1) Abstract of the study

STUDY OBJECTIVES: This is a randomized, double blind, placebo controlled, tolerability-based, dose escalating inpatient trial to determine the effect and duration of multiple doses of clavulanic acid (CLAV) on glutamate (Glu) levels, using neuroimaging, in an addiction related brain area (the anterior cingulate cortex [ACC]) in subjects with cocaine use disorder (CocUD) who have achieved one week of abstinence.

Primary Objective: The primary objective of this study is to determine whether once-a-day repeated CLAV 500 (or higher, 750/1000 mg, see dose escalation in study design) in patients with CocUD in early remission produces reductions in brain Glu levels at day 10 compared to baseline, as assessed by Magnetic Resonance Spectroscopy (MRS) in the anterior cingulate (ACC).

Secondary Objectives: A) To assess changes in craving-associated neurocircuitry (frontal-striatal-thalamic connectivity) using resting state functional Magnetic Resonance Imaging (rs-fMRI). Subjects with CocUD will have decreased functional connectivity between nodes within the frontal-striatal-thalamic network (Wang et al. 2018) involving mesocorticolimbic circuit nodes (Gu et al. 2010). After repeated CLAV, we expect that the fronto-striatal-thalamic within network functional connectivity will increase. We also will determine whether improved network connectivity as associated with decreased craving as determined by the Cocaine Craving Questionnaire (CCQ) and a Visual Analog Scale (VAS). B) To evaluate whether CLAV 500, 750, 1000 mg a day given repeatedly for 10 days (to steady state, rationale below) and then stopped, is associated with a sustained reduction in brain glutamate concentration measured in the ACC one day after cessation of CLAV dosing (to determine the duration of CLAV action on glutamate after last dose and to determine the feasibility of once daily CLAV dosing). C) To evaluate whether 10 days of treatment with CLAV is associated with increases in brain glutamine concentration as assessed by MRS in the ACC. D) To assess CLAV 500, 750, and 1000 mg/day safety and tolerability by: a) the rates of occurrence of adverse events; b) changes in vital signs; c) EKG parameters; and d) laboratory study changes.

Exploratory Objectives: A) To evaluate whether repeated CLAV treatment 500, 750, 1000 mg/day suppresses cue-induced limbic fMRI activation. B) To evaluate whether CLAV treatment 500, 750, 1000 mg/day for 10 days is associated with subjective effects measured by Visual Analog Scales (VAS), the Profile of Mood States (POMS). C) To evaluate whether CLAV treatment 500, 750,1000 mg/day for 10 days is associated with cognitive and executive function deficits as assessed by the Cambridge cognition survey batteries. D) To evaluate whether Adverse Childhood Experiences (ACEs) are associated with increased outcomes of subjective reports of mood and craving.

STUDY ENDPOINTS:
Primary Endpoint: Change in brain glutamate concentration in the ACC at Day 10 compared with baseline.
Secondary Endpoints:

A) Brain connectivity change in the ACC on resting state fMRI. CCQ and VAS for craving.
B) Change in brain glutamate concentration in the ACC at Day 11 compared with Day 10.
C) Change in brain glutamine concentration in the ACC at Day 10 compared with baseline.
D) Safety and tolerance as assessed by the rates of occurrence of adverse events, changes in vital signs, Columbia Suicide Severity Rating Scale (C-SSRS), EKG parameters and laboratory studies compared with baseline.

Exploratory Endpoints:

A) Suppression of cocaine cue-induced limbic activation during imaging task.
B) Subjective effects will be compared before and after CLAV 500, 750,1000 mg/day for 10 days using the following instruments: Visual Analog Scales (VAS), Profile of Mood States (POMS).
C) Scores from the Cambridge Cognition Cognitive battery at multiple timepoints compared with baseline.
D) Relationship between scores from the Adverse Childhood Experiences (ACE) scale, POMS, and VAS.

STUDY DESIGN: This is a randomized, double-blind, placebo-controlled, parallel group inpatient study of clavulanic acid, 500, 750,1000 mg given orally once a day for 10 days. Subjects are adults (18-70) in early remission who are seeking treatment for cocaine use disorder. In rodents, CLAV 1 mg/kg is associated with a decrease in cocaine intake after 5-7 days, which is then maintained and can be considered steady state. A conservative estimate for steady state in humans is CLAV administration for 10 days. For those subjects who can tolerate 500 mg/day for 3 days (or matched placebo), there will be a forced dose escalation to 750 mg/day for 3 days. For those subjects who can tolerate 750mg/day for three days, there will be a forced dose escalation to 1000mg for 4 days. Subjects who cannot tolerate an increased dose will return to the last tolerable dose for the remainder of the study.

Structural MRI, functional MRI, and MRS will be done before study drug administration at baseline, after 3 days of study drug administration (prior to 750mg dose escalation), after 6 days of study drug administration (prior to the 1000mg dose escalation) on the last day of study drug administration (day 10), and one day after the last dose of study drug (day 11). The final MR scan session will be used to gather information on the duration of CLAV's effect on anterior cingulate cortex glutamate concentration after cessation of CLAV dosing. At the time of each scan, safety of the subject to complete the scan will be re-assessed. Subjective and cognitive assessments will be administered daily in the inpatient setting. Assessments of adverse effects, blood pressure and pulse will also be performed daily.

STUDY DURATION: Study duration is 3 outpatient visits (screening and follow up) and 11 inpatient days. There will be 5 MRI/MRS studies during the inpatient portion of the study. The pre-intake screening will last up to 30 days. After participants are discharged

from the inpatient portion of the study, they will be asked to return for the follow up visit 5-8 days after discharge. The visit will include an assessment of adverse events to determine withdrawal symptoms. All adverse events will be followed by study staff until resolution.

TREATMENT: The oral administration of CLAV 500,750,1000 mg/day or matched placebo for 10 days. Day 1 dosing is 1 capsule (250 mg) twice a day. Participants will receive 500mg CLAV in the morning on days 2 and 3 if the day 1 dose is safely tolerated. For those subjects who can tolerate 500 mg/day for 3 days (or matched placebo), there will be a forced dose escalation to 750 mg/day (or matched placebo) for 3 days. For those subjects who can tolerate 750mg/day (or matched placebo) for three days, there will be a forced dose escalation to 1000mg (or matched placebo) for 4 days. Participants who are unable to tolerate dose escalation will resume their previously tolerated dose. Nine subjects will be randomized to CLAV and 3 to placebo.

2) Protocol Title

A Phase IB Double Blind, Placebo Controlled, Pharmaco- Magnetic Resonance Spectroscopy (MRS) inpatient study of Clavulanic acid 500, 750,1000 mg daily repeated administration in early remitted cocaine use disorder subjects.

3) IRB Review History

Date:
03/27/2020 Initial submission to IRB (Modifications required)
04/17/2020 Modifications required to secure approval submitted (approved)
07/01/2020 Modification to include Covid Testing and Ace Questionnaire submitted (modifications required)
08/03/2020 Modifications required to secure approval submitted (approved)
09/17/2020 Modification to change dose self-administration procedures submitted (modifications required)
10/23/2020 Modifications required to secure approval submitted (approved)
11/02/2020 Modification to change screening and bonus schedule (modifications required)
11/03/2020 RNI (scanning schedule change) submitted
11/18/2020 Modifications for RNI submitted (approved)
11/30/2020 Response to modifications required for approval (approved)
12/01/2020: Modification to split screen into two parts and provide $25 gift card compensation for Covid-19 testing **(**Modifications required)
12/23/2020: Response to modifications required to secure approval (approved)
03/29/2021: Temple Main Hospital and Jeanes added as back up inpatient sites (modifications required)
04/15/2021: Response to modifications required (approved)
05/13/2021: Eligibility Criteria Revised (approved)

4) Investigator

Primary Investigator/Medical Monitor:	Mary F. Morrison, M.D., M.S. (Temple University)
Co-Investigator/Imaging Specialist:	Helene Philogene-Khalid, Ph.D. (Temple University)
Co-Investigator/Back up Medical Monitor:	M. Ingre Walters, M.D. (Temple University)

Other Key Personnel

Neuroimaging Supervisor:	Huiling Peng Ph.D. (Temple University)

5) Objectives

STUDY OBJECTIVES: This is a randomized, double blind, placebo controlled, tolerability-based, dose escalating inpatient trial to determine the effect and duration of multiple doses of clavulanic acid (CLAV) on glutamate (Glu) levels, using neuroimaging, in an addiction related brain area (the anterior cingulate cortex [ACC]) in subjects with cocaine use disorder (CocUD) who have achieved one week of abstinence.

Primary Objective: The primary objective of this study is to determine whether once-a-day repeated CLAV 500 (or higher, 750/1000 mg, see dose escalation in study design) in patients with CocUD in early remission produces reductions in brain Glu levels at day 10 compared to baseline, as assessed by Magnetic Resonance Spectroscopy (MRS) in the anterior cingulate (ACC).

Secondary Objectives: A) To assess changes in craving-associated neurocircuitry (frontal-striatal-thalamic connectivity) using resting state functional Magnetic Resonance Imaging (rs-fMRI). Subjects with CocUD will have decreased functional connectivity between nodes within the frontal-striatal-thalamic network (Wang et al. 2018) involving mesocorticolimbic circuit nodes (Gu et al. 2010). After repeated CLAV, we expect that the fronto-striatal-thalamic within network functional connectivity will increase. We also will determine whether improved network connectivity as associated with decreased craving as determined by the Cocaine Craving Questionnaire (CCQ) and a Visual Analog Scale (VAS). B) To evaluate whether CLAV 500, 750, 1000 mg a day given repeatedly for 10 days (to steady state, rationale below) and then stopped, is associated with a sustained reduction in brain glutamate concentration measured in the ACC one day after cessation of CLAV dosing (to determine the duration of CLAV action on glutamate after last dose and to determine the feasibility of once daily CLAV dosing). C) To evaluate whether 10 days of treatment with CLAV is associated with increases in brain glutamine concentration as assessed by MRS in the ACC. D) To assess CLAV

500, 750, and 1000 mg/day safety and tolerability by: a) the rates of occurrence of adverse events; b) changes in vital signs; c) EKG parameters; and d) laboratory study changes.

Exploratory Objectives: A) To evaluate whether repeated CLAV treatment 500, 750, 1000 mg/day suppresses cue-induced limbic fMRI activation. B) To evaluate whether CLAV treatment 500, 750, 1000 mg/day for 10 days is associated with subjective effects measured by Visual Analog Scales (VAS), the Profile of Mood States (POMS). C) To evaluate whether CLAV treatment 500, 750,1000 mg/day for 10 days is associated with cognitive and executive function deficits as assessed by the Cambridge cognition survey batteries. D) To evaluate whether Adverse Childhood Experiences (ACEs) are associated with increased outcomes of subjective reports of mood and craving.

STUDY ENDPOINTS:

Primary Endpoint: Change in brain glutamate concentration in the ACC at Day 10 compared with baseline.

Secondary Endpoints:

A) Brain connectivity change in the ACC on resting state fMRI. CCQ and VAS for craving.
B) Change in brain glutamate concentration in the ACC at Day 11 compared with Day 10.
C) C) Change in brain glutamine concentration in the ACC at Day 10 compared with baseline.
D) D) Safety and tolerance as assessed by the rates of occurrence of adverse events, changes in vital signs, Columbia Suicide Severity Rating Scale (C-SSRS), EKG parameters and laboratory studies compared with baseline.

Exploratory Endpoints:

A) Suppression of cocaine cue-induced limbic activation during imaging task.
B) Subjective effects will be compared before and after CLAV 500, 750,1000 mg/day for 10 days using the following instruments: visual Analog Scales (VAS), Profile of Mood States (POMS).
C) Scores from the Cambridge Cognition Cognitive battery at multiple timepoints compared with baseline.
D) Relationship between scores from the Adverse Childhood Experience (ACE) scale, POMS, and VAS.

STUDY DESIGN: This is a randomized, double-blind, placebo-controlled, parallel group, dose-escalating inpatient study of clavulanic acid, 500, 750, 1000 mg given orally once a day for 10 days.

In rats, CLAV 1 mg/kg is associated with a decrease in cocaine intake after 5-7 days, which is then maintained and can be considered steady state. A conservative estimate for steady state in humans is CLAV administration for 10 days. For those subjects who can tolerate 500 mg/day for 3 days (or matched placebo), there will be a forced dose escalation to 750 mg/day for 3 days. For those subjects who can tolerate 750 mg/day for three days (or matched placebo), there will be a forced dose escalation to 1000 mg (or matched placebo) for 4 days.

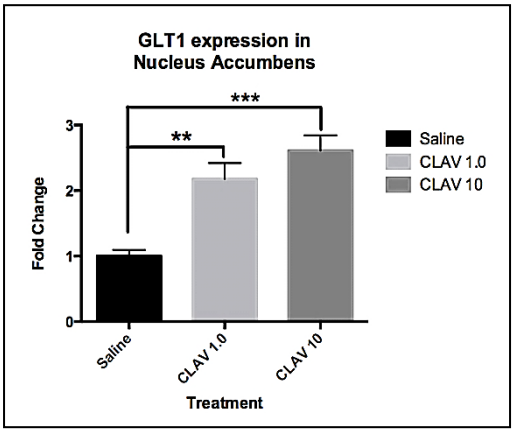

Figure 1. CLAV (1.0 mg/kg, 10 mg/kg) increased GLT-1 expression in nucleus accumbens. n=5-6/group; bars are S.E.M. ** and *** indicates significance from vehicle as determined by Bonferroni posttest $p<0.01$ and $p<0.001$ respectively.

Structural MRI and a MRS scan will be done before CLAV administration at baseline, on day 3 of the study prior to the 750mg dose escalation, on day 6 of the study before the 1000 mg escalation, on day 10 of the study (maximum CLAV dose), and one day after the last dose of CLAV to gather information of the duration of CLAV's effect on brain glutamate concentration after cessation of CLAV dosing. Before each scan, safety of the subject to complete the scan will be re-assessed. Assessments of subjective and cognitive effects will be administered at the beginning of each inpatient study day. In addition, safety assessments of adverse effects, blood pressure, and pulse will be performed during each study day. The C-SSRS will be conducted at screening, baseline, and on the discharge day. A full list of assessments is included in table 1 in section 10: study design. A medication questionnaire (Med-Q) will be used to determine whether participants believe they have been given study drug or placebo.

STUDY DURATION: Study duration will be 10 days of study drug with 5 MRS scans over that time as an inpatient. This is in addition to the pre-intake screening and a follow up visit. The pre-intake screening will last up to 30 days. The follow up visit will occur 5-8 days after discharge. The follow up visit will involve study assessments and an evaluation of adverse events to determine any withdrawal symptoms. Subjects with adverse events that require further in person assessments may be asked to come in for an additional visit. All adverse events will be followed until resolution.

TREATMENT: The oral administration of CLAV 500, 750, 1000 mg/day or matched placebo for 10 days. Day 1 dosing is 1 capsule (250 mg) twice a day. Participants who safely tolerate the initial 250 mg dose will be provided the second 250 mg dose for self-administration. For those subjects who can tolerate 500 mg/day for 3 days (or matched placebo), there will be a forced dose escalation to 750 mg/day (or matched placebo) for 3 days. For those subjects who can tolerate 750mg/day (or matched placebo) for three

days, there will be a forced dose escalation to 1000 mg (or matched placebo) for 4 days. Subjects who are unable to tolerate an increased dose will resume the previously tolerated dose when medically appropriate (usually the next day).

6) Background

Rationale for CLAV, a GLT-1 Transport Activator

The glutamate system is critical to understanding and treating CocUD. A large body of evidence suggests that inhibiting glutamatergic transmission decreases COC use in addiction. Glutamatergic projections from the amygdala and dorsal prefrontal cortex to the nucleus accumbens drive drug-seeking following an addiction reinstatement trigger (Uys and LaLumiere 2008). Preclinical studies at Temple and elsewhere suggest that activation of GLT-1, the dominant astroglial glutamate transporter (Rothstein et al. 2005) may provide a breakthrough approach to managing COC addiction. Through a complex mechanism, chronic COC use reduces the basal extracellular concentration of glutamate. Consequently, during stress- or drug-induced reinstatement of COC seeking, there is an increase in synaptic release of glutamate into the nucleus accumbens (Kalivas 2009). These effects on glutamate signaling contribute to its reinforcing properties, the acquisition of self-administration behavior, and the maintenance, extinction, and subsequent reinstatement of drug seeking (Knackstedt and Kalivas 2009).

Data from animal studies show that CLAV, a component of the commonly used antibiotic Augmentin, is an activator of the glutamate transporter GLT-1 (excitatory amino acid transporter, EAAT2) (**Fig. 1**) and reduces COC-seeking behavior (**Fig. 2**).

CLAV is a Potent GLT-1 Activator that Decreases COC Use. The data below are presented to show that: 1) CLAV is a potent GLT-1 activator; 2) CLAV decreases COC use in addicted rodents; 3) CLAV is superior to available beta-lactam drugs in its potential for clinical use.

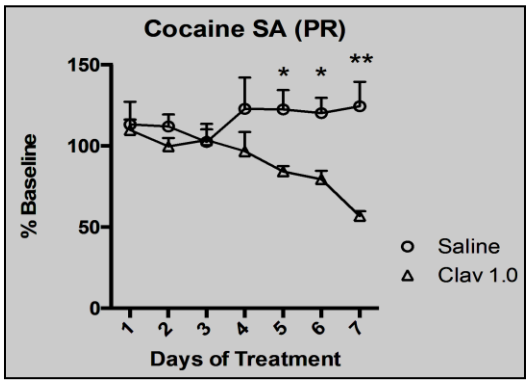

Figure 2. CLAV 1 mg/kg inhibited motivation to self-administer COC (0.56mg/kg/inf) under PR schedule of reinforcement. n=4-6/group. Bars are S.E.M. * significantly different from vehicle by Bonferroni post-test.

GLT-1 activators inhibit COC self-administration. Excessive synaptic glutamate activity is buffered by the transport of glutamate into the glial cells via GLT-1 (Rothstein et al. 2005). Since glutamate release in nucleus accumbens leads to COC self-administration, treatments that enhance the activity of GLT-1 might be expected to inhibit COC self-administration. Drugs containing the β-lactam structural motif activate GLT-1 and thereby increase glial glutamate uptake. For example, the β-lactam antibiotic ceftriaxone (CTX) displayed anti-glutamate activity *in vitro* (Rothstein et al. 2005, Chu et al. 2007) *and in vivo* (Miller et al. 2008, Rasmussen et al. 2011). CTX (200 mg/kg) decreased COC self-administration, with statistically significant differences seen by Day 7 (Ward et al. 2011). As shown in **Fig. 2**, CLAV (1 mg/kg) also decreases COC self-administration, with statistically significant differences seen by Day 5 (Kim et al. 2016).

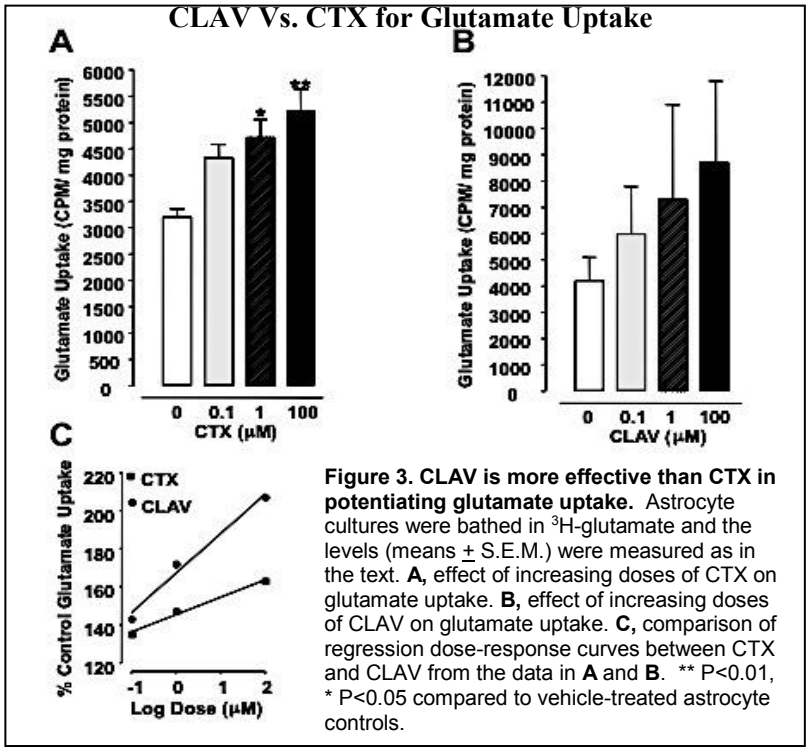

Figure 3. CLAV is more effective than CTX in potentiating glutamate uptake. Astrocyte cultures were bathed in ^{3}H-glutamate and the levels (means ± S.E.M.) were measured as in the text. **A,** effect of increasing doses of CTX on glutamate uptake. **B,** effect of increasing doses of CLAV on glutamate uptake. **C,** comparison of regression dose-response curves between CTX and CLAV from the data in **A** and **B**. ** P<0.01, * P<0.05 compared to vehicle-treated astrocyte controls.

CLAV has glutamate modulating properties similar to ceftriaxone (CTX). Preclinical experiments from the Rawls' lab provide a proof-of-principle that CLAV, a β-lactam compound structurally related to CTX, mimics CTX efficacy against neuropsychiatric disorders that result from excessive glutamate transmission. CLAV also displayed anti-glutamate activity in three different neurochemical assays: enhanced GLT-1 expression in nucleus accumbens (**Fig. 1**), increased glutamate uptake in astrocytes (**Fig. 3B**), and reduced extracellular glutamate in nucleus accumbens (data not shown). This is supported by findings demonstrating that CLAV has neuroprotective properties in animal models of neurodegenerative diseases (Huh et al. 2010). The β-lactam compounds also display substance abuse-deterrent properties in animal models. CTX administration inhibited acquisition and motivation of COC self-administration in mice (Ward et al. 2011) and prevented relapse to COC seeking in rats (Ward et al. 2011, Sari et al. 2009). In a model of chronic cocaine abuse, CTX ameliorated myelin loss in the nucleus accumbens, suggesting neuroprotection (Kovalevich et al. 2012). CTX also inhibited sensitized behavioral responses produced by amphetamine in rats (Rasmussen, Unterwald, and Rawls 2011, Rawls, Baron, and Kim 2010). Similarly, CLAV inhibits motivational and reinforcing properties of COC in mice (**Fig. 2**).

CLAV may be a more potent GLT-1 activator than CTX. As shown in **Fig. 2** CLAV (1 mg/kg) had a potent effect on inhibiting COC intake in mice (P<0.05). Repeated administration of CLAV at both 1 mg/kg and 10 mg/kg significantly increased GLT-1

protein expression in rat nucleus accumbens (**Fig. 1**). In fact, CLAV (10 mg/kg) produced a ~1.4-fold increase in GLT-1 expression, comparable to that detected with a much higher dose of CTX (200 mg/kg, 10 days) (Miller et al. 2008, Rasmussen et al. 2011). Both CLAV and CTX increased glutamate uptake in primary astrocytes (**Fig. 3B, A**). The magnitude of the CLAV effect was actually greater than that of CTX, and regression analysis indicated that CLAV displays enhanced anti-glutamate properties relative to CTX (**Fig. 3C**). Additional support for CLAV having greater potency than CTX in glutamate-associated disorders was obtained in an invertebrate assay designed to screen for anti-epileptic activity (Rawls et al. 2010). CLAV displayed greater potency than did CTX against glutamate- and COC-induced planarian seizure-like activity. [(glutamate, COC): (1.44, 0.010 mM for CLAV) and (5.8, 24.5 mM for CTX)]. Thus, both vertebrate and invertebrate models demonstrate that CLAV displays anti-glutamate properties, but at lower doses than CTX.

CLAV is preferable to CTX for testing the hypothesis that GLT-1 activation can prevent COC self-administration and other glutamate-associated toxicities. CTX has 3 drawbacks as a drug for human use. First, it must be given parenterally. Second, it is an antibiotic, so its use can give rise to drug resistant bacteria. Third, CTX displays poor blood brain barrier (BBB) penetrability, which requires the use of high doses for CNS efficacy (typically 200 mg/kg/ day in rodents). These doses equate to about 13 g/day in a human, approximately 5 times greater than CTX doses used for meningitis. Compared with CTX, CLAV displays greater BBB permeability with mean CLAV ratios, cerebrospinal fluid to plasma, of ~23% in neurosurgical patients with normal BBB (Nakagawa et al. 1994). Chronic cocaine use has been associated with a pro-inflammatory state, so the BBB permeability of CLAV may be increased in chronic users (Fiala et al. 1998). CLAV has negligible antibiotic activity (Saudagar, Survase, and Singhal 2008), so there is very low risk of developing drug resistant strains. CLAV is an oral drug, which is a practical delivery system for an inpatient study. We hypothesize that CLAV, an existing drug that is brain penetrable, safe and orally active offers a realistic candidate for cocaine pharmacotherapy. Repeated CTX administration produced a dose-dependent reduction in glutamate levels in that persist for up to 20 days following discontinuation of drug exposure (Rasmussen, Unterwald, and Rawls 2011). The prolonged reduction in glutamate levels after CTX discontinuation suggest that CTX's effect on glutamate is not a PK-mediated mechanism, since the half-life of CTX is short (~ 6 hours). We plan to investigate whether CLAV, given repeatedly for 10 days, is also associated with reduced glutamate levels after discontinuation of drug exposure with an MRS scan 24 hours after the last CLAV dose.

CLAV may be effective for combined cocaine/opiate addiction. Recently, cocaine related overdose deaths have increased significantly. In non-treatment samples, much of the cocaine use are in combination with opiates (Leeman et al. 2016). CLAV might be an effective treatment as a monotherapy or as an adjunctive treatment for comorbid cocaine and opioid use disorder based on available preclinical data. Male rats treated with morphine at 4mg/kg demonstrate conditioned place preference (Schroeder et al. 2014). Co-treatment with either CLAV (10 mg/kg) or the beta-lactam, CTX (200 mg/kg), inhibited the development of conditioned place preference associated with morphine by

approximately 70%, suggesting efficacy in the treatment of opiate addiction. In a heroin study, male rats were trained in heroin self-administration (Shen et al. 2014). After extinction, the rats were given 7 days of CTX (200mg/kg) and CTX treatment was associated with a reduction in cue associated relapse to heroin seeking. Therefore beta-lactams appear to have efficacy in two preclinical models of opiate addiction, with one study utilizing heroin and another study, morphine. CLAV, an oral beta-lactam, may be effective for combined cocaine and opiate addiction.

Pharmacology*.* Potassium clavulanate is a beta-lactamase inhibitor and is the potassium salt of CLAV. CLAV is structurally related to penicillin with a beta-lactam ring.

Pharmacokinetics*.* The half-life of CLAV is short (between 0.8 and 2 hours) and there is no accumulation between doses (Sánchez Navarro 2005).

Previous Human Experience. CLAV is unavailable by itself. CLAV is part of Augmentin/Augmentin XR®, along with amoxicillin, which has been FDA approved since 1984 for the treatment of patients with acute bacterial sinusitis. Augmentin® is considered reasonably safe during pregnancy and lactation (Berkovitch et al. 2004, Benyamini et al. 2005). CLAV is not an effective antibiotic and is unlikely to disturb bowel flora (Saudagar, Survase, and Singhal 2008). There is no safety data in the scientific literature on CLAV alone.

CLAV/COC Interaction Study: CLAV Is Safe to Use in People Who Have Taken Concurrent COC. We performed an inpatient, placebo-controlled cocaine interaction safety study with 3 acute doses of CLAV (250 mg, 500 mg, and 750 mg (N=5 for 750 mg dose) in ten subjects (8 men and 2 women). The study report was received by the FDA in December 2018. This study was performed under double-blind conditions (for the 250 mg and 500 mg doses) and single blind for the 750 mg dose, which was added later in the study. There was no indication that any dose of clavulanic acid produced medical instability or increased clinical risk in conjunction with COC. No serious or severe adverse events occurred during the trial. No clinically significant changes in diastolic blood pressure, pulse or electrocardiogram parameters occurred related to CLAV. Minor increased systolic blood pressure occurred in the 250mg session compared to the placebo and 500mg CLAV sessions. The pharmacokinetic (PK) data suggested that CLAV PK levels generally increased from the 40-minute timepoint to the 70-minute timepoint post dose, as expected. Participant CLAV PK levels had high variability between subjects which has been noted in healthy controls (De Velde et al. 2018). There was no pupillometry evidence to support a pharmacodynamic effect of CLAV on cocaine-associated pupil size increase. Thirty-two adverse events (AEs) occurred in 10 subjects during the study. Of these AEs, 11 occurred either during the safety day (2 doses of cocaine, N=8) or the placebo day (N=3), 4 occurred on the 250 mg dose of CLAV day, 6 occurred during the 500 mg dose day, and 2 occurred on the 750 mg dose day, 5 on the day of discharge and 4 at the outpatient follow up visit. The AEs deemed to be potentially related to study drug included: headache, nausea, indigestion, drowsiness, and minor elevations of serum calcium.

We performed a phase 1B open label imaging pilot study of CLAV 500mg for 10-day in five completed subjects (4 men and 1 woman), with 8 subjects total. No serious or severe adverse events occurred during the trial. The AEs deemed to be potentially related to study drug included: headache, nausea, hunger, diarrhea, and constipation.

Based on the benign adverse event profile of CLAV in combination with cocaine in our cocaine interaction study, and our procedures ensuring careful observation for significant blood pressure elevations and arrhythmias during and after cocaine administration, the data obtained from the cocaine interaction study provide confidence that CLAV 500 mg/day can be safely used in an inpatient setting for 10 days in recent cocaine users. Side effects reported in the Phase I studies of CLAV from the FDA approval include: nausea, vomiting, drowsiness, diarrhea, indigestion, headache, increased stomach noises, flatulence (passing gas), “very slight increase in liver size” with increased liver tests, cholestatic jaundice, and dizziness. In the present study one male participant experienced priapism, without pain, for 5 hours after the first day of study drug (study drug not unmasked). He informed the study team after resolution. During the screening visit, male subjects will be evaluated for priapism risk factors, abnormal anatomy of the penis, and previous episodes of unexpected, prolonged erections. The PI consulted with Dr. Jack Mydlo, the Temple Chair of Urology, and determined that a participant with an erection of 4 hours or longer will be transferred to the Emergency Room. Participants experiencing priapism will have their cavernosal blood gas evaluated to determine whether the priapism is high or low flow. Emergency Room physicians at Temple are familiar with priapism evaluation, and will discuss the results with the Urology Resident on call for further management.

Common adverse events for Augmentin include: diarrhea (14.5%), vaginal mycosis (3.3%), nausea (2.1%) and loose stools (1.6%). As a beta lactam drug, CLAV has a risk of allergic reactions for those with known penicillin allergy. The risk of hepatitis for Augmentin® is estimated at between 1/10,000 to 1/100,000, with an increased risk for older males (Gresser 2001). Hepatotoxicity associated with amoxicillin/ CLAV is generally self-limited with cessation of medication and generally associated with complete recovery (Saudagar, Survase, and Singhal 2008, Gresser 2001, Larrey et al. 1992). Single dose studies with sodium clavulanate were performed at both 750 mg (5 subjects) and 1000 mg (2 subjects) (FDA 05/09/1988). After 750 mg, 4 of 5 subjects had symptoms, although they were mild in 3 and consisted of “slight sleepiness, borborygmi and a heavy feeling in the epigastrium. The fourth subject had marked malaise, indigestion, and slight headache between ½-2 hours after dosing and later epigastric discomfort and diarrhea which persisted for several hours.” The medical literature supports the hypothesis that CLAV at doses up to 500 mg/day and CLAV given as a chronic medication is generally safe and well tolerated. Combined amoxicillin clavulanate (CLAV 250 mg a day) has been given to men to treat actinomycetoma for a mean of 9.6 months with no reported side effects (Bonifaz et al. 2007). Combined meropenem/clavulanate (CLAV 375 mg a day) has been given to 6 patients with drug-resistant tuberculosis for up to 36 weeks with no reported side effects (Payen et al. 2012). Timentin® is an intravenous combination of ticarcillin and CLAV, with 100 mg of CLAV in a 3.1 gram infusion of Timentin. In a retrospective study of 127 pediatric cystic

fibrosis patients who received Timentin, they received a mean of 450 mg CLAV /day +/- 227 mg/day for a mean duration of 13.5 days (Zobell et al. 2010). No adverse effects on laboratory measures, including liver function tests, were found. While there is substantial clinical experience with Augmentin to treat infections, there is no published data on either CLAV or Augmentin in cocaine dependent adults. In our inpatient study of 3 doses of CLAV in combination with cocaine 40 mg, 10 subjects have received single doses of CLAV 500 mg, and 5 subjects have received single doses of CLAV 750 mg in combination with cocaine. All doses have been reasonably well tolerated without serious adverse effects.

CLAV 500 mg Decreased Craving with a large effect size compared to PBO. The CLAV 500 mg dose, given acutely in the cocaine interaction study, was associated with a decrease in craving by -2.1 units on the Cocaine Craving Questionnaire (CCQ). The placebo session was associated with an increase in craving by 3.6 units. Thus, craving was decreased by 5.7 units in the CLAV 500 mg compared with the placebo group, with a calculated effect size of Cohen's d=1.25, representing a large decrease in craving associated with CLAV.

MRS Pilot Study of CLAV on Brain Glutamate We completed an outpatient human MRS imaging Pilot study to gather pilot data regarding the effect of 10 days of open label treatment with CLAV 500 mg/day on brain Glu levels (n=5 completers). The levels were obtained from a brain area associated with addiction, the anterior cingulate (ACC), in CocUD subjects with 7+ days of abstinence. We present the data from Subject 1 in **Fig. 4**. This subject had a decrease in the ACC glutamate level compared to baseline 30 minutes after the first dose of CLAV 250 mg. The change in Glu levels was sustained after 10 days of CLAV 500 mg, and slightly attenuated at Day 11, 24 hours after the last CLAV dose. Thus, on initial study, CLAV-associated changes in brain Glu in the AC, our biomarker for CLAV effect, are reasonably stable for 24 hours after the last dose. This supports the idea that CLAV can be dosed

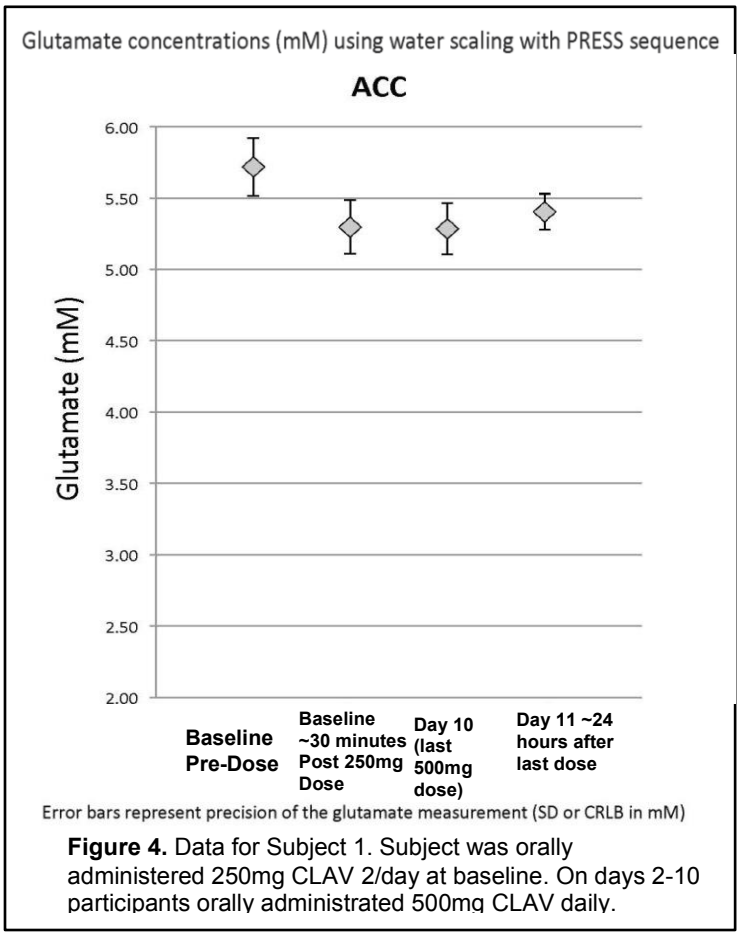

Figure 4. Data for Subject 1. Subject was orally administered 250mg CLAV 2/day at baseline. On days 2-10 participants orally administrated 500mg CLAV daily.

daily. We also measured whether 10 days of treatment with CLAV is associated with increases in brain glutamine concentration (data pending).

We enrolled 8 subjects into the study, and 5 completed the protocol. We utilized the pilot study to refine the MRS imaging sequence for the imaging protocol.

There were 21 AEs throughout the course of the study. All AEs were mild and similar to those in the inpatient COC interaction study. There were no serious or severe adverse events during the study. AEs deemed likely to be study drug related were constipation (n=1), hunger (n=1), loose stool (n=1), nausea (n=9), and stomach pain (n=1).

7) Setting of the Human Research

Episcopal Hospital/Health Sciences Center/Jeanes Hospital – Screening and inpatient days

This is an inpatient study to be conducted on a medical unit at the Episcopal Hospital campus of the Temple University Health System (T-EH). In the event that space is unavailable on C6 for medical reasons, Temple University Hospital Main (TUH-Main) and Jeanes Hospital medical floors which can provide nursing staff who are not currently assigned Covid patients will serve as back up sites. T-EH,TUH-Main and Jeanes are fully equipped hospitals, with 24-hour Emergency Departments. The Hospitalist teams for Episcopal Hospital, TUH Main, and Jeanes Hospital will be fully briefed on the study. The Chief Medical officer of Episcopal Hospital, Dr. William R. Dubin, Executive Vice President and Chief Medical officer of TUH-Main Dr. Tony S. Reed, nursing management, nurses on all shifts of the medical unit, pharmacy and security will be briefed on the study and will be updated at least every six (6) months and more frequently if needed.

Interested candidates between the ages of 18 and 70 who have been determined to be cocaine dependent subjects with 7+ days of abstinence*,* or who express interest in remaining abstinent from cocaine, will meet with the investigators/study team by phone or in person and receive an explanation of the study purpose and requirements at the inpatient sites. If still interested after receiving an explanation of the study, the candidate will complete a prescreen questionnaire. Interested candidates who complete the prescreen are given an ID and have their data from the prescreen questionnaire stored in REDCap. Participant names are not stored in REDCap and are kept separately in a password protected excel file on a secure Temple server. If a candidate expresses interest in the study but has already completed a prescreen questionnaire, the study team will review their prior prescreen to determine whether they were excluded based on criteria that may have changed since they last contact the study team. If a participant may still be eligible, the study team will ask the candidate if they can update their information to determine whether they may be eligible for the study.

Participants who are potentially eligible based on the prescreen questionnaire will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the Temple University Institutional Review Board *(*IRB). Screening of

subjects to establish eligibility will occur over the phone or video (for screening part 1) or in person (part 1 and 2) at the inpatient unit to establish cocaine use, appropriate age, and no excluded medical or psychiatric conditions.

Temple University Main Campus – Scans

MRI scans will be conducted with the Siemens MAGNETOM Prisma 3-Tesla whole-body MRI scanner in Weiss Hall of the main campus of Temple University. It supports a collection of structural MRI, MRS, BOLD fMRI, ASL, perfusion MRI and DTI sequences. This instrument provides the strongest commercially available gradient field (80mT/m) in combination with the fastest available gradient switching rate (200mT/m/s). The magnet's coil uses an ultra-high-performance cooling and force-compensated design to reduce vibrations, which results in a minimization of eddy currents and acoustic noise. The advanced fully-dynamic parallel transmit radiofrequency (RF) technology in this system integrates all transmit and receive components within the magnet housing, providing industry leading signal-to-noise performance and high image stability with minimal RF noise artifact. The complete system is equipped with a 64-channel phased-array parallel transmit and receive RF head/neck coil, providing maximal image quality with exceptionally high spatial and temporal resolution for all brain imaging pulse sequences.

The scanner is housed within the Temple University Brain Research and Imaging Center (TUBRIC), a 3400sf, multi-modal, research imaging center serving the neuroimaging research community on Temple's main campus. TUBRIC is a fully functional research-dedicated facility with immediately adjacent participant preparation, testing, and interview space, furnished with a range of integrated and supplemental research instruments to complement basic imaging work. The facility is staffed by a director, a neuroimaging supervisor who has a PhD in Biomedical Engineering, and administrative and IT support personnel. TUBRIC has a standardized certification process to ensure study personnel utilize the scanner and imaging center to maximize subject and personnel safety.

8) Resources Available to Conduct the Human Research

INTRODUCTION and rationale

Therapeutic Strategies for Treating Cocaine Use Disorder

Cocaine (COC) related overdose deaths in non-Hispanic black populations are on par with heroin and prescription opioid associated deaths in non-Hispanic white populations (Shiels et al. 2018). Cocaine is a consistent and important contributor to deaths in non-Hispanic white populations and Hispanic populations. Prevention of cocaine-related deaths, which disproportionally affect older non-Hispanic blacks, is urgently needed. A variety of neuropharmacological strategies are being pursued in the search for an effective treatment for Cocaine Use Disorder (CoCUD). These include: 1) blocking cocaine's effects, 2) restoration of central nervous system homeostasis, 3) reducing craving or enhancing the addict's ability to manage his/her response to craving, 4)

treating underlying comorbid conditions that may predispose subpopulations toward dependence, and 5) stress reduction to prevent relapse.

Study Site
This is an inpatient study that will take place at the Episcopal, TUH Main, Jeanes Hospital, and Main campus of Temple University. The first part of the screening visit can be completed in person or over the phone/video. Inpatient sessions are conducted at Centennial 6 at the Episcopal Hospital campus of the Temple University Health System (T-EH). In the event that space is unavailable on C6 for medical reasons, Temple University Hospital Main (TUH-Main) and Jeanes Hospital medical floors which can provide nursing staff who are not currently assigned Covid patients will serve as back up sites. Subject rooms are semi-private (on a unit with other patients) and subjects will be able to complete all study surveys privately.

Blood will be drawn at TUBRIC or on the inpatient unit for all study sessions by staff who are trained and certified to draw blood for research studies. TUBRIC and the inpatient units have a fully equipped blood draw room that will be stocked with all necessary blood draw supplies.

Research Staff Training
Training of research study staff will be conducted by Drs. Morrison, Peng (or TUBRIC staff), Khalid and the research specialist. Training will include background on cocaine use disorders, remission and assessing medication adherence in substance abuse populations, information about the rationale for *CLAV*, and information about performing MRS studies safely. TUBRIC staff will conduct training regarding the TUBRIC scanner and subject safety. The training team will ensure that study staff understand and accept the nature of the protocol and the requirements for an adequate, safe and ethical study. Specifically, their obligation to conduct the clinical investigation in accordance with Good Clinical Practices (GCP) and any other regulations will be reinforced. Study conduct training will include protocol review, patient confidentiality, procedures regarding study drug administration, procedures with assessments and urine testing. Procedures for correctly accounting for and disposing of extra study drug will be reviewed. Procedures for assessing and treating adverse events will be discussed.

9) Prior Approvals
The Investigational New Drug (IND) application with the FDA (IND# 113621) was approved in 2015. This protocol will be submitted to the FDA concurrently with the submission to the Temple IRB. CLAV has been approved for Fast Track Designation by the FDA for CocUD.

10) Study Design

This Phase IB study of CLAV will investigate brain regional glutamate levels before and after repeated 10-day CLAV dosing to determine whether glutamate is reduced in the ACC after repeated CLAV dosing in a dose escalating study. The study will be performed with 5 imaging days (5 MRS scans) over 11 inpatient study days in total with three outpatient visits. It will be conducted in subjects with moderate to severe cocaine use disorder in with 1 week or more of abstinence.

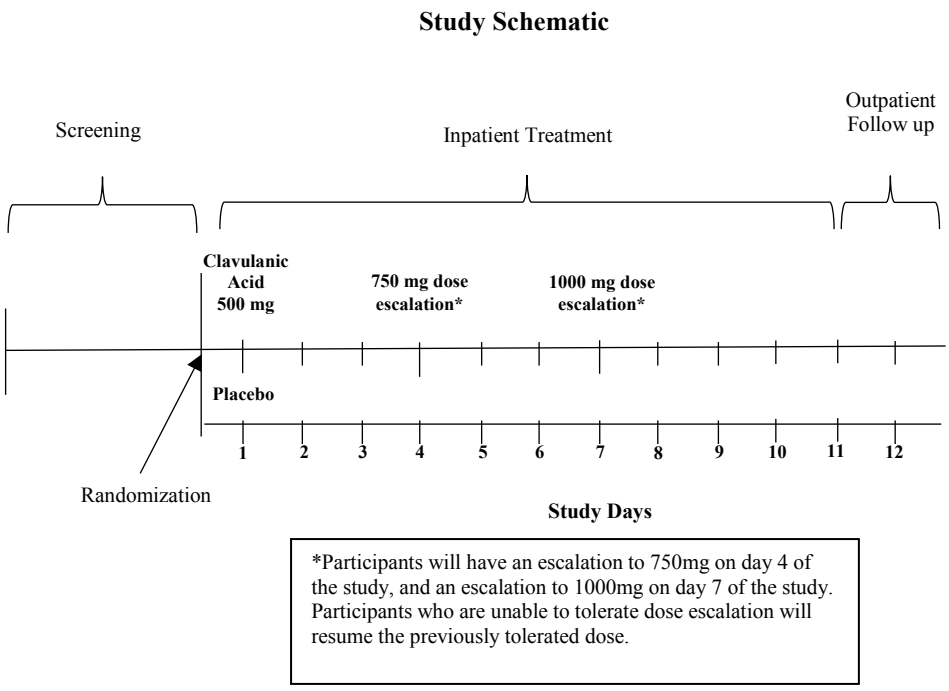

Figure 5. Enrollment-Discharge Participant Schedule

Structural MRI, functional MRI, and MRS will occur before CLAV administration at baseline, after 3 days of study drug administration (prior to 750mg dose escalation), after 6 days of study drug administration (prior to the 1000mg dose escalation) on the last day of CLAV dosing (day 10), and one day after the Cessation of CLAV dosing (day 11). The final MR scan session will be used to gather information on the duration of CLAV's effect on ACC Glu concentration after cessation of CLAV dosing. Before each scan, safety of the subject to complete the scan will be re-assessed. Subjective and cognitive assessments will be administered daily in the inpatient setting. Assessments of adverse effects, blood pressure and pulse will also be performed daily.

The study will end with a follow up visit 5-8 days after discharge. The follow visit will involve an assessment of adverse events to determine withdrawal symptoms. Subjects with adverse events that require further in person assessments may be asked to come in for an additional visit. All adverse events will be followed until resolution.

Informed Consent and Screening Part 1 (Approximately 120 minutes, in- person or over the phone)

In-Person Consent and Screening Procedure

In a private setting, each participant will receive a description by a study staff member of the study protocol, its risks, potential benefits, and alternative treatments available. A study physician will be present and involved in the consent process. A consent quiz will be administered after review of the consent, and prior to when participants sign the consent form. Participants will need to understand the answer to all questions correctly before signing. Participants who answer questions incorrectly will review those questions with research staff, who will explain the sections of the consent form that are

relevant to the incorrect quiz questions. Following completion of the consent quiz and resolution of any questions, participants who understand the nature of the study and consent will be asked to sign the study consent form, which will also be signed by the physician present. A copy of the informed consent form will be given to each participant and participants will be reminded that the consent expresses willingness to participate but that the subsequent screening process will determine final eligibility. Further, each participant will be reminded that participation is voluntary, and at any time, s/he may withdraw from the study. Following the informed consent process, a research coordinator will perform assessments during the outpatient screening visit including: 1) collection of demographic information, 2) a timeline follow back (TLFB) interview covering the preceding 42 days 3) cocaine use questionnaire, including reactions to cocaine, history of other substance use (including cigarettes), number of prior cocaine quit attempts and reasons for relapse. A trained coordinator or clinician will perform the MINI, a psychiatric diagnostic interview Vital signs will be collected. A study physician will take a medical history including drug allergies and medications. 4) Participants who are potentially eligible at this stage of the screening will be provided transport to the Temple Health Sciences campus to receive a Covid-19 test. Participants who test negative will be scheduled for the second half of the screening visit.

Phone Consent and Screening Procedures

Participants who complete the first part of the screen over the phone will review the consent with a study physician and complete a consent quiz. After completion of the consent quiz, participants will be provided a RedCAP link which will allow them to virtually sign the consent form. Participants who sign the consent form virtually will complete the same assessments as individuals who complete the screening visit 1 in person. At the end of the part 1 screening visit participants will be sent a copy of the consent form by e-mail or mail.

Participants who are interested in the study but do not have internet access to complete the form can be sent a preaddressed and stamped envelope with a blank consent form, which they can return to the research team. The screening visit will be completed at a later date when the signed form is received.

If a participant is determined to be eligible for the research study, they will be scheduled for a Covid-19 test on the Temple Health sciences campus. Participants who test negative will be scheduled for the second half of the screening visit.

Screening Part 2 (Approximately 90 minutes, in- person)

Participants have up to 90 days after the completion of screening part 1 to complete screening part 2. Participants who attend screening part 2 more than 30 days after screening part 1 will update their medication history, medical history and recent substance use information.

Upon arrival for the part 2 visit, participants will be asked to show legal picture identification. Participants who completed the first part of the screen virtually will be asked to sign a physical copy of the informed consent and will be provided a copy. A physician will perform a physical exam. Laboratory assessments (blood & urine) will be checked including a comprehensive metabolic panel, CBC, infectious disease panel, including human immunodeficiency virus (HIV) type 1 and 2, and urine tests for drugs of abuse, pregnancy (women) and urinalysis. Approximately 15ml (1 tablespoon) of blood will be collected at this visit. A breathalyzer test will be completed. An EKG will be performed and reviewed.

If a participant can be scheduled for admission within 96 hours, they will be provided transport to the Temple Health Sciences campus to receive a Covid-19 test. If participants cannot be scheduled for admission within 96 hours at the time of the screening part 2 visit, they will be scheduled for a test within 96 hours prior to their admission date.

Participants can receive up to 2 additional Covid-19 tests (4 total) as needed to account for unanticipated scheduling changes, and increase scheduling flexibility for admission.

Table 1: Study Assessments

	Screening visit 1 (-30 to 0 days)	Screening Visit 2 (-30 to 0 days)	Day 1 Baseline	Day 2	Day 3	Day 4	Days 5	Day 6	Days 7-9	Day 10	Day 11	Follow Up (Day 16 - 19)
ICF with HIPAA	X											
Cocaine Use Questionnaire	X											
Illicit Drug Use TLFB (preceding 30 days or less on follow up)	X		X									X
Medical record review	X											
Demographics	X											
Vital signs	X[1]	X	X	X	X	X	X	X	X	X	X	X
Medical History	X											
Nasopharyngeal swab (Covid-19 test)	X	X										
Physical Exam		X										
Labs (CBC, Metabolic Panel)		X			X			X		X		
Labs (Hepatitis B, C, HIV)		X										
EKG		X								X		
Breathalyzer		X	X									
Urine Drug Screen		X	X									X
Urine Pregnancy		X	X									X
Urinalysis		X								X		
MINI	X											
ASI	X											
Adverse Childhood Experiences (ACEs) Scale	X											
MRS scan			X		X			X		X	X	
Craving Assessments (CCQ-Brief, Craving VAS)			X	X	X	X	X	X	X	X	X	X
Subjective Assessments (POMS, VAS)			X	X	X	X	X	X	X	X	X	X
CANTAB (Cognitive Tests)			X		X			X		X	X	
C-SSRS scale	X		X							X		
MED-Q					X					X		
Assessment of AEs			X	X	X	X	X	X	X	X	X	X
Assessment for Dose Escalation					X			X				

Baseline and Intake (Approximately 180 minutes)

After determination of eligibility on the screening day, the subject will be scheduled for a baseline visit (Day1) at TUBRIC. Subjects are instructed to refrain from non-prescription drugs and alcohol prior to the baseline/intake visit. Upon arrival, participants will be asked to complete a breathalyzer test and provide a urine sample to confirm abstinence

[1] Vital signs will only be taken at screening visit 1 if it is conducted in person.

from illicit substances. Participants who have a positive urine drug test will not be admitted to the study with an exception for marijuana with either a diagnosis of mild use disorder or no use disorder. Participants who have a positive breathalyzer test will be reevaluated by the PI to determine alcohol dependence and study eligibility. Participants will not conduct study activities prior to providing negative breathalyzer test.

Female participants will have a pregnancy test. Female participants who have a positive pregnancy test will not be enrolled into the study and will be offered referrals to appropriate health care services.

Participants will also complete a TLFB covering the time back to the screening visit, and complete assessments including the C–SSRS, CCQ-Brief, POMS-SF, VAS, ACEs, and CANTAB cognition tests will be performed before scan.

After the assessments, the study team will perform the first MR scan session.

After the completion of the MR scan the study team will accompany participants to the inpatient unit for intake. Upon arrival, participants will need to provide a photo ID so they can be registered as an inpatient on the unit. Potential candidates will need to provide any of the following government issued photo identification:

- Driver's license
- Non-driver ID
- Passport
- Military ID

Alternatively, potential candidates can provide non-governmental photo ID supported by additional documentation (social security card or birth certificate) that includes the same name on the photo ID.

Inpatient sessions are conducted at Centennial 6 at the Episcopal Hospital campus of the Temple University Health System (T-EH). In the event that space is unavailable on C6 for medical reasons, Temple University Hospital Main (TUH-Main) and Jeanes Hospital medical floors which can provide nursing staff who are not currently assigned Covid patients will serve as back up sites. Subjects are oriented to the rules of the medical unit during intake screening. After participants have been admitted to the medical unit, they will self-administer the first dose of study drug CLAV 250 mg dose (1 capsule). Participants will self-administer under study personnel supervision the second 250mg dose later in the day if the initial dose is tolerated.

Aside from the times participants need to travel to TUBRIC, participants will remain on the inpatient unit until discharge. A study team member will remain with the participant during travel times.

Study Day 2
This session includes adverse events assessment, craving assessments, and subjective assessments (Table 1). Vital signs (BP, pulse) will be obtained. Subjects self-administer study drug. This session will take approximately 30 minutes.

Study Day 3
This session includes MR scan session 2, laboratory tests, adverse events assessment, and subjective/craving assessments. The MR scan takes 1 hour. Laboratory tests will include a complete blood count with differential, and a comprehensive metabolic panel. Approximately 15ml (1 tablespoon) of blood will be collected at this session. Vital signs (BP, pulse) will be obtained. Staff members supervise subject self-administration of study drug. This session will take approximately 3 hours.

Subjects who have safely tolerated the study drug will have a forced escalation to 750mg on study day 4.

Study Day 4-5
This session includes Adverse events assessment, and subjective/craving assessments. Vital signs (BP, Pulse) will be obtained. Subjects will self-administer study drug under staff supervision. This session will take approximately 30 minutes.

Study Day 6
This session includes MR scan session 3, laboratory tests, adverse events assessment, and subjective/craving assessments. Laboratory tests will include a complete blood count with differential, and a comprehensive metabolic panel. The MR scan takes 1 hour. Approximately 15ml (1 tablespoon) of blood will be collected at this session. Vital signs (BP, pulse) will be obtained. Subjects self-administer study drug under staff supervision. This session will take approximately 3 hours.

Subjects who have safely tolerated the study drug will have a forced escalation to 1000 mg on study day 7.

Study Days 7-9
These sessions include adverse events assessment and subjective/craving assessments. Vital signs (BP, pulse) will be obtained. Subjects self-administer study drug under staff supervision. These sessions will take approximately 30 minutes.

Study Day 10
This session includes MR scan session 4, adverse events assessment, and subjective/craving assessments. Vital signs (BP, Pulse) will be obtained. Subjects self-administer the final dose of study drug under staff supervision. An EKG will be performed and reviewed. Laboratory tests will include a complete blood count with differential, and a comprehensive metabolic panel. Approximately 15ml (1 tablespoon) of blood will be collected at this session. This session will take approximately 2 hours.

Study Day 11
This session includes MR scan session 5, adverse events assessment, subjective/craving/C-SSRS assessments, and laboratory assessments. Vital signs (BP, Pulse) will be obtained. This session will take approximately 3 hours and will occur before and after the subject is discharged from the hospital.

Follow up Visit
5-8 days after discharge, participants will return for a follow up visit. The visit will involve an assessment of adverse events to determine any withdrawal symptoms. Participants will complete subjective/craving assessments, the TLFB covering the time back to discharge, and will have a UDS. This visit will take approximately 1 hour.

All adverse events will be followed until resolution.

Early Termination Procedures
Participants who are discharged from the study early will complete the day 11 discharge procedures, including scan, laboratory tests, and CANTAB cognitive test battery. Participants will be compensated at the day 11 discharge rate ($230). Participants will then be scheduled for a follow up visit. Participants may be scheduled for additional follow up visits and bloodwork if a study physician determines they are needed to monitor subject AEs. Unscheduled follow up visits will take appropriately 30 minutes.

At the early termination visit participants will receive the final payment for time and travel for the study in the form of gift cards, cash, or Greenphire ClinCard. Participants are given the option to choose which form of compensation they would prefer. There is no monetary difference between the compensation methods. The early termination (end of study) visit will take approximately 1 hour.

Study Drug Supply Description
CLAV will be supplied in 250mg capsules. CLAV will be made at the Investigational Drug Service (IDS) pharmacy at the University of Pennsylvania in Philadelphia, Pennsylvania, as 250mg capsules. Matching placebo pills will also be made at IDS at UPENN. Bulk CLAV has been procured from BOC Sciences (Shirley NY). Stability testing completed by Protoform (Westampton, NJ) for the clavulanic acid pills demonstrated that the current formulation of clavulanic acid is stable at room temperature in a space with controlled humidity for 6 months. Controlling humidity is important to clavulanic acid stability. To ensure stability, both the medication manufacturer, Investigational Drug Services (IDS), and the Temple Pharmacy, keep the study drug at room temperature in a space with controlled humidity. All new batches of pills manufactured by IDS are tested by Protoform before release.

Study medication will be stored at room temperature until dispensed for distribution to participants in the Episcopal Hospital Pharmacy.

Table 2.Treatment Regimen

Dosing Schedule			
Dose	**Baseline-Day3**	**Day 4-6**	**Days 7-10**
500 mg	**X**		
750 mg (if tolerated)		**X**	
1000 mg (if tolerated)			**X**

Participants will receive CLAV at the end of Day 1 after MRS scans. The first dose of CLAV will be 1 capsule or 250 mg. A second dose (one 250 mg capsule) will be taken later that day if the first dose is safely tolerated. On days 2-3, participants will receive 2 capsules (500 mg) each day. Forced dose escalation will occur on days 4 (750 mg, 3 capsules) and 7 (1000 mg. 4 capsules).

Staff will provide study drug for self-administration each day. Medication dispensing will be done directly by the research nurse, physician, or research staff (trained and supervised by the nurse or physicians), who will ensure that the patient understands the medication regimen. Study personnel will not administer the study drug but will dispense study drug to participants for self-administration. Study staff will assess participants after self-administration for AEs. Participants and inpatient staff are reminded that the primary investigator is available at the 24-hour emergency number listed on the first page of the consent form.

Randomization

The TUHS Investigational Research Pharmacist will supply the Temple-Episcopal Chief Pharmacist, Dr. Kim, with pre-coded envelopes with treatment assignments and study medication obtained from IDS. On study day #1, the investigator or study coordinator will obtain the study medication from the Episcopal Pharmacist. Codes linking randomization number to actual treatment will be secured in a sealed, opaque envelope and maintained in the Episcopal Hospital Pharmacy. The Episcopal Pharmacist will dispense the coded bottle/blister pack of investigational agent for the subject to the investigator/research specialist. The nurse or trained research staff will observe ingestion of the study drug to ensure medication adherence. Nine subjects will be randomized to CLAV and 3 to placebo.

Blinding.

Subjects, investigators, nursing and research staff are blinded to study drug allocation. The subject and investigator will be assessed on study days 3, 6, and 10, regarding study drug allocation to determine whether blinding was successful with the MED-Q and Med-Q-Investigator developed at the University of Pennsylvania.

a) Recruitment Methods

Research staff will advertise in media, including online classifieds such as Craigslist, newspapers (print and online), magazines, radio, and social media. Staff will post and distribute recruitment material in community settings with public posting areas or other means of providing community access to materials (such as substance abuse treatment centers, town halls, public libraries, YMCAs, health fairs). Staff will obtain permission at select locations before distributing or posting the approved recruitment materials

(ensuring compliance with other institutions guidelines, including seeking IRB approval as needed to conduct recruitment activities). Study staff will review clinical records of potentially eligible subjects who have expressed interest in the research study through the EPIC system. EPIC will only be accessed by IRB approved study staff and will not be accessed unless potential participants initiate contact and express an interest in the study. Staff will conduct a brief in-person pre-screening questionnaire and a screening interview over the phone or in-person at the participant's clinic to assess study eligibility criteria. Participants will be contacted by phone or e-mail. Prospective participants who appear to meet eligibility criteria for the study will be scheduled for an in-person Informed Consent and Screening visit.

Table 3. Participant compensation schedule

Visit	Visit Compensation	Blood Sample Compensation	MRI Compensation	Survey Compensation	Participant Compensation
Outpatient screen-Visit -1	$20	$0	$0	$0	**$20**
Outpatient Visit 2	$0	$20	$0	$0	**$20**
Covid-19 Test 1+2	$25[2]	$0	$0	$0	**$25**
Day 1	$30	$0	$150	$30	**$210**
Day 2	$30	$0	$0	$30	**$60**
Day 3	$30	$20	$150	$30	**$230**
Day 4	$30	$0	$0	$30	**$60**
Day 5	$30	$0	$0	$30	**$60**
Day 6	$30	$20	$150	$30	**$230**
Day 7	$30	$0	$0	$30	**$60**
Day 8	$30	$0	$0	$30	**$60**
Day 9	$30	$0	$0	$30	**$60**
Day 10	$30	$0	$150	$30	**$210**
Day 11	$30	$20	$150	$30	**$230**
Outpatient Follow up visit	$70	$0	$0	$30	**$100**
Study Completion Bonus					**$730**
Total Payment for Full Participation					**$2340**

* Subjects will be compensated for reasonable travel costs [up to a maximum of $100 per subject over the course of study with qualifying receipts or given tokens (or equivalent) for local travel on mass transit.

[2] Covid-19 Test compensation will be in gift cards

Inclusion and Exclusion Criteria

Inclusion Criteria

In order to participate in the study, subjects must:

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

2. Be male or female adult volunteers ages 18-70 inclusive.

3. Have a DSM-5 diagnosis of cocaine use disorder, moderate to severe in early remission[B] with a duration of regular (weekly or more) cocaine (either snorted, smoked or injected) for at least one year, with at least 1 week(or more) without cocaine use, verified by UDS.

4. Have a Body Mass Index (BMI) of 17.5 to 39.9 kg/m2; and a total body weight of at least 45 kg (99 lbs.)

5. Have a history and brief physical examination that demonstrate no clinically significant contraindication for participating in the study, and/ or significant or unstable medical or psychiatric illness.

6. If female: have a negative pregnancy test within 48 hours prior to receiving the first dose of investigational agent and agree to use an effective method of birth control for a minimum of 30 days after study participation, or be postmenopausal, or have had a hysterectomy, or have been sterilized, or be male. Effective forms of birth control include:

a) complete abstinence from sexual intercourse
b) oral contraceptives, Depo-Provera, Norplant, or intrauterine progesterone contraceptive system and condom by partner
c) diaphragm and condom by partner
d) intrauterine device and condom by partner
e) sponge and condom by partner

7. Be able to comply with protocol requirements, rules and regulations of the study, and be likely to complete the entire study.

8. Must remain local for at least 2 months

Exclusion Criteria

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

[B] Early remission is defined as 7 or more days of cocaine abstinence and will be determined through a timeline follow back calendar that is completed at screen and updated at the baseline visit.

1. Have a current DSM-V substance use disorder, of any drug of abuse other than nicotine, caffeine, cocaine, alcohol, marijuana use disorder verified by UDS. Alcohol use disorder and marijuana use disorder are not permitted if there are seizures or psychotic symptoms associated with withdrawal or medication is required to treat withdrawal symptoms from alcohol or marijuana use.

2. Have any previous medically adverse reaction to CLAV, Augmentin, penicillin, Ticarcillin, cephalosporin, or any beta-lactam drug.

3. Have any illness, condition, and use of medications, in the opinion of the principal investigator, sub-investigators which would preclude safe and/or successful completion of the study.

4. Have moderate to severe liver disease or current elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) exceeding 2.0 times the upper limit of normal (> 2.0 X ULN).

5. Have a diagnosis of adult (i.e., 21 years or older) asthma, or chronic obstructive pulmonary disease (COPD), with an exacerbation of their asthma/COPD within last six (6) weeks before study enrollment that required medication treatment.

6. Report having human immunodeficiency virus (HIV) infection or test positive for HIV during screening

7. Be pregnant (females).

8. Have participated in another investigational medication or device study within 12 weeks.

9. Have systolic blood pressure ≥ 150 after three (3) measurements or have diastolic blood pressure ≥ 95 after three (3) measurements.

10. Have any current DSM-5 defined unstable[C] major psychiatric illness.

11. Have a suicide attempt in the past year, or score high risk (17 or greater) on the suicidality MINI module, or answer “yes’ on Questions 4 or 5 on Columbia Suicide Severity Rating Scale (C-SSRS)

12. Any implanted object in their body as described on the Temple Magnetic Resonance Environment Screening Form for individuals.

[C] Prone to change significantly in the two weeks before assessment and including severe symptoms

13. Previous injury to any part of the body (including the eye) involving a metallic object, metallic slivers, or foreign body which left behind ferrous magnetic metal.

14. Chronically taking a medication that is associated with changes in glutamate, glutamine, GABA. Common medications excluded by this criterion include beta lactams, N-acetylcysteine, tiagabine, and lorazepam. A comprehensive list of prohibited medications is included as part of this protocol as Appendix I.

15. Be taking any herbal supplements that are associated with changes in glutamate, glutamine, GABA, including kava and other herbals listed in Appendix I.

16. Unable to tolerate MRI scan for duration of 60 minutes for physical or psychological reasons.

17. Have a history of head injury with loss of consciousness greater than five (5) minutes.

18. Have any impending incarceration or be in a treatment facility in accordance with a court mandate

b) Number of Subjects

SAMPLE SIZE: 12 subjects will complete the study. Dropouts will be replaced.

POPULATION: Subjects are adult male and female volunteers, 18-to-70 years of age, who have cocaine use disorder in early remission.

c) Study-Wide Number of Subjects
Same as above.

d) Study Timelines

- **Submit Final Protocol** to Temple IRB and FDA
- **First Patient Entered**, recruitment ~1.5 patients/month
- start intellectual property review with VistaGen
- Last Patient Entered, 12 study completers
- Final Data Set, drafting FDA study report
- Data Analysis complete, Milestone discussion with NIDA
- Study Report Complete

e) Study Endpoints

Primary Endpoint: Change in brain glutamate concentration in the ACC at Day 10 compared with baseline.

Secondary Endpoints:

A) Brain connectivity change in the ACC on resting state fMRI.
B) Change in brain glutamate concentration in the ACC at Day 11 compared with Day 10
C) Change in brain glutamine concentration in the ACC at Day 10 compared with baseline.
D) Safety and tolerance as assessed by the rates of occurrence of adverse events, changes in vital signs, Columbia Suicide Severity Rating Scale (C-SSRS), EKG parameters and laboratory studies compared with baseline.

Exploratory Endpoints:

A) Suppression of cocaine cue-induced limbic activation during imaging task.
B) Subjective effects will be compared before and after CLAV 500,750, 1000 mg/day for 10 days using the following instruments: the Visual Analog Scales (VAS), Profile of Mood States (POMS) (Curran, Andrykowski, and Studts 1995), and the scores from the Cambridge Cognition Cognitive battery at multiple timepoints compared with baseline
C) Relationship between scores from the Adverse Childhood Experience (ACE) scale, POMS, and VAS.

Procedures Involved in the Human Research

Before the MR scan, subjects will have the option to go inside a mock scanner to have a feeling of the MR setting to reduce anxiety. Before each scan, subjects will have to fill out a safety screen form. In addition to the safety screen form, subjects will be scanned with a wand to detect any ferromagnetic materials. For the actual imaging session, subjects will be asked to lie down on a platform that can be slid into the bore of the magnet. Because of beeping and hammering sounds made by the machine, it is somewhat noisy inside the magnet. Disposable earplugs will be provided to diminish the noise. A 64 channel MRI imaging coil will be placed around the subject's head. This coil is simply a number of wires covered in plastic. Subjects will not come into direct contact with the coil during the MRI study. Foam pads will be placed around the subject's head to limit movement during the study. Subjects will then be slid into the magnet and will be asked to lie still for approximately one hour, during which several images will be acquired. During the study, a physician will be available for any medical questions or problems. The technicians involved in the study will advise subjects on the progress of the study. Subjects will be able to contact staff at any time if they feel uncomfortable or do not wish to continue study activities.

Imaging. Participants will undergo MR scans at 3 T using MR scanner on Main Campus, Temple University. There will be 5 MR scans performed for each subject. (**Table 4**) For any MR scan, there is no injection of exogenous contrast agent or interventions other than CLAV, which is described previously in this protocol. Imaging procedures are detailed in **Fig. 6** and specific scan information is detailed below

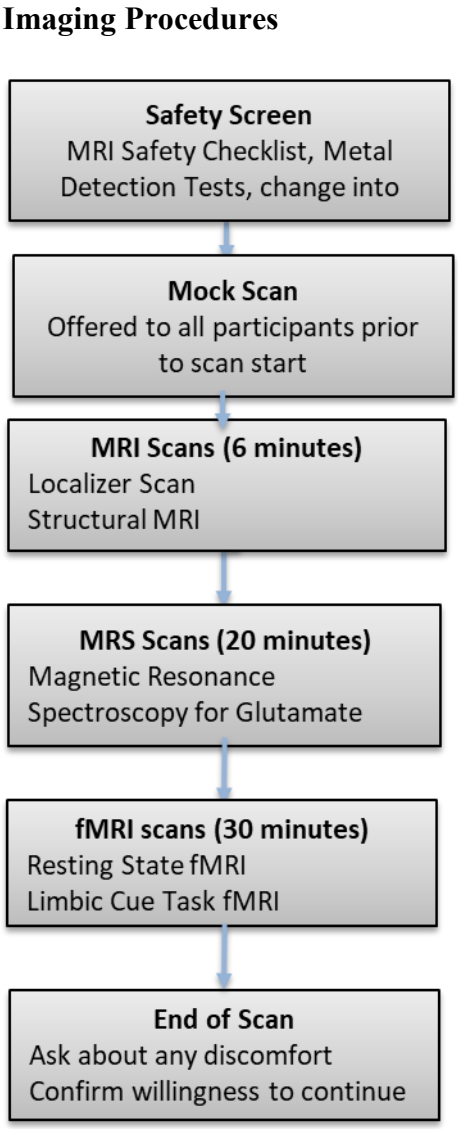

Figure 6: Imaging and safety procedures for each scan day

1) Localizer scan. Fast MRI along the x, y, and z direction will be performed to define the physical imaging space in order to locate placement of the following scans. This will take approximately 25-30 secs.

2) Structural MRI. High resolution anatomical scan will be performed with a T1-weighted 3D MPRAGE product sequence from Siemens with 160 slices, 1.0 mm thickness, 22cm field-of-view (FOV), 192x256 matrix, TI/TR/ TE=1100/1630/3 ms. Parallel imaging with 2-fold acceleration will be used to shorten acquisition time. The scan time will be around 5.3 mins.

3) MR spectroscopy (MRS). MRS will be performed using the Siemens product single-voxel spin-echo point-resolved spectroscopy (PRESS) sequence using short TE (30ms) with 128 averages and water suppression to measure Glutamate, Glutamine and other metabolites (Ramadan, Lin, & Stanwell, 2013). In addition, a special 32-echo multiecho PRESS sequence (8 averages, TE = 30ms to 185ms, with increments of 5ms) will also be used for selective detection of glutamate and glutamine signal. For each sequence, the un-suppressed water signal will be acquired for absolute quantification of metabolites using water scaling. The 2 x 2 x 2 cm3 (8 ml) MRS voxel will be positioned in the ACC. This region will take 20 minutes.

4) Resting State fMRI. Resting state fMRI will be performed using Siemens product Gradient-Echo EPI with multiband factor of 3. 60 axial slices with gap of 0.1mm, 2.0 mm thickness, FOV is 200 x 200 mm2, 100 x 100 matrix, TR/TE= 2000/29 ms., 2 x 2 x 2 mm3 voxel resolution, 180 volumes per run will be used to

measure functional connectivity of ACC while subjects are instructed to relax, keep eyes open and stare at a cross. Data will be acquired in 2 runs of 6 minutes each. This scan will take 12 minutes.

5) Limbic Cue Associated fMRI Activation. After the resting state scan, a brief cue will be presented, either a cocaine related cue or a neutral cue from the Childress laboratory. Subjects will then be crossed over to receive exposure to the other cue (cocaine or neutral). This scan will take 18 minutes.

Table 4: Timetable for Pharmaco-MRI study of Clavulanic Acid for Cocaine Use Disorder

Imaging Study Day	Scan 1 (Day 1)	Scan 2 (Day 3)	Scan 3 (Day 6)	Scan 4 (Day 10)	Scan 5 (Day 11)
MRS scan	X	X	X	X	X
CLAV	No dose given prior to scan	500 mg given prior to scan	750mg given prior to scan	1000 mg given prior to scan	No CLAV given

Methods for Assessment of Secondary and Exploratory Outcome Measures

The secondary outcome measure craving for cocaine is assessed using CCQ-Brief, and VAS for craving. Exploratory outcomes are measured using psychological, mood, and personality tests including the POMS, VAS, ACE scale, and Cambridge Cognition Cognitive Battery. Refer to Table 1 as well for schedule of Assessments.

1) Cocaine Craving Questionnaire-Brief (CCQ-Brief)

The CCQ-Brief is a self-administered assessment that asks the subject to rate his or her craving for cocaine. The CCQ-Brief used for this study is a modification of the Cocaine Craving Questionnaire-Now (Sussner et al. 2006). This measure will be completed every inpatient study day.

2) Visual Analog Scales (VAS)-Craving

The Visual Analog craving scale is a 0-100 scale asking participants to self-report their current feelings of craving. Subjects will complete this form every inpatient study day.

3) Profile of Mood States Short Form (POMS-SF)

The POMS-SF is shortened version of the POMS questionnaire that measures dimensions of affect or mood and has comparable internal consistency to the standard POMS assessment (Curran, Andrykowski, and Studts 1995). The POMS-SF consists of 37 adjectives to which the client responds according to a 5-point scale ranging from “not at all” to “extremely” (Curran, Andrykowski, and Studts 1995). Subjects will complete this measure every inpatient day.

4) Columbia Suicide Severity Rating Scale (C-SSRS)

Columbia Suicide Severity Rating Scale (C-SSRS) will be assessed at screening, baseline, and on the discharge day. The C-SSRS uses a series or probes to help physicians determine the presence of suicidal ideation (Posner et al. 2008). The physician’s judgment of subject responses will determine the presence of suicidal behavior or ideation. Validity studies support the C-SSRS’s use in research and clinical settings (Posner et al. 2011).

5) Cambridge Cognition Cognitive Battery

CANTAB tasks are computerized measures of cognition which will be assessed every scan day.

6) Visual Analog Scales (General)

The VAS will be assessed at every inpatient day. VAS is a battery of 21 computerized visual analog scales with items related to psychological response and will be administered with a continuous scale of 0 to 100.

7) Adverse Childhood Experience (ACE) scale

The ACE is a 10-item measure of adverse childhood experiences that will be administered at baseline (Felitti et al. 1998).

a. Data Banking

Following completion of an imaging session, the raw data will immediately be transferred to electronic storage by the study staff/MR technician for later processing. This storage is in a locked room with access limited to the investigators and data processors. Subjective and physiological data are likewise kept in a locked area accessible only to the investigators/data processors. Subjective assessments (besides Cognitive tasks), C-SSRS, adverse events, and morning blood pressure and pulse will be collected through REDCap. No personal health information will be entered into REDCap.

Cognitive data will be captured electronically, encrypted at source and processed using a study-specific build of the CANTAB data management software.

Participants will be given a unique ID code. The key to the ID codes will be stored electronically in an encrypted and password protected document on a Temple University computer. Only the study staff will have access to the document that links participant IDs to a participant's personal health information.

Cases are coded by a number detached from the patient's name. No published or presented materials will identify subjects by names, initials, or any other means that could be used to identify the participant. Whenever possible, designated team members will only see de-identified information during the study.

Research study records may only be accessed by staff engaged in the research project or clinical care of the subjects, or by representatives of the National Institute on Drug Abuse, the Food and Drug Administration, or other government agencies as required and permitted by law.

Already collected data will not be destroyed if a subject withdraws or is discharged from the study.

b. Data Management

Data and Safety Monitoring
Every two months, the PI or a specially designated Investigator will check the active research charts for compliance with the research protocol and with Good Clinical Practice procedures. Corrective actions will be taken as needed, and results of the monitoring will be included in our regular updates to the Temple IRB and Data Safety Monitoring Board. Any safety concerns arising from the review will be immediately reported to the regulatory bodies.

Statistical Plan

Primary Outcome Measures

The primary outcome measures are changes in brain glutamate concentration in the anterior cingulate (ACC) after 10 days (steady state) of CLAV 500, 750, 1000 mg/day in subjects with cocaine use disorder compared with baseline. To normalize MRS data, an unsuppressed water signal acquired prior to or after the water-suppressed MRS scan in addition to the total creatine resonance will be used. The molecules present will be determined using the area under the curve corresponding to the concentration of the metabolite. Dr. Bolo, Harvard University, will supervise and perform the data analysis of the imaging data.

Secondary Outcome Measures

Secondary objectives are to:
A) To assess changes in craving-associated neurocircuitry (frontal-striatal-thalamic connectivity) using resting state functional Magnetic Resonance Imaging (rs-fMRI). Subjects with CocUD will have decreased functional connectivity between nodes within the frontal-striatal-thalamic network (Wang et al. 2018) involving mesocorticolimbic circuit nodes (Gu et al. 2010). After repeated CLAV, we expect that the fronto-striatal-thalamic within network functional connectivity will increase. We also will determine whether improved network connectivity as associated with decreased craving as determined by the Cocaine Craving Questionnaire (CCQ) (Sussner et al. 2006) and a Visual Analog Scale (VAS). B) To evaluate whether CLAV 500, 750, 1000 mg a day given repeatedly for 10 days (to steady state, rationale below) and then stopped, is associated with a sustained reduction in brain glutamate concentration measured in the ACC one day after cessation of CLAV dosing (to determine the duration of CLAV action on glutamate after last dose and to determine the feasibility of once daily CLAV dosing). C) To evaluate whether 10 days of treatment with CLAV is associated with increases in brain glutamine concentration as assessed by MRS in the AC. D) To assess CLAV 500, 750, and 1000 mg/day safety and tolerability by: a) the rates of occurrence of adverse events; b) changes in vital signs; c) EKG parameters; and d) laboratory study changes.

Exploratory Outcome Measures

Exploratory objectives are to: A) To evaluate whether repeated CLAV treatment 500, 750, 1000 mg/day suppresses cue-induced limbic fMRI activation. B) To evaluate whether CLAV treatment 500, 750, 1000 mg/day for 10 days is associated with subjective effects measured by the Visual Analog Scales (VAS), the Profile of Mood States (POMS). C) To evaluate whether CLAV treatment 500, 750, 1000 mg/day for 10 days is associated with cognitive and executive function deficits as assessed by the Cambridge cognition survey batteries.

Data Statistical Analysis Plan

Demographic and Baseline Comparability Analyses

Demographic variables will be summarized both separately and together for all male and female patients.

Primary Analyses:

ACC glutamate concentrations at days 0, 10 and 11 are the primary assessment variables. Glu level differences assessed by MRS in the ACC after 10 days of CLAV dosing 500, 750, 1000 mg/day will be compared with baseline and presented. The MRS raw data will be taken directly from the scanner and the software package, TARQUIN (http://tarquin.sourceforge.net/) will be used to measure the quantities of metabolites present in the AC. The software recognizes scanning parameters from the data and

generates model basis set of MRS signals for the following 17 metabolites: alanine, aspartate, creatine (Cr), phosphocreatine (PCr), gamma-aminobutyric acid (GABA), glycerophosphocholine (GPC), phosphocholine (PCh), glucose, glutamine, glutathione, Glu, myo-inositol, lactate, Nacetylaspartate (NAA), N-acetylaspartate-glutamate (NAAG), scyllo-inositol and taurine as well as the combinations of Glu and glutamine (Glx), Cr and PCr (total creatine or TCr), of GPC and PCh (cholines or Cho), and macromolecules. After several iterations of data preprocessing, it fits the model basis set to the data and calculates the absolute concentration of each metabolite in mM taking the area under the corresponding fitted curve scaled to the water signal in the voxel. Processing of the multi-echo MRS data set allows precise measurement of Glu from the selective TE-averaged Glu signal, and can take into account T2 relaxation effects in the voxel. Water concentration in the voxel will be estimated by calculating the fractions of grey and white matter and cerebrospinal fluid in the voxel after segmentation of the T1-weighted structural MRI (Gasparovic et al., 2006; Kreis, Ernst, & Ross, 1993). Dr. Bolo and/or his assistant will perform the MRS data processing. Glutamate level will then be compared between pre and post study drug administration. Changes in ACC glutamate level will be compared between the CLAV and placebo group using a one-sided Mann-Whitney-Wilcoxon Test at a significance level set to 0.05.

For all variables, first, preliminary and descriptive analyses will be conducted to assess data quality and integrity by descriptive statistical and graphical methods. Balances in terms of the demographic or disease characteristic variables between the groups will be empirically examined. Any systematic differences so identified will be noted in the study report of this proposal. Note that given the dramatically reduced new group sizes, all data analyses will be mostly descriptive and hypothesis generating in nature, and the results will be used primarily to guide the decision-making for the next step of this project.

Using the intent-to-treat framework, the data will be reported using descriptive summary statistics such as mean, median, range, quartiles and standard deviation for a continuous variable and frequency and percentage for a categorical variable overall as well as by study group. Whenever appropriate, both point estimates and confidence intervals will be reported on the study endpoints of interest (e.g., changes in brain glutamate concentration and glutamate/creatine ratio). Differences for continuous variables will be assessed using t-tests (with unequal variances if appropriate) or the Wilcoxon rank sum test if the distributional assumption is violated for two-group comparisons. Proportions will be compared using the chi-square test or Fisher's exact tests. Multiple comparison adjustments will not be made due to the small sample size. Demographics and medical history variables (e.g., age, gender, and race) may be correlated to the study endpoints of interest, if strongly warranted. Some exploratory statistical approaches (e.g., Pearson/Spearman correlation coefficients, and linear regression for continuous variables) may be considered, if absolutely indicated by the study, to explore possible associations between the study endpoints and various covariates. We do recognize, however, due to small group sizes, such approaches

(correlation and regression analyses) may be not feasible to implement. Such analyses will not be employed unless absolutely warranted. To safeguard a possible departure from the normal distribution assumption, the appropriate nonparametric methods such as Wilcoxon rank sum test and Spearman correlation will be employed for analysis in addition to the usual parametric data analyses methods. SAS version 9.4 or higher will be used for all the data analyses.

Secondary Analyses

Assessment of ACC Glu level one day after the last CLAV dose will be compared with the level on the last day of CLAV dosing. Resting state fMRI data preprocessing and analyses will be performed using statistical parametric mapping (SPM) (http://www.fil.ion.ucl.ac.uk/spm) based custom batch scripts (Wang et al. 2015, Wang et al. 2017, Li, Kadivar, et al. 2012, Li, Zhu, et al. 2012). Seed region-based functional connectivity (SRFC) will be calculated as the correlation coefficient (CC) of the resting state fMRI signal from a seed and any voxel in the rest of the brain. A Priori seeds will be defined in anterior cingulate (ACC), amygdala, ventral striatum (VS), insula, ventromedial prefrontal cortex (VMPFC), posterior cingulate cortex (PCC), and lateral prefrontal cortex (PFC). These regions are known to be affected by cocaine addiction, suggesting that their connections to other regions may be impaired as shown in (Gu et al. 2010) and may be predictive of relapse (Adinoff et al. 2015). ACC Regions of Interest (ROI) in the Montreal Neurological Institute (MNI) standard brain will be defined based on the previous SRFC work in cocaine addiction (Gu et al. 2010). Other seeds will be based on suprathreshold clusters from the literature or manually defined using the SPM Pickatlas utility (Maldjian et al. 2003). The individual subjects' FC maps will be first registered into the image space of the T1-weighted structural MRI and then registered into the MNI standard brain using SPM (version 12). The registration transform will be derived from the projection from the T1-weighted structural MRI to the MNI space.
There will be an assessment of glutamate level one day after the last dose compared with the last day of dosing after last dose.

Assessments for glutamine will be similar to those for glutamate.

Adverse events will be tabulated overall as well as by study group, and by body system and organ class if desired. In addition, all adverse events (AE's) noted during the study will be listed. The listings will include each occurrence of the AE, when it was reported, the severity and the duration. Adverse event data will be compiled for CLAV and placebo and presented as summary statistics. Subjective craving effects of CLAV from the visual analog scale and CCQ will be evaluated similarly as described in the above for glutamate.

Exploratory Analyses:
Cue reactivity task will be analyzed using a standard general linear model (GLM) with the task design function convolved with a generic hemodynamic response function as the regressors for brain activity during each task condition; an ANOVA may be used to

examine treatment group (CLAV vs. placebo) and cue condition effects in a second level analysis (Young et al. 2014). The hemodynamic response function convolution allows for correction of hemodynamic delay.

Subjective effects of CLAV, as measured by check lists, rating scales, and cognitive tests will be listed for each patient and summarized for each group.

Rationale for Sample Size:

Sample sizes are derived based on a 12% difference between CLAV and placebo groups in the mean changes in Glu in anterior cingulate cortex from a human crossover MRS imaging study of N-acetylcysteine, another (weaker) GLT-1 activator (Schmaal et al. 2012). Summary glutamate data on changes in glutamate with reference to the unsuppressed water signal were reported by Schmaal et al, 2012. Specifically, based on this article, we assume the mean change (SD) in Glu for the placebo group is 8.39 (0.76) while the mean (SD) is 7.38 (0.76) for the CLAV group. Note that the standard deviations (estimated based on the SEM and number of subjects) are relatively small and the target 12% difference is relatively large. Because of budget reductions, the proposed sample size has been reduced to 12, with 9 subjects allocated to CLAV and 3 to placebo. Group sample sizes of 3 and 9 achieve 63% power to detect a difference of -1.01 between the null hypothesis mean difference of 0.0 and the actual mean difference of 1.01 at the 0.05 significance level (alpha) using a one-sided Wilcoxon Test (the actual alpha=0.075). However, if the actual group difference is 20% instead of 12%, group sample sizes of 3 and 9 achieve 94% power to detect a difference of -1.68 between the null hypothesis mean difference of 0.0 and the actual mean difference of 1.68 at the 0.05 significance level (alpha) using a one-sided Wilcoxon Test (the actual alpha=0.085). These results are based on 2000 Monte Carlo samples from the null distributions: Normal(M0 S) and Normal(M0 S), and the alternative distributions: Normal(M0 S) and Normal(M1 S). Randomization assignment tables will be generated by study statistician Dr. Daohai Yu and stratification on sex and last use of cocaine (≤1 month vs. > 1 month) will be considered.

c. Confidentiality

Confidentiality of Data

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

Confidentiality of Patient Records

To maintain subject confidentiality, all laboratory specimens shipped outside the Temple Health System, reports and other records will be identified by a coded study subject number only. Research and clinical records will be stored securely. Only research staff and sponsor or sponsor's representative will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by the FDA or sponsor. Upon approval of the study by the IRBNIH automatically grants a certificate of confidentiality.

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

d. Provisions to Monitor the Data to Ensure the Safety of subjects

Participant Compliance Monitoring

Study staff will be present for the self-administration of all study drug/placebo doses. Participants will be closely observed during self-administration and asked to open their mouths and lift their tongue to the roof of their mouths to confirm the dose was swallowed.

Compliance with NIDA Policy on Monitoring Plans:

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

This protocol complies with that policy. The procedures for reporting Serious Adverse Events (SAEs) to NIDA, the IRB and FDA are contained under the adverse events reporting section below. A DSMB will be reviewing the data and safety information from this trial. Please see the attached Data Safety and Monitoring Plan for complete details regarding safety monitoring. A safety monitoring board has been established with the following purpose (according to NIDA guidelines): to assure that the safety of study subjects is protected while the scientific goals of the ongoing studies are being met. Specifically, the DSMB is charged with monitoring the safety of participants and the quality of the data, as well as the appropriate termination of studies either when significant benefits or risks have been uncovered.

All board members meet NIDA requirements regarding background and experience, and none will have ethical conflicts, including financial interest related to study outcome. Individuals invited to serve on the board disclose any potential conflicts in writing. The board meets every 3-4 months (unless more frequent meeting is deemed necessary) and is chaired by Huaqing Zhao, Ph.D. Huaqing Zhao, Ph.D., is an Associate Professor of Biostatistics at Lewis Katz School of Medicine at Temple University. Other members include (Jaakko Lappalainen PhD, M.D) who is the chief of addiction psychiatry at the Crozer-Chester Medical center, and Mark Weiner MD is the deputy chief information officer for health system and research analytics at Cornell University. The current study is reviewed using a DSMB Progress Report reviewed in an open session, followed by a closed session under the direction of Dr. Zhao. Issues related to recruitment, subject safety and efficacy, whether the primary study question is being answered, conflict of interest, confidentiality, and ongoing study review (including AEs, SAEs, and regulatory issues) are assessed. Following each DSM Board meeting, Dr. Zhao will make recommendations to Dr. Morrison, and a final report (edited by all Board members) will be prepared and submitted to NIDA and the Temple IRB (and if required the FDA), according to each bodies' reporting requirements.

Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Adverse Events Reporting

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

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

Serious Adverse Event

Adverse events are classified as serious or non-serious. Based on the seriousness of the adverse event or reaction appropriate reporting procedures will be followed. The

International Conference on Harmonization (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995, as implemented by the U.S. Food and Drug Administration states that a ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the participant wellbeing and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in inpatient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Any SAEs due to any cause, which occur during the course of this investigation, whether or not related to the investigational agent, must be reported within 24-hours by telephone or e-mail to: all study physicians, the NIDA Study Medical Monitor, NIDA grant Program Officer and the Temple IRB.

24-hour Reporting Requirements

Any serious adverse event, including death due to any cause, which occurs to any subject from the time of admission through discharge whether related to the study drug/placebo, must be reported ***within 24 hours***.

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

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

- Any action taken with the study drug, alteration to protocol defined schedule, diagnostics, and treatments secondary to the SAE/unexpected AE.

The telephone/e-mail report is to be followed by submission of a completed SAE Form within 3 days with demographic information and a narrative explanation of the event. Supporting documentation is listed below. All serious medical events are to be reported to the Temple IRB within 3 days. All study investigators will be also notified of any serious and unexpected AE requiring submission to the FDA in an IND safety report.

3-day Supporting Documentation Requirements

Written documentation for all SAEs/unexpected AEs must be received by the NIDA Program Officer and Science Officer , the Temple IRB and the DSMP within 3 days of reporting the event and will be in narrative form. Required documents that must be submitted to NIDA include the following:

- SAE Form
- Concomitant Medication CRF pages
- Adverse Events CRF pages
- Copies of source documents pertinent to the event (lab reports, EKG tracings, medical chart notes, etc.)
- Any other relevant information necessary to facilitate the investigator's judgment regarding the SAE's relatedness to the severity OR by request of the Medical Monitor/Alternate

Follow-Up of All Adverse Events/Serious Adverse Events

All adverse medical events must be followed until they are resolved, or until all attempts to determine the resolution of the AE/SAE are exhausted. This may require an extended inpatient period. All treatments, outcomes and information regarding whether the subject was referred to their Primary Care Provider for additional follow-up must be recorded in the source document. All serious and unexpected adverse events occurring 30 days after administration of the last dose of study drug/placebo must be reported.

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

Reporting to the FDA

The IND sponsor, Dr. Morrison, is required to report SAEs to the FDA:

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

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

- in an annual report in all other cases.

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

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

Pre-existing Condition
A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

At screening, any clinically significant abnormality or disorder should be recorded as a pre-existing condition. At the end of the study, any new clinically significant findings/abnormalities or disorder that meets the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events will be followed by the investigator until the events are resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the IRB of any adverse event occurring at any time after a participant has discontinued or terminated study participation that may reasonably be related to this study. The IRB will also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a participant that has participated in this study.

Other Safety Considerations

No patients with allergies to penicillins, cephalosporins and beta-lactam related drugs will be enrolled in the study. Subjects will not be allowed to take concomitant over the counter (OTC) medications without the permission of the investigator. Any medication with effects on glutamate or GABA such as N-acetylcysteine, tiagabine, or lorazepam is excluded. A table of excluded medication is provided in Appendix I. For an urgent medical problem after working hours after inpatient discharge, please contact the study doctor using the 24-Hour phone number at 610-247-2126.

Covid-19 Safety Procedures
Participants who are determined to be potentially eligible from the prescreen questionnaire will complete an illness screening questionnaire. Participants who endorse Covid-19 related symptoms within the past 14 days will be asked to seek appropriate care and will have their screening visit scheduled a minimum of 14 days after their symptoms resolve. Covid PCR testing will be recommended for participants with symptoms, and participants with negative tests will be scheduled for a screening visit.

Participants who are scheduled for a screening visit will be asked to contact the study team should they develop any symptoms related to Covid-19. Participants who develop Covid-19 related symptoms will be asked to reschedule their visit a minimum of 14 days after their symptoms resolve.

Participants will have their temperature taken and be provided a surgical mask prior to starting study procedures. Session rooms will be arranged so that participants can maintain a 6-foot social distance when possible, and rooms will be disinfected between participants.

Eligible participants will receive a Covid-19 test prior to screening visit part 2, and receive a Covid-19 PCR viral test within 96 hours prior to the baseline visit. Participants who test positive for Covid-19 will be instructed to seek appropriate medical care and will have their visit rescheduled a minimum of 14 days after their symptoms resolve.

e. Withdrawal from Study

Early Withdrawal of Participants

1. When and How to Withdraw Participants

Participants who experience severe psychological symptoms (e.g., suicidal thoughts), fail to adhere to protocol requirements, or withdraw consent will be withdrawn from the study and, if applicable, referred for appropriate clinical care. Participants who report active suicidal ideation (determined by MINI or C-SSRS) will be referred to the crisis center or the outpatient clinic for evaluation. Participants will be reminded that they will

be responsible for any costs related to treatment. Any participant experiencing a serious adverse event that the Principal Investigator believes to be related to study drug and a potential threat to the health and safety of the participant will be withdrawn from the study.

Participants will be informed about any new information that may affect their health, welfare, or choice to stay in this research.

2. Data Collection and Follow-up for Withdrawn Participants

We will make a strong effort (via phone calls and alternative contact information) to obtain follow-up information on all participants who are prematurely withdrawn from the project.

11. Risks to Subjects

MRI and MRS have proven to be of great value in the noninvasive diagnosis and understanding of neuropsychiatric brain disorders. The overall risk to subjects from participation in MRS research scans is minimal. The levels of energy used to make magnetic resonance measurements is far less than is used in a single X-ray, and many patients have been safely studied using magnetic resonance techniques. However, some people become uncomfortable or claustrophobic while inside the magnet. If subjects become uncomfortable inside the magnet, they may withdraw immediately from the study.

The greatest risk from an MRS scan is a metallic object flying toward the magnet and hitting them. To reduce this risk, we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. Subjects are scanned wearing clothing provided by TUBRIC though they retain their underpants. No metal objects are allowed in the magnet room at any time. In addition, once a subject is in the magnet, the door to the room will be closed so that no one inadvertently walks into the magnet.

During some of the MRI scans, subjects have occasionally reported “tingling” or “twitching” sensations in their arms or legs, especially when their hands are clasped together. Further, because of the strong magnetic field, people with pacemakers, metal fragments in the eye, or certain metallic implants cannot participate in this study. Subjects are given a checklist before entering the MRI room at each scan which is reviewed so that subjects do not encounter this problem. All women of childbearing potential are to take a pregnancy test (urine) to verify that they are not pregnant before they are enrolled in the study. Clavulanic Acid by itself is not FDA approved and its current use in this study is experimental. The medication could pose an unknown risk to a fetus or embryo, and pregnant women will be excluded from this study to mitigate this risk. While there are no known harmful effects to embryos of multiple brain MRIs within a couple weeks, there is

no clear unique knowledge or benefit gained from including this population in the current study.

This study may include the use of custom manufactured head coils and experimental imaging sequences that are not FDA-approved but are considered non-significant risks.

The primary risks of this study are those of possible adverse reaction to the study drug, CLAV. There is substantial safety data on Augmentin, but it is not known whether CLAV alone confers increased medical risk to cocaine dependent people who have 7+ days of cocaine abstinence. Our experience with our cocaine interaction study and outpatient imaging study with CLAV does not suggest serious risk of multiple dose CLAV 500 mg in the cocaine dependent population. CLAV is a beta-lactamase inhibitor and is the potassium salt of CLAV. CLAV is part of Augmentin/Augmentin XR®, along with amoxicillin. Augmentin® has been FDA approved since 1984 for the treatment of patients with community-acquired pneumonia or acute bacterial sinusitis and has been used globally for the treatment of infectious diseases. Augmentin® is considered reasonably safe during pregnancy and lactation (Berkovitch et al. 2004, Benyamini et al. 2005). CLAV is not an effective antibiotic and is unlikely to disturb bowel flora (Saudagar, Survase, and Singhal 2008). CLAV levels in tissue are too low to affect human flora in healthy subjects (Earnshaw et al. 1987, Finlay, Miller, and Poupard 2003). However, one report of an experimental murine model suggested that CLAV may have efficacy for the treatment for Acinetobacter baumannii, a gram negative rod that is an opportunistic pathogen in immunocompromised patients (Beceiro et al. 2009). CLAV is unavailable by itself, without amoxicillin. Thus, there is no safety data in the scientific literature on CLAV alone. The Augmentin approval package includes single dose data on CLAV 750 mg and 1,000 mg (FDA 05/09/1988). Side effects reported in the Phase I studies of CLAV from the FDA approval data include: nausea, vomiting, drowsiness, fatigue, diarrhea, indigestion, headache, increased stomach noises, nausea (sometimes with increased heart rate), flatulence (passing gas), “very slight increase in liver size” with increased liver tests, cholestatic jaundice, and dizziness. In the present study one male participant experienced priapism without pain for 5 hours after the first day of study drug (study drug not unmasked). During the screening visit male subjects will be evaluated for priapism risk factors, abnormal anatomy of the penis, and previous episodes of unexpected prolonged erections. The PI consulted with Dr. Jack Mydlo, the Temple Chair of Urology, and determined that a participant with an erection of 4 hours or longer will be transferred to the Emergency Room. Participants experiencing priapism will have their cavernosal blood gas evaluated to determine whether the priapism is high or low flow. Emergency Room physicians at Temple are familiar with priapism evaluation, and will discuss the results with the Urology Resident on call for further management.

Common adverse events for Augmentin include: diarrhea (14.5%), vaginal mycosis (3.3%), nausea (2.1%) and loose stools (1.6%). As a beta lactam drug, CLAV has a risk of allergic reactions both for those with known penicillin allergy, as well as for those with no known allergy. No patients with allergies to penicillins, cephalosporins and beta-lactam related drugs will be enrolled in the study. The risk of hepatitis for Augmentin®

is estimated at between 1/10,000 to 1/100,000, with an increased risk for older males (Gresser 2001). Hepatotoxicity associated with amoxicillin/ CLAV is generally self-limited with cessation of medication and generally associated with complete recovery (Saudagar, Survase, and Singhal 2008, Gresser 2001, Larrey et al. 1992). The medical literature supports the hypothesis that CLAV at doses up to 500 mg/day and CLAV given as a chronic medication is generally safe and well tolerated. Combined amoxicillin clavulanate (CLAV 250 mg a day) has been given to men to treat actinomycetoma for a mean of 9.6 months with no reported side effects (Bonifaz et al. 2007). Combined meropenem/clavulanate (CLAV 375 mg a day) has been given to 6 patients with drug-resistant tuberculosis for up to 36 weeks with no reported side effects (Payen et al. 2012). Timentin® is an intravenous combination of ticarcillin and CLAV, with 100 mg of CLAV in a 3.1-gram infusion of Timentin. In a retrospective study of 127 pediatric cystic fibrosis patients who received Timentin, they received a mean of 450 mg CLAV /day +/- 227 mg/day for a mean duration of 13.5 days (Zobell et al. 2010). No adverse effects on laboratory measures, including liver function tests, were found. While there is substantial clinical experience with Augmentin to treat infections, there is no published data on either CLAV or Augmentin in cocaine dependent adults.

Blood being drawn is a risk of the study. Blood drawn from all subjects should be considered infectious and extreme caution will be used to avoid needle sticks and direct contact with blood or plasma.

The nasoparyngeal Covid-19 swab is a risk of the study. The swab can be uncomfortable and some participants experience mild bleeding from their nose afterwards (5-8% patients). Headache and ear discomfort after the swab test are rarely experienced (1-5% patients). Participants will be instructed to hold very still to ensure the swab is properly administered and does not cause further discomfort. The swab should be considered infectious after administration, and staff will use extreme caution to avoid direct contact with the swab.

Questions from the ACE scale include information about childhood abuse, neglect, and other adverse childhood experiences. Participants may find some of the questions from the ACE scale distressing to answer. Participants will be reminded their participation is voluntary, and they can refuse to answer any question that is asked in the questionnaire. Staff will provide emotional support to participants who are distressed by the questionnaire, and if necessary, referrals will be provided for outpatient care.

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

Note: "Minimal risk" means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests.

12. Potential Benefits to Subjects

Although there is little immediate benefit to the subjects who undergo this study including MRI imaging, there is great potential for the study of drug abuse, which remains a major source of social, economic, and medical disability in the United States and elsewhere. Increasing knowledge about the brain response to a drug being studied for cocaine addiction may aid in the development of therapeutic strategies for this addiction. Furthermore, the technical development is also expected to lead to valuable methodologies for all studies of behavioral state and will have general applicability in basic and clinical neuroscience. If the study staff observes a brain abnormality during the scan, a professionally licensed radiologist will be consulted at no cost to the participant. If the radiologist recommends clinical follow-up, the team will inform the participant of the recommendation, make images from the scan session available to them, and provide a referral to a professional upon the subject's request. Participants are reminded that the study team is not responsible for any medical costs related to the incidental finding. Subjects may experience benefit from having a medical history, physical, laboratory testing and associated counselling performed. These potential benefits can be contemplated as the risk of participation in the study is considered.

13. Privacy and Confidentiality

Privacy is a subject's ability to control how other people see, touch, or obtain information about the subject.

Research study records may only be accessed by staff engaged in the research project or clinical care of the subjects, or by representatives of the National Institute on Drug Abuse, the Temple IRB, the Food and Drug Administration, or other government agencies as required and permitted by law.

The following data may be collected. It contains protected health information (PHI)

- Name
- Street address, city, county, precinct, zip code, and equivalent geocode
- date of birth/age/gender
- Personal information regarding past medical or drug therapies to ensure eligibility for inclusion in the study
- Telephone numbers
- Electronic mail addresses
- Social security numbers (for payment processing)
- Health plan ID numbers to register subjects in Temple systems for MRI if there is a need
- Brain images/lab test results
- Responses to study safety questionnaires

14. Compensation for Research-Related Injury

There will be no compensation for research-related injury. The study team will help arrange appropriate medical care, but participants will be informed there is no commitment by Temple University, Temple University Health System or its subsidiaries to provide monetary compensation or free medical care in the event of a research-related injury. Participants will be given the contact information for Dr. Mary F. Morrison or the study physician covering the study.

15. Economic Burden to Subjects

The study drug will be provided to participants for no charge. Participants will receive compensation for time and transportation. There are no charges to subjects for participating in this research study.

16. Consent Process

All study personnel will follow Temple University's SOP "INVESTIGATOR GUIDANCE: Informed Consent (HRP-802)."

Non-English-Speaking Subjects
We will not be enrolling non-English speaking subjects at this time.

Waiver or Alteration of the Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)
Not Applicable.

Subjects who are not yet adults (infants, children, teenagers)
Not Applicable.

Cognitively Impaired Adults
Cognitively impaired adults are not appropriate for enrollment in the study.

Adults Unable to Consent
If the adult is deemed unable to provide consent, then they will not be included in this study.

17. Process to Document Consent in Writing

All study personnel will follow Temple University's SOP "INVESTIGATOR GUIDANCE: Documentation of Informed Consent (HRP-803)."

18. Vulnerable Populations

No vulnerable populations will be included in this study. All subjects will be told that they may choose not to participate in this study and their decision will not have any impact on their current care if they choose not to participate in the study. We will not use coercive language before, during or after the consent process and study procedures.

19. Drugs or Devices

The study drug (*CLAV*) will be stored in the Episcopal inpatient pharmacy. The trained research staff will observe ingestion of each study drug dose by the participant to ensure medication adherence.

The initial dose of *CLAV* (250 mg) for the first day was picked to be higher than 10 mg/kg *CLAV* (in rodents or ~162 mg in humans). In addition, 500 mg dose has been reasonably well-tolerated in the cocaine interaction study and MRS pilot study. 750 mg was tolerated in the cocaine interaction study. 1000 mg will be tested. The Augmentin NDA, the published literature, and our studies support the safety of testing these doses for 10 days on an inpatient basis with daily evaluations.

20. Dose Justification.

The range of 1 -10 mg/kg CLAV was associated with behavioral changes suggesting efficacy for substance abuse disorders in our rodent models at Temple (S Rawls' lab). One way to translate rodent doses to humans is to match the net systemic exposure of *CLAV* in each species. A single intravenous dose of 10 mg/kg in rats gave an AUC (area under the curve) of 7.9 mg.h/L (Woodnutt, Kernutt, and Mizen 1987). A single oral dose of 125 mg in humans gave an AUC of 6.1 mg.h/L (Sánchez Navarro 2005). Linear PK is assumed, based on data in the Augmentin NDA (New Drug Application to the FDA) and the scientific literature (FDA 05/09/1988). We then calculate that a single oral dose of 16.2 mg in a 70 kg human would achieve comparable systemic exposure to a single 1mg/kg IV/IP (intraperitoneal) dose in rats (and 162 mg ~10mg/kg). The initial dose of *CLAV* (250 mg) was picked to be higher than 10 mg/kg *CLAV* (in rodents or ~162 mg in humans). For this study, we plan to study a minimum of 500 mg/day (2 capsules) for 10 days to maximize the possibility of detecting any change in the concentration of glutamate in the ACC brain regions after repeated administration using what may be an efficacious dose of CLAV, based on efficacious doses found in rodents. The maximum tested dose in the Augmentin New Drug Application (NDA) was 1000 mg in healthy volunteers, but it is not clear whether this is the maximum tolerated dose (Augmentin New Drug Application to the FDA). For safety purposes participants will receive 250mg of CLAV on the first day of dosing. Participants who safely tolerate the 250 mg dose will be instructed to self-administer the second 250mg dose later in the day under staff supervision. Participants will take a 500mg dose (2 capsules) at a single time for the next 2 days. Participants who tolerate the 500mg dose will be

escalated to a 750mg dose for 3 days. Participants who tolerate the 750mg dose will be escalated to the 1000mg. Participants will be administered the 750mg and 1000mg doses to maximize the possibility of detecting any adverse pharmacodynamic effect, using what may be an efficacious dose of CLAV. Participants who are unable to tolerate dose escalation will resume their previously tolerated dose. No MTD in healthy controls or cocaine dependent subjects has been established. For a drug development program for CLAV in the cocaine disorder population, it is reasonable to study a higher dose under close supervision in case higher doses are needed for efficacy. The inpatient clinical trial examining IV cocaine in combination with *CLAV* had 10 subjects who have been exposed to the 500 mg dose, 5 subjects have been exposed to a 750 mg dose with no severe side effects. No adverse pharmacodynamic interactions between CLAV or Augmentin and cocaine have been reported.

21. Multi-Site Human Research

Not Applicable.

22. Sharing of Results or Incidental Findings with Subjects

The MRI will not be reviewed by a neuroradiologist. Results will only be shared with subjects if they ask for the results of the study. Study results will be published without identifying information. If a subject is interested in knowing the results from the study, they will be directed to the publication and the published results may be discussed. No individual results will be discussed regarding the study.

APPENDIX I: Table of Glutamate/GABA Affecting Drugs

Glutamate/GABA Affecting Drugs	Chronic Use	Episodic Use[D]
Acamprosate	N	N
Acetazolamide	N	Y
Agmatine	N	N
Alcohols (including ethanol)	N	Y
Amantadine	N	N
Antidepressants (SSRI, SNRI, Wellbutrin)	N	N
Atomoxetine	N	N
Baclofen	N	Y
Barbiturates	N	N
Benzodiazepines	N	Y
Beta-Lactam Drugs	N	N
Bromides	N	N
Buprenorphine	N	N
Cannabinoids (including marijuana)	N	Y once only. Negative UDS for entry.
Carbamates (carisoprodol (SOMA), meprobamate)	N	N
Chloral hydrate	N	Y
Chloroform	N	Y
D-cycloserine	N	N
Delucemine	N	N
Dexoxadrol: etoxadrol	N	N
Dextromethorphan	N	Y
Dextrorphan	N	N
Diphenidine	N	N
Eliprodil	N	Y
Etifoxine	N	N
Eszopiclone	N	Y
Etoxadrol: similar to PCP.	N	N
Felbamate	N	N
Gabamide	N	N
Gabapentin	N	N
Gaboxadol	N	N

[D] Episodic Use is defined as use 1-2 times a week and no use 3 days prior to the scan

Gammahydroxybutyrate (GHB)	N	N
Glutamine	N	N
Huperzine A	N	N
Ibogaine	N	N
Ibotenic Acid	N	N
Ivermectin and other avermectins	N	N
Kavalactones	N	N
Ketamine	N	N
Kratom	N	N
Lamotrigine	N	N
Levetiracetam	N	N
Loreclezole	N	N
Magnesium	N	Y
Memantine	N	N
Meprobamate	N	N
Methadone	N	N
Minocycline	N	N
Muscimol	N	N
N-acetylcysteine	N	N
Neramexane	N	N
Neuroactive steroids (such as allopregnanolone)	N	N
Nitromemantine	N	N
Nitrous oxide	N	Y
Opioids	N	Y
Perampanel	N	N
Phencyclidine	N	N
Phenibut	N	Y
Picamilon	N	N
Pregabalin	N	N
Progabide	N	N
Propofol	N	Y
Primidone	N	N
Remacemide	N	N
Retigabine	N	N
Riluzole	N	N
Selegiline	N	N
Tiagabine	N	N
Topiramate	N	N
Tricyclic antidepressants	N	Y
Valerian	N	Y

Vigabatrin	N	N
Zaleplon	N	Y
Zolpidem	N	Y

APPENDIX II: Certificate of Confidentiality

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

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

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

Effective October 1, 2017 Certificates of Confidentiality (COCs) will be issued automatically for any NIH-funded project using identifiable, sensitive information that was on-going on/after December 13, 2016.

The CoC will be issued as a term and condition of award and there will be no physical certificate issued.

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

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

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

or

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

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

APPENDIX III: MRI Safety Questionnaire

TUBRIC TEMPLE UNIVERSITY BRAIN RESEARCH & IMAGING CENTER

Subject MRI Safety Screening Form

The MR system has a **very strong magnetic field** that may be hazardous to individuals entering the MR environment/MR system room if they have certain metallic, electronic, magnetic, or mechanical implants, devices, or objects. Therefore, **ALL** individuals are required to fill out this form **BEFORE** entering the MR environment/MR system room. Be advised, the MR system magnet is **ALWAYS** on.

Subject Information	STUDY CODE:		SUBJECT ID:		
Name (First, Middle, Last):	Date of Birth:	Age:	Gender:	Height:	Weight:
Address:		Email:		Phone (best number):	

Have you had prior surgery or an operation (e.g., arthroscopy, endoscopy, etc.) of any kind? If yes, please indicate type and approximate date of surgery:	Yes ☐ No ☐
Have you had a prior MRI examination? If yes, did you experience any difficulties related to the examination? Yes ☐ No ☐	Yes ☐ No ☐
Have you had an injury to the eye involving a metallic object/fragment (metal slivers, shavings, foreign body,…)? If yes, please describe:	Yes ☐ No ☐
Have you ever been injured by a metallic object or foreign body (e.g., BB, bullet, shrapnel, etc.)? If yes, please describe:	Yes ☐ No ☐
Have you ever been a machinist, welder, metal worker or lathe operator?	Yes ☐ No ☐
Are you currently taking any medication or drug, or receiving any hormonal or fertility treatments? If yes, please describe:	Yes ☐ No ☐
Are you pregnant or possibly pregnant (e.g., experiencing a late menstrual period)?	Yes ☐ No ☐
Are you claustrophobic?	Yes ☐ No ☐

Do you have any of these items in (or on) your body?

Aneurysm clip	Yes ☐ No ☐	Implanted drug infusion device	Yes ☐ No ☐	Hearing aid	Yes ☐ No ☐
Cardiac pacemaker	Yes ☐ No ☐	Any type of prosthesis	Yes ☐ No ☐	Body piercings	Yes ☐ No ☐
Implanted cardioverter defibrillator (ICD)	Yes ☐ No ☐	Heart valve prosthesis	Yes ☐ No ☐	Medication/Transdermal patch	Yes ☐ No ☐
Electronic Implant or Device	Yes ☐ No ☐	Eyelid spring or wire	Yes ☐ No ☐	Metal fragment or foreign body	Yes ☐ No ☐
Magnetically-activated implant or device	Yes ☐ No ☐	Artificial or prosthetic limb	Yes ☐ No ☐	Wire mesh implant	Yes ☐ No ☐
Neurostimulation system	Yes ☐ No ☐	Metallic stent, filter, or coil	Yes ☐ No ☐	Tatoo/Permanent Makeup	Yes ☐ No ☐
Spinal cord stimulator	Yes ☐ No ☐	Shunt (spinal or intraventricular)	Yes ☐ No ☐	Surgical staples, clips, or metallic sutures	Yes ☐ No ☐
Internal electrodes or wires	Yes ☐ No ☐	Vascular access port and/or catheter	Yes ☐ No ☐	Colored contact lenses	Yes ☐ No ☐
Bone growth/bone fusion stimulator	Yes ☐ No ☐	Radiation seeds or implants	Yes ☐ No ☐	Bone/joint replacement, pin, screw, wire, plate, etc.	Yes ☐ No ☐
Cochlear, otologic, or other ear implant	Yes ☐ No ☐	Swan-Ganz or thermodilution catheter	Yes ☐ No ☐	IUD, diaphragm, or pessary	Yes ☐ No ☐
Insulin or other infusion pump	Yes ☐ No ☐	Tissue expander (e.g., breast)	Yes ☐ No ☐	Braces, retainer, dentures, or partial plates	Yes ☐ No ☐

If you answered yes to any of the above questions this may indicate a contraindication for entry into the MRI suite (Control Room, MRI Room). Your responses must be reviewed by a qualified TUBRIC staff member, and any potential contraindications discussed. **DO NOT ENTER** the room if you have any questions/concerns regarding safety to yourself or others.

IMPORTANT: Before entering the MRI room you must remove all metallic objects, including hearing aids, colored contact lenses, dentures, partial plates, keys, cell phone, eyeglasses, hair pins, barrettes, jewelry, body piercings, watch, safety pins, paperclips, money clip, credit/debit cards, magnetic strip cards, coins, pens, pocket knife, nail clipper, tools, clothing with metal fasteners, & clothing with metallic threads. Please consult the MRI Operator if you have any question or concern **BEFORE** you enter the MRI room.

SUBJECT'S SIGNATURE (PARENT/LEGAL WARD IF MINOR) _____ PRINTED NAME _____ DATE _____

SCREENER'S SIGNATURE _____ SCREENER'S PRINTED NAME _____ DATE _____

REVIEWED BY (Must be TUBRIC Level 3 or higher): _____

Temple University Brain Research & Imaging Center • B050 Weiss Hall • 1701 N 13th St. Philadelphia, PA, 19122

References

Adinoff, B., H. Gu, C. Merrick, M. McHugh, H. Jeon-Slaughter, H. Lu, Y. Yang, and E. A. Stein. 2015. "Basal Hippocampal Activity and Its Functional Connectivity Predicts Cocaine Relapse." *Biol Psychiatry* 78 (7):496-504. doi: 10.1016/j.biopsych.2014.12.027.

Beceiro, A., R. López-Rojas, J. Domínguez-Herrera, F. Docobo-Pérez, G. Bou, J. Pachón, and Spanish Network for Research in Infectious Diseases (REIPI). 2009. "In vitro activity and in vivo efficacy of clavulanic acid against Acinetobacter baumannii." *Antimicrob Agents Chemother* 53 (10):4298-304. doi: 10.1128/AAC.00320-09.

Benyamini, L., P. Merlob, B. Stahl, R. Braunstein, O. Bortnik, M. Bulkowstein, D. Zimmerman, and M. Berkovitch. 2005. "The safety of amoxicillin/clavulanic acid and cefuroxime during lactation." *Ther Drug Monit* 27 (4):499-502.

Berkovitch, M., O. Diav-Citrin, R. Greenberg, M. Cohen, M. Bulkowstein, S. Shechtman, O. Bortnik, J. Arnon, and A. Ornoy. 2004. "First-trimester exposure to amoxycillin/clavulanic acid: a prospective, controlled study." *Br J Clin Pharmacol* 58 (3):298-302. doi: 10.1111/j.1365-2125.2004.02138.x.

Bonifaz, A., P. Flores, A. Saúl, E. Carrasco-Gerard, and R. M. Ponce. 2007. "Treatment of actinomycetoma due to Nocardia spp. with amoxicillin-clavulanate." *Br J Dermatol* 156 (2):308-11. doi: 10.1111/j.1365-2133.2006.07557.x.

Chu, K., S. T. Lee, D. I. Sinn, S. Y. Ko, E. H. Kim, J. M. Kim, S. J. Kim, D. K. Park, K. H. Jung, E. C. Song, S. K. Lee, M. Kim, and J. K. Roh. 2007. "Pharmacological Induction of Ischemic Tolerance by Glutamate Transporter-1 (EAAT2) Upregulation." *Stroke* 38 (1):177-82. doi: 10.1161/01.STR.0000252091.36912.65.

Curran, S. L., M. A. Andrykowski, and J. L. Studts. 1995 "Short form of the Profile of Mood States (POMS-SF): Psychometric information. ." *Psychological assessment* 7 (1):80.

De Velde, F., B. C. M. De Winter, B. C. P. Koch, T. Van Gelder, J. W. Mouton, and COMBACTE-NET consortium. 2018. "Highly variable absorption of clavulanic acid during the day: a population pharmacokinetic analysis." *J Antimicrob Chemother* 73 (2):469-476. doi: 10.1093/jac/dkx376.

Earnshaw, J. J., R. C. Slack, G. S. Makin, and B. R. Hopkinson. 1987. "Tissue and serum concentrations of amoxycillin and clavulanic acid in patients having reconstructive vascular surgery." *J Int Med Res* 15 (4):205-11. doi: 10.1177/030006058701500403.

FDA. 05/09/1988. Original FDA approval package for Augmentin

Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998;14(4):245-258.

Fiala, M., X. H. Gan, L. Zhang, S. D. House, T. Newton, M. C. Graves, P. Shapshak, M. Stins, K. S. Kim, M. Witte, and S. L. Chang. 1998. "Cocaine enhances monocyte migration across the blood-brain barrier. Cocaine's connection to AIDS dementia and vasculitis?" *Adv Exp Med Biol* 437:199-205.

Finlay, J., L. Miller, and J. A. Poupard. 2003. "A review of the antimicrobial activity of clavulanate." *J Antimicrob Chemother* 52 (1):18-23. doi: 10.1093/jac/dkg286.

Gresser, U. 2001. "Amoxicillin-clavulanic acid therapy may be associated with severe side effects -- review of the literature." *Eur J Med Res* 6 (4):139-49.

Gu, H., B. J. Salmeron, T. J. Ross, X. Geng, W. Zhan, E. A. Stein, and Y. Yang. 2010. "Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by

resting-state functional connectivity." *Neuroimage* 53 (2):593-601. doi: 10.1016/j.neuroimage.2010.06.066.

Huh, Youngbuhm, M. Sun Ju, H. Park, S. Han, Y. Bang, CF. Ferris, and GA. Koppell. 2010. "Clavulanic acid protects neurons in pharmacological models of neurodegenerative diseases." *Drug Development Research* 71 (6):351-357.

Kalivas, P. W. 2009. "The glutamate homeostasis hypothesis of addiction." *Nat Rev Neurosci* 10 (8):561-72. doi: 10.1038/nrn2515.

Kim, J., J. John, D. Langford, E. Walker, S. Ward, and S. M. Rawls. 2016. "Clavulanic acid enhances glutamate transporter subtype I (GLT-1) expression and decreases reinforcing efficacy of cocaine in mice." *Amino Acids* 48 (3):689-96. doi: 10.1007/s00726-015-2117-8.

Knackstedt, L. A., and P. W. Kalivas. 2009. "Glutamate and reinstatement." *Curr Opin Pharmacol* 9 (1):59-64. doi: 10.1016/j.coph.2008.12.003.

Kovalevich, J., G. Corley, W. Yen, S. M. Rawls, and D. Langford. 2012. "Cocaine-induced loss of white matter proteins in the adult mouse nucleus accumbens is attenuated by administration of a β-lactam antibiotic during cocaine withdrawal." *Am J Pathol* 181 (6):1921-7. doi: 10.1016/j.ajpath.2012.08.013.

Larrey, D., T. Vial, A. Micaleff, G. Babany, M. Morichau-Beauchant, H. Michel, and J. P. Benhamou. 1992. "Hepatitis associated with amoxycillin-clavulanic acid combination report of 15 cases." *Gut* 33 (3):368-71.

Leeman, R. F., Q. Sun, D. Bogart, C. L. Beseler, and M. Sofuoglu. 2016. "Comparisons of Cocaine-Only, Opioid-Only, and Users of Both Substances in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)." *Subst Use Misuse* 51 (5):553-64. doi: 10.3109/10826084.2015.1122063.

Li, Z., A. Kadivar, J. Pluta, J. Dunlop, and Z. Wang. 2012. "Test-retest stability analysis of resting brain activity revealed by blood oxygen level-dependent functional MRI." *J Magn Reson Imaging* 36 (2):344-54. doi: 10.1002/jmri.23670.

Li, Z., Y. Zhu, A. R. Childress, J. A. Detre, and Z. Wang. 2012. "Relations between BOLD fMRI-derived resting brain activity and cerebral blood flow." *PLoS One* 7 (9):e44556. doi: 10.1371/journal.pone.0044556.

Maldjian, Joseph A, Paul J Laurienti, Robert A Kraft, and Jonathan H Burdette. 2003. "An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets." *Neuroimage* 19 (3):1233-1239.

Miller, B. R., J. L. Dorner, M. Shou, Y. Sari, S. J. Barton, D. R. Sengelaub, R. T. Kennedy, and G. V. Rebec. 2008. "Up-regulation of GLT1 expression increases glutamate uptake and attenuates the Huntington's disease phenotype in the R6/2 mouse." *Neuroscience* 153 (1):329-37. doi: 10.1016/j.neuroscience.2008.02.004.

Nakagawa, H., M. Yamada, K. Tokiyoshi, Y. Miyawaki, and T. Kanayama. 1994. "Penetration of potassium clavulanate/ticarcillin sodium into cerebrospinal fluid in neurosurgical patients." *Jpn J Antibiot* 47:93-101.

Payen, M. C., S. De Wit, C. Martin, R. Sergysels, I. Muylle, Y. Van Laethem, and N. Clumeck. 2012. "Clinical use of the meropenem-clavulanate combination for extensively drug-resistant tuberculosis." *Int J Tuberc Lung Dis* 16 (4):558-60. doi: 10.5588/ijtld.11.0414.

Posner, K., D. Brent, C. Lucas, M. Gould, B. Stanley, G. Brown, and J. Mann. 2008. Columbia-suicide severity rating scale (C-SSRS). . *New York, NY:* : *Columbia University Medical Center* . .

Posner, K., G. K. Brown, B. Stanley, D. A. Brent, K. V. Yershova, M. A. Oquendo, G. W. Currier, G. A. Melvin, L. Greenhill, S. Shen, and J. J. Mann. 2011. "The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults." *Am J Psychiatry* 168 (12):1266-77. doi: 10.1176/appi.ajp.2011.10111704.

Rasmussen, B. A., D. A. Baron, J. K. Kim, E. M. Unterwald, and S. M. Rawls. 2011. "beta-Lactam antibiotic produces a sustained reduction in extracellular glutamate in the nucleus accumbens of rats." *Amino acids* 40 (2):761-764.

Rasmussen, B., E. M. Unterwald, and S. M. Rawls. 2011. "Glutamate transporter subtype 1 (GLT-1) activator ceftriaxone attenuates amphetamine-induced hyperactivity and behavioral sensitization in rats." *Drug Alcohol Depend* 118 (2-3):484-8. doi: 10.1016/j.drugalcdep.2011.03.022.

Rawls, S. M., D. A. Baron, and J. Kim. 2010. "beta-Lactam antibiotic inhibits development of morphine physical dependence in rats." *Behav Pharmacol* 21 (2):161-4. doi: 10.1097/FBP.0b013e328337be10.

Rawls, S. M., F. Karaca, I. Madhani, V. Bhojani, R. L. Martinez, M. Abou-Gharbia, and R. B. Raffa. 2010. "β-lactamase inhibitors display anti-seizure properties in an invertebrate assay." *Neuroscience* 169 (4):1800-4. doi: 10.1016/j.neuroscience.2010.06.041.

Rothstein, J. D., S. Patel, M. R. Regan, C. Haenggeli, Y. H. Huang, D. E. Bergles, L. Jin, M. Dykes Hoberg, S. Vidensky, D. S. Chung, S. V. Toan, L. I. Bruijn, Z. Z. Su, P. Gupta, and P. B. Fisher. 2005. "Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression." *Nature* 433 (7021):73-7. doi: 10.1038/nature03180.

Sánchez Navarro, A. 2005. "New formulations of amoxicillin/clavulanic acid: a pharmacokinetic and pharmacodynamic review." *Clin Pharmacokinet* 44 (11):1097-115.

Sari, Y., K. D. Smith, P. K. Ali, and G. V. Rebec. 2009. "Upregulation of GLT1 attenuates cue-induced reinstatement of cocaine-seeking behavior in rats." *J Neurosci* 29 (29):9239-43. doi: 10.1523/JNEUROSCI.1746-09.2009.

Saudagar, P. S., S. A. Survase, and R. S. Singhal. 2008. "Clavulanic acid: a review." *Biotechnol Adv* 26 (4):335-51. doi: 10.1016/j.biotechadv.2008.03.002.

Schmaal, L., D. J. Veltman, A. Nederveen, W. van den Brink, and A. E. Goudriaan. 2012. "N-acetylcysteine normalizes glutamate levels in cocaine-dependent patients: a randomized crossover magnetic resonance spectroscopy study." *Neuropsychopharmacology* 37 (9):2143-52. doi: 10.1038/npp.2012.66.

Schroeder, J. A., N. G. Tolman, F. F. McKenna, K. L. Watkins, S. M. Passeri, A. H. Hsu, B. R. Shinn, and S. M. Rawls. 2014. "Clavulanic acid reduces rewarding, hyperthermic and locomotor-sensitizing effects of morphine in rats: a new indication for an old drug?" *Drug Alcohol Depend* 142:41-5. doi: 10.1016/j.drugalcdep.2014.05.012.

Shen, H. W., M. D. Scofield, H. Boger, M. Hensley, and P. W. Kalivas. 2014. "Synaptic glutamate spillover due to impaired glutamate uptake mediates heroin relapse." *J Neurosci* 34 (16):5649-57. doi: 10.1523/JNEUROSCI.4564-13.2014.

Shiels, M. S., N. D. Freedman, D. Thomas, and A. Berrington de Gonzalez. 2018. "Trends in U.S. Drug Overdose Deaths in Non-Hispanic Black, Hispanic, and Non-Hispanic White Persons, 2000-2015." *Ann Intern Med* 168 (6):453-455. doi: 10.7326/M17-1812.

Sussner, B. D., D. A. Smelson, S. Rodrigues, A. Kline, M. Losonczy, and D. Ziedonis. 2006. "The validity and reliability of a brief measure of cocaine craving." *Drug Alcohol Depend* 83 (3):233-7. doi: 10.1016/j.drugalcdep.2005.11.022.

Uys, J. D., and R. T. LaLumiere. 2008. "Glutamate: the new frontier in pharmacotherapy for cocaine addiction." *CNS Neurol Disord Drug Targets* 7 (5):482-91.

Wang, W., P. D. Worhunsky, S. Zhang, T. M. Le, M. N. Potenza, and C. R. Li. 2018. "Response inhibition and fronto-striatal-thalamic circuit dysfunction in cocaine addiction." *Drug Alcohol Depend* 192:137-145. doi: 10.1016/j.drugalcdep.2018.07.037.

Wang, Z., J. Suh, D. Duan, S. Darnley, Y. Jing, J. Zhang, C. O'Brien, and A. R. Childress. 2017. "A hypo-status in drug-dependent brain revealed by multi-modal MRI." *Addict Biol* 22 (6):1622-1631. doi: 10.1111/adb.12459.

Wang, Z., J. Suh, Z. Li, Y. Li, T. Franklin, C. O'Brien, and A. R. Childress. 2015. "A hyper-connected but less efficient small-world network in the substance-dependent brain." *Drug Alcohol Depend* 152:102-8. doi: 10.1016/j.drugalcdep.2015.04.015.

Ward, S. J., B. A. Rasmussen, G. Corley, C. Henry, J. K. Kim, E. A. Walker, and S. M. Rawls. 2011. "Beta-lactam antibiotic decreases acquisition of and motivation to respond for cocaine, but not sweet food, in C57Bl/6 mice." *Behav Pharmacol* 22 (4):370-3. doi: 10.1097/FBP.0b013e3283473c10.

Woodnutt, G., I. Kernutt, and L. Mizen. 1987. "Pharmacokinetics and distribution of ticarcillin-clavulanic acid (Timentin) in experimental animals." *Antimicrob Agents Chemother* 31 (11):1826-30.

Young, K. A., T. R. Franklin, D. C. Roberts, K. Jagannathan, J. J. Suh, R. R. Wetherill, Z. Wang, K. M. Kampman, C. P. O'Brien, and A. R. Childress. 2014. "Nipping cue reactivity in the bud: baclofen prevents limbic activation elicited by subliminal drug cues." *J Neurosci* 34 (14):5038-43. doi: 10.1523/JNEUROSCI.4977-13.2014.

Zobell, J. T., K. Ampofo, J. Cash, K. Korgenski, and B. A. Chatfield. 2010. "High dose intermittent ticarcillin-clavulanate administration in pediatric cystic fibrosis patients." *J Cyst Fibros* 9 (4):280-3. doi: 10.1016/j.jcf.2010.04.003.