated for completing the Iowa Gambling cognitive task (see below) and will earn \$10 per completed test session for a possible maximum of \$30. The following pertain to the initial 85 participants who will undergo neurocognitive testing: Participants who complete the neurocognitive testing will be randomized to the pay or no pay condition based on their assigned screening identification (SID) number, where an SID ending in an even number will be assigned to the pay condition and an SID ending in an odd number will be assigned to the no pay condition for the remainder of the study. In addition, subjects will earn \$20 for completing the cognitive test battery during week 4 and at termination (week 13) and \$5 each time they complete the Connors' CPT task (weeks 2, 6, and 10 for a total of \$15 possible). For all participants, during weeks 13, 14 and 15, participants will receive \$10 for each weekly visit attended. Finally, subjects are reimbursed \$15 for completing the final study close out visit (week 16). The total reimbursement that participants could earn during the trial is \$595 (pay condition for Iowa Gambling Task) or \$565 (no pay condition for Iowa Gambling Task) for participants completing the neurocognitive testing and \$510 for participants participating after the close of the neurocognitive testing portion of the trial.

Study Measures and Assessments: The following assessments have been selected to provide a comprehensive assessment of participants' medical and psychological status and severity of MA dependence at baseline as well as response to treatment including MA use, psychological symptoms and cravings, and adverse events. Appendix II presents all study assessments in a table format.

Addiction Severity Index (ASI) Lite (McLellan, Kushner et al. 1992) estimates the severity of participants' reported addiction-related problems. The ASI is a standardized 40-minute clinical research instrument widely used in addiction research to quantify problem areas of alcohol/drug user populations. The following seven areas of functioning are measured: medical, employment, drug use, alcohol use, legal, family/social, and psychiatric conditions. This measure will be administered during the lead-in period.

An adverse event (AE) is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered related to the study medications. For this study, AEs will include events reported by the subject, as well as clinically significant abnormal

findings on physical examination or laboratory evaluations. AEs will be assessed during screening, weekly during the medication phase, and at follow up.

Barratt Impulsiveness Scale-11 (BIS-11), administered during screening, is a 30-item questionnaire (e.g., “I act on impulse”, “I plan tasks carefully”) that has been validated in several different populations. The BIS-11 includes three subscales labeled attentional, nonplanning, and motor (Patton et al., 1995).

Brief Symptom Inventory (BSI, Derogatis, 1993) is a 53-item self-report clinical rating scale used to assess psychological distress. This measure will be administered during screening and monthly.

Columbia-Suicide Severity Rating Scale (C-SSRS) is a brief questionnaire that was developed at the request of the FDA for monitoring of suicidality in subjects in clinical trials. The questionnaire takes 5 minutes to administer and tracks both suicidal behavior and ideation and provides a summary measure of suicidality that can be serially tracked over the course of a clinical trial (Posner, Oquendo et al. 2007). This measure will be administered during the lead-in period and weekly during the medication and follow up phase.

Concomitant Medications: All subjects will be asked about concomitant medications weekly during the lead-in and outpatient treatment period. Concomitant medications include both OTC and prescribed medications.

Early Life Stress Questionnaire (ELSQ): The Early Life Stress Questionnaire (McFarlane, Clark et al. 2005) (ELSQ) is a self-report questionnaire that considers 19 adverse life events (crime, sexual abuse, family conflict, bullying, etc.). High ELS is defined as exposure to ≥ 3 ELS events prior to age 19 (Cohen, Paul et al. 2006, Paul, Henry et al. 2008, Seckfort, Paul et al. 2008, Clark, Cohen et al. 2012), consistent with the rates of ELS in the general population (Cohen, Paul et al. 2006). Previous studies (Cohen, Grieve et al. 2006, Cohen, Paul et al. 2006, Seckfort, Paul et al. 2008, Clark, Cohen et al. 2012) have shown that using a cut-point of ≥ 3 ELS events provides the greatest discrimination on the basis of ELS for behavioral and neural measures. The ELSQ will be administered during week 3.

Perceived Stress Scale (PSS-14): The PSS-14 is a validated, self-report questionnaire that assesses the extent to which individuals perceive their life to be stressful (Cohen and Williamson 1988). The PSS-14 will be administered during baseline.

Posttraumatic Stress Disorder Checklist - Civilian version (PLC-C): is the most commonly used self-report questionnaire assessing number and severity of PTSD symptoms. The PLC-C will be administered during week 3.

Genotyping/SNP: 10 ml whole blood will be collected at baseline for DNA extraction for genotyping analyses.

Hamilton Depression Rating Scale (HAMD) (Riskind, Beck et al. 1987): Completed in just 5 to 10 minutes, the HAMD can be used to quickly evaluate symptom severity, to confirm a diagnosis of depression, to explore depressive symptoms, and to measure treatment outcome. The HAMD will be administered during the lead-in period and weekly during the medication and follow-up phase.

HIV CD4 Count and Viral Load: Participants who are HIV+ will have CD4 count and viral load measured at baseline, at the termination of medication (week 13), and at the last follow-up visit (week 16).

HIV medication adherence: Participants who are HIV positive will have their HIV medication adherence assessed monthly by asking them to estimate the proportion of their medications that they took in the past month.

HIV Risk-taking Behavior Scale: This is a self-administered assessment of the subject's engagement in activities that increase the likelihood of contracting HIV (Darke et al, 1991). This measure will be administered at screening (McDonald and Calhoun 2010) and monthly during the medication phase.

MA Craving Visual Analog Scale (Griffiths et al., 1993): Craving is a complex biological and psychological phenomenon. Subjective effects will be measured using a visual analog scale that ranges from 0 (not at all) to 100 (extremely) assessing strongest craving in the past 24 hours, the ability to refuse MA, “want” of methamphetamine, use if access to drug, etc. This measure will be administered during screening and weekly during the medication and termination.

Medication compliance: As described above, aliquots (5 ml) from each twice weekly urine sample as well as a serum sample (10 ml) during week 3 of study medication will be collected for measurement of concentrations of IBUD and its primary metabolite as a marker of medication adherence.

Physical examination/medical and neurological history/labs/EKG: A medical history, neurological history, and physical exam with all participants during the screening period. An EKG, blood chemistry panel (including liver profile and GGT), HIV and hepatitis C virus serology, PPD (if not previously completed), CBC, and urinalysis will be completed during screening and at termination. Hematology and chemistry labs (including liver panel and GGT) and an EKG will be repeated during week 3 and week 8 of study medication as well as at termination (week 13) for safety monitoring purposes. Female participants will have a urine pregnancy test monthly.

Self-Report of Medication Adherence/Pill Count: Using a the participant's medication blister package as a visual aide, research staff will sit with each participant at each study visit and review study medication-taking in the period since the participant's last visit. All study medications drugs taken will be plotted on the pill count record and deviations from the prescribed dosage will be noted. Non-adherent subjects will review medication dosing procedures with a study clinician and barriers to compliance will be discussed.

Inflammatory and neurotrophic markers: Serum and plasma will be collected from whole blood during baseline and during weeks 3, 8 and 13 for assessment of these markers.

Structured Clinical Interview for DSM-IV (SCID) (Spitzer, Williams et al. 1995): Participants must meet DSM-IV criteria for methamphetamine dependence, as determined by the SCID during screening. A full SCID, as well as the Antisocial Personality Disorder (ASPD) subsection of the SCID-II will be completed by a study clinician (following training on the instrument) These results will be used to estimate the extent of co-morbid psychiatric diagnoses, and to verify that the participant does not have an active psychiatric disorder that precludes safe study participation.

Timeline Follow-Back method (TLFB) (Sobell, Sobell et al. 1986) will be used to determine days of use and quantities of use of cigarettes, alcohol, and other drugs over a 30-day period prior to screening. The same method anchored in the past 7 days will be used weekly during the second week of screening and during the medication and follow up phases.

Urinary Cotinine: Cigarette smoking status will be monitored biologically weekly via measurement of urinary cotinine.

Urine Drug Screening for benzodiazepines, marijuana, opiates, cocaine, and MA will be monitored using an onsite qualitative urine test device. Subjects will be warned that tampering with samples and taking OTCs that cross-react with the MA panel will be interpreted as positive for illicit substance use with consequences of being dropped from study participation. Urine drug screening will be completed at *each* study visit. If a participant is unable to attend a clinic visit (e.g. out of town, holiday, etc.), subjects may provide drug screening samples using oral test kits.

Urinary Riboflavin concentration will be measured on each urine specimen via fluorimetry using a Quantifluor Fluorometer (Promega Corp). Urinary riboflavin ≥ 900 ng/ml will be considered positive for active pill taking.

Vital Signs: Blood pressure, pulse, respiration rate, and temperature will be collected at each study visit.

Wender Utah Rating Scale (WURS) (Wender, 1995), administered during screening, retrospectively assesses ADHD-relevant childhood behaviors and symptoms in adults consisting of 25 items. Estimates of ADHD in the population of MA abusers are between 15%-35%.

Assessment of Neurocognitive Endophenotypes Implicated in MA Dependence

Neurocognitive testing will be performed on the initial 85 participants enrolled. Beginning in July 2016 (N = 85) only the MOCA will be administered at baseline and again at weeks 4 and 13. While we will include selected clinical NP tests to allow characterization of traditionally studied NP domains and to facilitate cross-study comparisons, our assessment strategy is focused on elucidation of underlying neurocognitive endophenotypes that are associated with chronic MA use and/or may serve as barriers to optimal engagement in treatment. We will employ tasks that are sensitive to disordered inhibitory control, risky decision making, attentional control, and procedural learning and probabilistic categorization. When feasible, clinical NP tests that are part of the MATRICS battery will be employed. The MATRICS battery (an acronym for Measurement and Treatment Research to Improve Cognition in Schizophrenia) is the product of an NIMH initiative to stimulate the development of pharmacological agents to treat NP deficits in schizophrenia. It is specifically designed to be used in clinical trials in which

it is crucial to measure cognitive change in a short period of time with good test-retest reliability, relationship to functional outcome, and tolerability (MATRICS Manual, 2006). While there are of course significant differences between the cognitive deficits seen in schizophrenia vs. MA dependence, there is also considerable overlap, making this test battery particularly well-suited for this study. We will also include NP tests that measure cognitive functions thought to be relatively unaffected by MA use (i.e., language, visuospatial processing) to evaluate the specificity of our measures.

Our brief serial assessments will include tests that target bottom-up and top-down cognitive processing approaches. Prior work has demonstrated that successful abstainers may attempt to control their intrusive drug-related cognitions either by diverting their attention away from drug-related stimuli (Baker, Lee et al. 2005, Kavanagh, Andrade et al. 2005, Schoenmakers, de Bruin et al. 2010) or suppressing their subjective craving (Brody, Mandelkern et al. 2007), an effect which may be facilitated by increased top-down cognitive processing. Similarly, drug-dependent individuals may demonstrate deficits in top-down cognitive processing, concomitant with increased bottom-up activity in such regions as the nucleus accumbens and amygdale (Due, Huettel et al. 2002, David, Munafò et al. 2005, McClernon, Hiott et al. 2007) which trigger the affective and appetitive signals of immediate drug outcomes (Bechara 2005). This may suggest that in successful abstainers, there will be increased top-down processing in areas responsible for cognitive control, error/ risk detection (Whalen, Bush et al. 1998, Bush, Luu et al. 2000, Bechara 2005, Lee, Pohlman et al. 2010). Additional details for each of these tests follow.

- **Inhibitory Control**

Stop Signal Test (SST). This task measures how long it takes for an individual to cancel an initiated motor response. On each of 256 trials a stimulus appears, and subjects must press a corresponding key as quickly as possible. Subjects are, however, also instructed to try to stop themselves from completing a response if they hear a “stop-signal” tone (25% of trials)

MATRICES Continuous Performance Test (MATRICS CPT-II). We will employ the Identical Pairs version CPT which is part of the MATRICS assessment battery (MATRICS, 2006). This is a computerized test of sustained attention and response inhibition which was developed at UCLA and has indices of response inhibition (commission errors), vigilance (omissions), and reaction time. The MATRICS CPT-II will be administered at baseline, week 4 and termination.

Connors' Continuous Performance Test (Connors' CPT-II). The Connors' CPT-II is a reliable and valid computer administered test of sustained attention that takes approximately 15 minutes to administer. The Connors' CPT-II will be administered at weeks 2, 6 and 10.

- **Risk Taking/Decision Making**

Iowa Gambling Task (Bechara et al. 1994). This task was developed to more closely simulate real-world decision making and risk taking than do most of the more typical neuropsychological “executive functions” tasks. To examine whether compensation enhances the ecological validity of this test, half of the participants will be randomized to receive \$10 per completed task during baseline and weeks 4 and 13 based on their SID assigned at consent.

- **Implicit learning/Procedural learning**

Pursuit Rotor Task. The Pursuit Rotor Task is well-known measure of procedural learning. Based upon prior research performed by our group with cocaine dependent participants (van Gorp et al., 1999), the rate of rotation for the turntable will be set at 50 revolutions per minute.

- **Traditional Clinical NP Tests**

(1) Learning & Memory – (a) Hopkins Verbal Learning Test-Revised (HVLT-R); (b) Brief Visuospatial Memory Test-Revised (BVM-T-R)

(2) Speed of Processing – (a) Trail Making Test (TMT); (b) Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV) Digit Symbol coding; (c) WAIS-IV Symbol Search

(3) Working Memory - (a) WAIS-IV Letter Number Sequencing; and (b) N-Back Task

The Delis-Kaplan Executive Function System (DKEFS) Color Word Interference test measures ability to inhibit a dominant and automatic verbal response.

The Wechsler Test of Adult Reading (WTAR, Wechsler, 2001) is a test that estimates premorbid level of intellectual function.

The Montreal Cognitive Assessment (MOCA, Nasreddine et al., 2005) is a brief (10 minute) screening instrument that samples behavior across 14 performance tasks including attention, language, visuospatial, executive, and memory.

The Wide Range Achievement Test 4 (WRAT4, Wilkinson & Robertson, 2006) is a norm referenced test with grade-based norms for reading.

Delay Discounting Task (DDT): Subjects are given a number of choices between smaller, immediate rewards, and larger, delayed rewards. The results provide an estimate of how steeply individuals discount the future value of money compared to their estimation of the present value. An increased rate of DD (signifying a steeper discounting of the future value of money) has been observed in alcoholics, heroin addicts, cocaine addicts, smokers, and pathological gamblers.

During weeks 4 and 13, participants will repeat the following tasks: Montreal Cognitive Assessment; MATRICS CPT-II; HVLIT-R; BVMT-R; SST; TMT; DDT; WAIS-IV Letter Number Sequencing ; WAIS-IV Symbol Search, WAIS-IV Digit Symbol Coding; N-Back Task; DKEFS Color Word Interference and the Iowa Gambling Task.

Data Analysis: The primary objective of this study is to determine the efficacy of IBUD as a treatment for MA dependence and to provide FDA with sufficient data to advise whether IBUD should move forward for marketing as a MA dependence treatment. The primary outcome variable is the FDA-specified criterion of significant MA abstinence at the end of treatment defined as no self-reported MA use during the final two weeks of treatment (weeks 11/12) confirmed via urine drug screens (at least one of the two possible urine specimens each week is available during weeks 11 and 12 and all available urine specimens are MA-negative). The study is powered to detect a significant difference in the proportion of participants achieving this outcome in the IBUD versus placebo groups. Additional measures of clinically meaningful reductions in MA use during treatment will also be assessed in the event that IBUD produces effects on MA use that do not meet the abstinent at end of treatment threshold. In addition to MA use outcomes, treatment retention, an important clinical variable that is associated with long-term treatment outcomes in substance abuse treatment (Hser, Evans et al. 2004), with IBUD versus placebo will be compared. Effects of potential confounders on each of these outcomes will also be examined including: (1) medication non-adherence, (2) medication safety and tolerability (adverse event rates), and (3) ability to achieve initial MA abstinence with the CM intervention during the two week lead-in period.

A general univariate strategy will be used to test for differences between conditions at baseline and along all outcome variables using bivariate analyses (i.e., t-tests/ANOVA for continuous variables; χ^2 for dichotomous variables). A multivariate analysis will also be used when appropriate to control for co-variables known to influence MA dependence treatment outcomes including age, gender, baseline severity of MA dependence, HIV status, and ability to achieve initial abstinence during the CM lead-in.

Aim 1: To determine whether IBUD reduces MA use more than placebo among MA dependent participants.

Hypothesis 1: IBUD will result in significantly greater reductions in MA use than placebo

Analysis: The outcome of reductions in MA use will be assessed using results from twice weekly urine drug screens for MA-metabolites and self-reported MA use (weekly time line follow-back). This analysis is an intent-to-treat analysis that involves the period from Day 0 to the end of the 12 week active medication period. Univariate composites of urine drug screen results include:

- FDA-Specified Criterion of significant abstinence – two weeks continuous MA abstinence at end of treatment (primary study outcome): The proportion of participants in the IBUD and placebo groups with two weeks continuous MA abstinence during weeks 11 and 12, defined as self-reported MA abstinence confirmed by urine drug screens (at least one of the two possible urine specimens possible each week is available and all available are MA-negative) during weeks 11 and 12.
- Treatment Effectiveness Score: mean number of MA-free urine specimens provided during the 12 week outpatient treatment period in the IBUD versus placebo groups.
- Joint Probability Index: Measures whether an average participant is retained and abstinent at a given point in the trial. The probability that a participant is retained at a given point is multiplied by

the probability a participant is abstinent at the same point. The measure will be calculated at the midpoint (end week 6) and termination (end week 12) for IBUD and placebo groups.

A logistic regression model will be used to compare the odds of the dichotomous outcome variable two weeks continuous MA abstinence at end of treatment for IBUD versus placebo groups, controlling for important co-variables including age, gender, severity of baseline MA dependence (number of MA use days in the past 30 days at baseline), and HIV status. Longitudinal modeling techniques including GEE will be then used to model MA use as measured via urine drug screen results and self-report of drug use, taking advantage of the twice-weekly urine specimens collected during the trial. Additional covariates such as gender, age, baseline MA use may be included as appropriate.

Examination of potential confounders Rates of adverse events and medication adherence in the IBUD and placebo groups will be calculated and compared. Medication adherence will be assessed as a continuous variable: the proportion of twice-weekly urine drug samples positive for riboflavin (≥ 900 ng/ml riboflavin as determined via quantitative fluorimetry), and as a dichotomous variable: medication adherent ($\geq 80\%$ of twice-weekly urine drug screens positive for riboflavin). Adherence will also be assessed via qualitative measurement of IBUD and metabolites in urine and serum samples, which is the gold standard for assessing adherence in the IBUD group but is limited by the fact that assessment of adherence in the placebo group is not possible. Models for MA use outcomes will be repeated including the continuous measure of adherence as a co-variate. The models will also be run with the sample stratified as medication adherent versus non-adherent. As pre-treatment abstinence is an important predictor of treatment outcomes and medication response in stimulant dependence trials (Elkashef, Rawson et al. 2008, Bisaga, Aharonovich et al. 2010), the sample will be stratified by ability to achieve initial abstinence with CM during the two-week lead-in period to explore whether medication effects may differ in these subgroups.

Aim 2: To determine whether IBUD results in longer treatment retention than placebo among MA dependent participants.

Hypothesis 2: IBUD will result in significantly greater treatment retention than placebo

Analysis: The mean number of days retained, defined as the number of days from the start of study medication to the final clinic visit during the 12 week treatment period, will be compared for IBUD versus placebo via t-test. Cox proportional hazards model will be used to compare days retained for IBUD versus placebo controlling for co-variables including age, gender, and baseline MA use. These analyses will then be repeated with the sample stratified by ability to achieve initial abstinence with CM during the two-week lead-in period to explore whether medication effects may differ in these subgroups.

The following exploratory HIV-related aims will be address in the HIV positive participants.

Aim 3: To determine whether IBUD improves biological (CD4 count; HIV RNA) and neurocognitive outcomes more than placebo among HIV-positive MA dependent participants.

Hypothesis 3: IBUD will result in greater improvements in CD4 count, HIV viral load, and neurocognitive functioning than placebo among HIV positive participants.

Analysis: Change scores for CD4 count, HIV viral load, and scores on neurocognitive assessments will be calculated between baseline and end of medication treatment. The mean change score for each measure will be calculated for IBUD versus placebo. A linear regression model will be used to assess the mean change in measures for IBUD versus placebo after controlling for possible confounders such as gender, MA abstinence during the two-week lead-in period, and medication adherence.

Aim 4: To determine whether IBUD improves behavioral outcomes (sexual transmission behaviors; uptake and/or adherence to HIV medications) relative to placebo among HIV-positive MA dependent participants.

Hypothesis 4: IBUD will result in greater reductions in HIV risk behaviors and increased HIV medication uptake/adherence than placebo among HIV positive participants.

Analysis: The proportion of participants reporting HIV sexual risk behaviors in the IBUD and placebo groups will be calculated. The proportion of participants reporting receipt of HIV medications as well as the proportion of medication they report taking will be calculated. The mean number of self-reported HIV

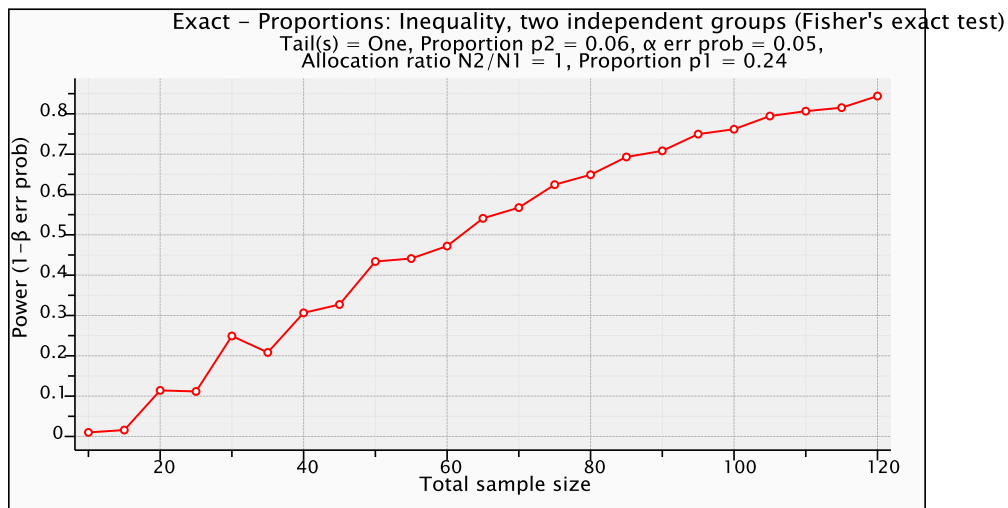
sexual risk behaviors for IBUD versus placebo will be compared via t tests and then in a linear regression model controlling for potential confounders. The mean HIV medication adherence rate (proportion of medication taken) for IBUD and placebo will also be compared via t test and then linear regression model.

Exploratory analyses Baseline neurocognitive functioning of participants will be described using results of the neuropsychiatric (NP) battery performed at baseline. Baseline to post-treatment changes in scores on tests in the NP battery will be calculated for IBUD and placebo groups. Effect sizes for IBUD on NP battery change scores will be calculated and used to determine whether future fully powered studies examining NP changes with IBUD are warranted. In addition, GEE models will be used to compare change in the brief serial weekly cognitive assessments (Balloon Analog Reaction Time task and Stop Signal test) during treatment with IBUD versus placebo. To explore whether severity/type of neurocognitive dysfunction at treatment entry mediates response to IBUD, baseline scores on NP assessments will be included as co-variables in the models assessing IBUD effects on MA use outcomes and treatment retention. Finally, potential effects of polymorphisms in dopaminergic genes and GDNF (Yoshimura, Usui et al. 2011), as well levels of inflammatory biomarkers and neurotrophic factors on treatment outcomes will be explored. The sample will be stratified by genotype for each SNP and changes in MA use and retention for IBUD versus placebo will be compared in these sub-groups. In addition, baseline versus post-treatment serum and plasma levels of inflammatory markers neurotrophic factors will be compared for IBUD versus placebo groups and by HIV serostatus. Correlation between early life stress measures and baseline severity of MA abuse as well as treatment outcomes, including potential early life stress-ibudilast interactions, will also be explored.

We recognize that the study is not powered to detect statistical significance in these analyses, especially if corrections for multiple testing are employed (Benjamini and Hochberg 1995) and as a result these analyses are by design for exploratory purposes only. Still we feel that including these probes of potential IBUD mechanisms of action within the context of this early clinical trial is important in that the results may bolster any observed effects of IBUD on MA use outcomes and direct the design of subsequent adequately powered confirmatory phase III trials.

Power calculations: Power is calculated (Figure 5) for the primary study outcome: the proportion of participants achieving MA abstinence during the final two weeks of treatment (weeks 11 and 12) in the IBUD versus placebo group. This is the FDA-preferred outcome for stimulant pharmacotherapy trials and was used in a previous study that found an effect size of 0.5 for bupropion relative to placebo for MA dependence (Elkashef, Rawson et al. 2008). For a Fischer's exact test comparing the proportion achieving abstinence during final two weeks on IBUD versus placebo, with an effect size similar to that in the previous bupropion trial (0.5), a one-tailed test assuming IBUD will be superior to placebo, and an $\alpha = 0.05$, 55 participants are required in each group (total N = 110) to achieve 80% power. Our total sample size of 140 exceeds 80% power. Note that the use of the outcome variable abstinent during the final two weeks of treatment accounts for attrition as participants who fail to complete the trial fail to achieve urine drug screen confirmed abstinence during the final two weeks (i.e. missing considered non-abstinent). This is a conservative approach but appropriate as an effective medication would be expected to sustain patients in treatment for the allotted time in addition to facilitating abstinence as longer treatment retention and treatment completion are strong predictors of superior long-term outcomes and sustained abstinence (Ahmadi, Kampman et al. 2006, Hillhouse, Marinelli-Casey et al. 2007).

Figure 5: Power by total sample size (IBUD plus placebo) calculated with G*Power 3.1.0 (Faul, Erdfelder et al. 2007).



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APPENDIX I

Standard Operating Procedure: Managing Behavioral Disruption in Methamphetamine Dependent Participants

OVERVIEW

PURPOSE: The purpose of this Standard Operating Procedure is to guide behavior of staff members in responding to behavioral disruptions on the part of participants who are methamphetamine dependent and who are either inpatient or outpatient study participants.

BACKGROUND: For the most part, methamphetamine dependent participants in outpatient studies are managed behaviorally in the same way as other participants in hospital studies. Predictability and calmness on the part of staff members will aid in keeping drama to a minimum, independent of whether the participant is methamphetamine dependent. Indeed, there is little to become concerned about in managing behavioral disruption from patients in studies of medications for methamphetamine dependence. Much of the skills necessary for managing participants who occasionally become disruptive during the hospital inpatient stay already exist in good measure among the staff. For example, if a methamphetamine dependent participant becomes argumentative with a staff member, that individual can ask the participant to calm down and that he may want to return to a room until he is less upset.

MANAGING MINOR BEHAVIOR DISRUPTIONS

Participants in this study will remain in the trial for a total of 18 weeks. In that time, some minor behavioral disruptions may occur. These behavioral disturbances will be managed successfully primarily by maintaining a general calm demeanor and using reasoning with the participants. Becoming upset in response to the patient's actions will generally exaggerate the crisis.

Signs: Participant's verbal and physical behaviors are the first clues of mild behavioral disruption.

- Participant becomes argumentative or complains about details of the clinic, the study or his life.
- Tone of voice is urgent, but generally not rude.
- Participant negotiates effectively with staff members who seek to resolve the disruptions.
- There is little indication participant will become physically assaultive.
- Participant is not being flagrant in other aspects of his behavior.

Using a calm demeanor, there are several responses you can use to successfully resolve a minor behavioral disruption caused by a methamphetamine dependent patient:

- Tell the participant you are willing to hear his complaint, but that you can do that only if he calms down.
 - When the participant calms down, *listen* to what s/he is saying and if possible, work with the participant to resolve the problem being expressed.
- Calmly ask the participant to remove him/herself from general community for a period (e.g., "time out" in a room) until his mood is calm and he can return to the community to discuss the problem.
- Ask if there is something that could be helpful to the participant in managing his upset mood (for example, food, snacks, movie, internet, cell phone).
- Check if the participant is experiencing tobacco withdrawal and whether he would like to be accompanied for a smoking break.

MANAGING MODERATE BEHAVIOR DISRUPTIONS

Signs: It is likely that one or two moderate behavior disruptions will occur as we complete 140 participants in this protocol. These disruptions are likely to involve display of strong and immediate concerns/desires to leave the clinic and to quit the study. You will be able to tell this is different than a minor disruption as you will find it difficult to "talk the participant down" or to get him to change his mind. It is unlikely that such moderate behavioral disruption will involve any threats of violence to staff or to self. It is far likelier that the participant will demand to be let out of

the unit (withdraw study consent). Still, if the participant threatens to leave the unit, it is critical that you reach Dr. Heinzerling, Dr. Shoptaw or Dr. Briones immediately.

MANAGING SEVERE BEHAVIOR DISRUPTIONS

Signs: Severe behavioral disruption is rare and obvious. Signs of severe behavioral disruption include extreme agitation (beyond being upset), threats, self-injurious behavior etc.

For managing severe behavior disruptions, the main issue is to maintain safety for the participant and the clinic.

If there are concerns of threats to self/others, the Distress Protocol is activated (see below).

If the situation is not sufficiently severe to summon security/police (e.g., participant destroys property, but is not a threat to self/others), manage as a moderate behavioral disruption above and get in touch with one of the study investigators to manage staff and participant ASAP.

DISTRESS PROTOCOL

Signs: Subjects give clear signs when they are a danger to themselves or to someone else. These include but are not limited to:

- They tell you they have thoughts about killing you, killing themselves, or killing someone else.
- When a subject endorses item 3 of the HAMD with 2 or greater.
- When a subject has a total HAMD score greater than 17.
- Sometimes a family member or friend will tell you the subject is talking about impulsive actions against self/others.

When **any sign** like this occurs, the following distress protocol is implemented:

- 1) Inform the subject you are seeking assistance, especially if the subject uses language that references wishes to die, thoughts of being better off dead, no more reason to live, threats to kill you or any person who is identifiable (i.e., a named individual – not just a vague reference such as “any A-hole who gets in my way today”), etc.
- 2) **Immediately** notify the study clinician and request a licensed mental health provider be called. Once a staff member decides there is reason to initiate contact with a responsible clinician, contact must be **immediate** and follow through must be **complete**. It is critical that staff continue contacting study Investigators until someone is located and a licensed clinician is on-site to speak with the distressed subject. Distressed subjects must be evaluated by a licensed clinician with **one hour** of discovery.
 - a. **Highest Levels of Distress:** In cases in which a licensed clinician determines that immediate intervention is required to manage a subject’s extreme distress (e.g., that the individual is making an unambiguous threat to the safety of himself or to an identifiable intended victim), immediate steps will be taken to arrange for an involuntary hold at the Psychiatric ER to guarantee the subject’s physical safety and/or the physical safety of an identifiable intended victim. In the event that an identifiable intended victim is named and clinical staff determine the threat to be credible, the information regarding the threat and the intended victim’s identity will be provided to the police. In keeping with laws following Tarasoff requiring a counselor to warn an intended victim of a potential threat to their physical safety, clinical staff also will make contact with the identifiable intended victim and inform the individual that a credible threat to his life has been made by the distressed subject and that the individual should take appropriate measures to ensure his physical safety.
 - b. **Moderate Level of Distress:** For subjects who are assessed as clinically distressed, but not in need of emergency intervention or containment, the clinician will speak briefly with the subject and inform him that we require the subject to freely engage a “no suicide/no homicide” contract. This type of contracting procedure is standard to psychological practices in managing distressed subjects and is identical to the procedures in use in our clinical research projects for the past 12 years. Distressed subjects who receive this distress evaluation experience the procedure not as “coercive,” but instead find it reassuring that the level of distress they report is recognized and addressed. The counseling and contracting process also signals to the subject the seriousness the team places in keeping subjects oriented toward health and away from injurious behaviors. Observing the distressed subject’s reaction after completing a clinical assessment and after informing him we wish to enter a commitment to avoid injurious behaviors using a clinical contract not to hurt self or others provides additional information as to the actual level of distress for the subject (e.g., should the subject escalate, we have information that we need to re-think the level of

distress for the subject and to consider activating procedures to ensure physical safety). While it is possible (but highly unlikely) that a subject would misrepresent his distress by misleading clinical staff and by agreeing to engage the no suicide/no homicide contract and then kill himself or kill someone else, it remains that suicide/homicide are low base rate behaviors and the clinical evaluation and contracting process remain the gold standard for addressing highly distressed subjects in clinical practice.

- 3) A trained staff member **will remain with the participant at all times** during assessment/ treatment until a Study Clinician deems the subject not at risk or the subject is handed off to another licensed clinician.
- 4) It is possible that a subject may provide misleading information to the clinic staff members about his distress level and/or his intent to hurt himself or another. The procedures detailed here provide the best and most consistent methods used in clinical practice to respond to subjects in distress and their intentions to hurt themselves or others.

APPENDIX II: Assessment Schedule for Ibudilast Phase 2 Trial

STUDY ASSESSMENT TABLE FOR IBUDILAST PHASE II TRIAL

Measures	Baseline	Medication Phase			Follow-Up
		Weekly Wks 1-12	Specific time	Monthly Wk 4, 8, 12	
	0.6 visits				Weekly Wk 13, 14, 15, 16
Clinical measures					
Medical history	X				
Physical	X				wk 13
EKG	X		wks 3, 8		wk 13
Labs	X		wks 3, 8		wk 13
HCV serology	X				wk 13
HIV test	X				wk 13
if HIV+, CD4/viral load	X				wks 13, 16
DNA/SNP sample	X				
Inf/NT markers (serum and plasma)	X		wks 3, 8		wk 13
Pregnancy test	X			X	
Adverse events	X	X			X
Urine drug screen	e	e			X
Vital signs	e	e			X
Progress note	e	e			X
Urinary cotinine	X	X			X
Concomitant medications	X	X			
Pill count		X			wk 13
HIV medication adherence	X			X	wk 16
Medication compliance (urine) via UV fluorimetry	e	e			wk 13
Stored urine aliquot	X	e			
Medication compliance (serum)			wk 3		
Behavioral assessments					
ASI	X				
BIS-11	X				
PSS-14	X				
ELSQ			wk 3		
PLC-C			wk 3		
SCID	X				
WURS	X				
HRBS	X			X	wk 16
BSI	X			X	wk 16
MA Craving VAS	X	X			X
C-SSRS	X	X			X
HAMD	X	X			X
TLFB	X (0.1, 0.4)	X			X
Medical Management Counseling	X	X			
Cognitive functioning measures <i>After July 2016, only MOCA is still being administered</i>					
WTAR	X				
WRAT4	X				
MOCA	X (0.1)		wk 4		wk 13
BVMT-R	X		wk 4		wk 13
HVLT-R	X		wk 4		wk 13
CPT-II (MATRICS version)	X		wk 4		wk 13
CPT-II (Connors' version)			wks 2, 6, 10		
TMT	X		wk 4		wk 13
SST (comp)	X		wk 4		wk 13
DDT (comp)	X		wk 4		wk 13
Iowa Gambling Task	X		wk 4		wk 13
Symbol Coding (WAIS-IV)	X		wk 4		wk 13
Symbol Search (WAIS-IV)	X		wk 4		wk 13
Letter Number Sequencing (WAIS-IV)	X		wk 4		wk 13
N-Back Task	X		wk 4		wk 13
DKEFS Color Word Interference	X		wk 4		wk 13
Pursuit Rotor Task	X		wk 4		wk 13

e: every visit.