PHASE 1, DOUBLE-BLIND, PLACEBO-CONTROLLED ASSESSMENT OF POTENTIAL INTERACTIONS BETWEEN INTRAVENOUS COCAINE AND CLAVULANIC ACID NCT02563769

U54 Principal Investigator: Kyle M. Kampman, M.D.

Principal Investigator: Mary F. Morrison, M.D., M.S.
Project 1 Professor of Psychiatry
Lewis Katz School of Medicine
Temple University
1316 West Ontario Street, Room 800
Philadelphia, PA 19140
T: 215-707-8688
C: 610-247-2126

Co-Investigator: M. Ingre Walters, M.D.

Co-Investigator and Medical Monitor: Kyle M. Kampman, M.D.

Statistician: Kevin Lynch, Ph.D.

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NIDA Investigators: [*name*]
NIDA Study Manager: [*name*]
National Institute on Drug Abuse
National Institutes of Health
6001 Executive Boulevard
Bethesda, MD 20892
301/443-3318

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Center for Cocaine Medication Development
University of Pennsylvania

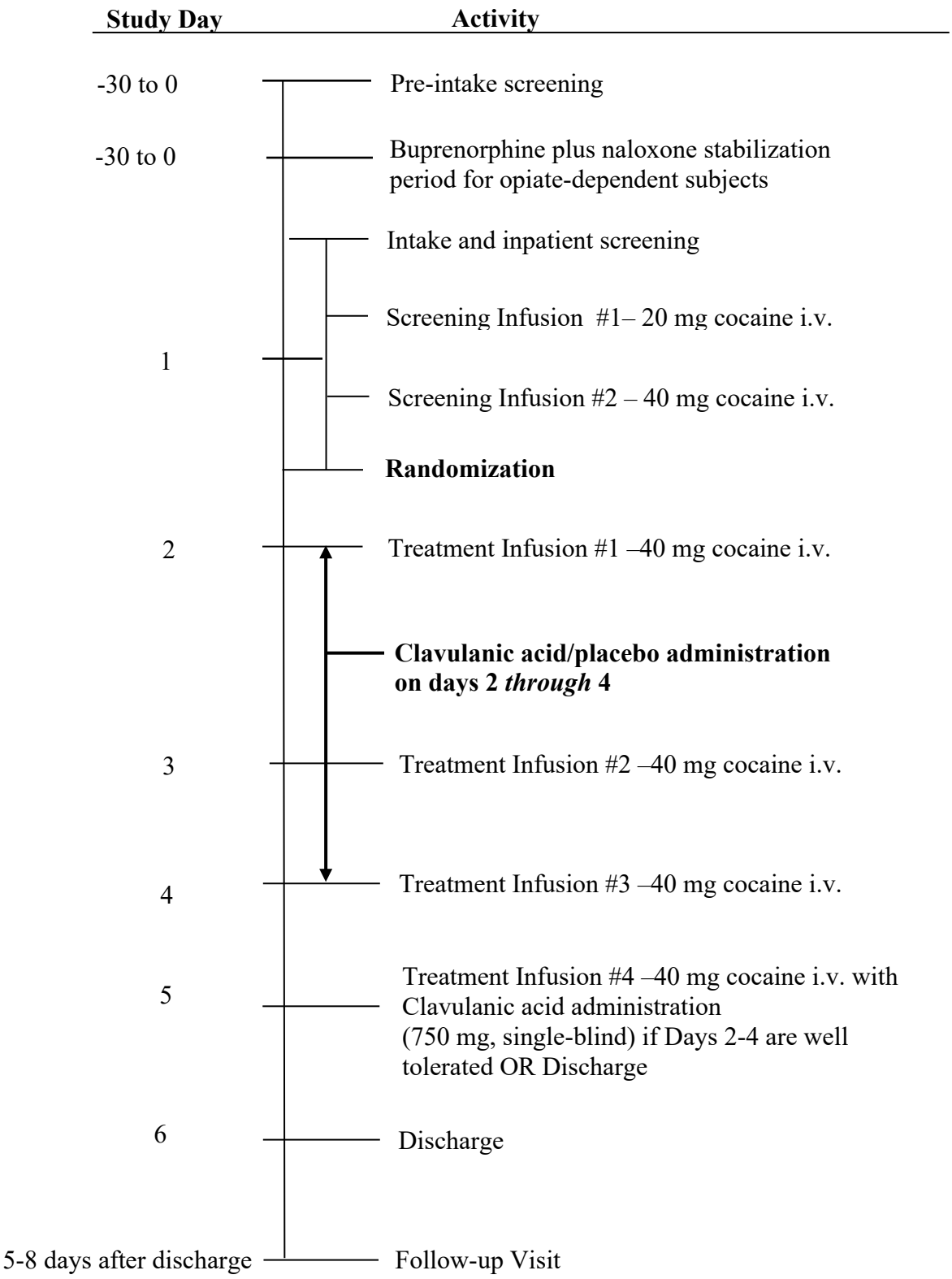
Data Coordinating Center: University of Pennsylvania
Perelman School of Medicine Department of Psychiatry

2 SYNOPSIS OF STUDY

Title	**Phase 1, Double-Blind, Placebo-Controlled Assessment of Potential Interactions Between Intravenous Cocaine and Clavulanic Acid**
Short Title	CLAV and Cocaine Interaction Safety Study
Phase	Phase Ib
Methodology	This is a prospective, placebo controlled inpatient crossover safety study of 3 doses (250 mg/day, 500 mg/day, 750 mg/day) of CLAV with an intravenous infusion of cocaine 40 mg. Subjects will be non-treatment seeking experienced cocaine dependent adults, ages 18-65 (N=12 completers, 21 estimated to enroll). Subjects will undergo a washout of the study drug for 5 half-lives between study drug administration sessions.
Study Duration	Approximately 1.5 years.
Study Center	Temple Episcopal Hospital. Centennial 6th floor, an inpatient medical unit with telemetry.
Primary Objective	To determine whether there are clinically significant adverse interactions between CLAV (250 mg/day; 500 mg/day; 750 mg/day) and intravenously administered cocaine in healthy, non-treatment seeking adults with cocaine use disorder.
Secondary Objectives	1. To evaluate whether administration of CLAV alters the pharmacokinetics (PK) of cocaine or its major metabolite, benzoylecgonine (BE). 2. To determine PK of CLAV during treatment at 250 mg/day (low dose) and 500 mg/day (medium dose). 3. To evaluate whether there are significant interactions between CLAV treatment concurrent with i.v. cocaine infusions of 40 mg by measuring the diameter of the pupil using a pupillometer.
Exploratory Objectives	3. To evaluate whether CLAV treatment alters the subjective effects of cocaine, the perceived value of the dose of cocaine, and craving. 4. To assess the effects of clavulanic acid on mood and personality and on the abuse

	liability.
Outcome Measures	Primary outcome measure is safety which will be measured by AEs, BP, HR, and ECG QTc interval. Secondary outcome measures include PK parameters of cocaine, PK parameters of CLAV, pupillometry. Exploratory outcome measures are subjective effects measurements assessed for cocaine in combination with CLAV and CLAV alone. Effect on mood (POMS), abuse liability (ARCI), and subjective effects measurements (VAQ, VAS) will be obtained. The effect of CLAV on cocaine craving will be assessed using the CCQ-Brief. The DVQ will be used to determine the perceived value of each dose of cocaine.
Number of Participants	12 completers, 21 estimated to enroll.
Diagnosis and Main Inclusion Criteria	Non-treatment seeking adults with cocaine use disorder, moderate to severe, ages 18-65.
Study Product, Dose, Route, Regimen	Clavulanic acid 250 mg/day (always given before 500 mg dose); 500 mg/day or placebo. Study drug doses administered on Days 2, 3, and 4 in a double-blind fashion. Clavulanic acid 750 mg/day dose will always be given on Study Day 5 in a single-blind fashion if both the low and medium doses are well tolerated.
Duration of Administration	6 day inpatient study, acute oral dosing of CLAV 250 mg/day, 500 mg/day, 750 mg/day and matching placebo
Reference Therapy	Placebo
Statistical Methodology	Data are gathered from a 3 period, 3 treatment crossover design (except 750 mg dose). Our primary analyses compare the rates of occurrences of adverse events across the first three periods (250 mg, 500 mg, placebo) within each person using standard mixed effects ANOVA models for binary responses.

3 MODEL STUDY SCHEMA



4 ABSTRACT

STUDY OBJECTIVES: This is a human laboratory clinical pharmacology study to assess potential interactions between intravenous cocaine and treatment with clavulanic acid (CLAV).

Primary: The primary objective of this study is to determine if there are significant interactions between CLAV treatment concurrent with i.v. cocaine infusions of 40 mg by measuring the frequency of adverse events and cardiovascular responses [heart rate (HR), blood pressure (BP), and electrocardiogram (ECG)] in adult subjects with cocaine use disorder.

Secondary:

1. To evaluate whether the acute administration of CLAV alters the pharmacokinetics (PK) of cocaine or its major metabolite, benzoylecgonine (BE) in adult subjects with cocaine use disorder.
2. To determine PK of CLAV in adult subjects with cocaine use disorder during treatment at 250 mg/day (low dose) and 500 mg/day (medium dose).
3. To evaluate whether there are significant pharmacodynamic (PD) interactions between CLAV treatment (250 mg, 500 mg) concurrent with i.v. cocaine infusions of 40 mg by measuring the diameter of the pupil using a pupillometer.

Exploratory:

1. To evaluate whether CLAV treatment alters the subjective effects of cocaine measured by Visual Analog Questionnaire (VAQ) and the Visual Analog Scales (VAS), the perceived value of the dose of cocaine measured by the Drug Value Questionnaire (DVQ), and craving measured by Cocaine Craving Questionnaire-Brief (CCQ-Brief).
2. To assess the effects of clavulanic acid on mood and personality using the Profile of Mood States (POMS) and on the abuse liability using the Addiction Research Center Inventory (ARCI).
3. To evaluate the safety of CLAV treatment concurrent with iv cocaine infusions with subjects with combined cocaine and opiate use disorder whose opiate use disorder symptoms are stabilized on buprenorphine plus naloxone.
4. To evaluate the safety and whether there are significant PD interactions between CLAV treatment 750 mg concurrent with i.v. cocaine infusions of 40 mg.

STUDY ENDPOINTS:

Primary endpoint: Safety and toleration as assessed by the **rates of occurrence of adverse events across the three study periods within each subject.** In addition, the following cardiovascular measures will be assessed during the three study periods: supine vital signs measurements (BP, HR) and ECG standard 12-lead monitoring (QTc prolongation).

Secondary endpoints:

1. **PK of cocaine alone will be compared statistically with PK when both Cocaine and CLAV (250 mg, 500 mg) are present**. Both the PK of cocaine and its major metabolite,

BE, will be evaluated with both doses of CLAV. PK will be sampled close to T_{max} and drug levels during combination therapy will be compared with drug levels during treatment with each drug alone.

2. ***PK of CLAV*** alone will be compared statistically at both doses of CLAV (250 mg, 500 mg) PK will be sampled close to T_{max}. If possible, important gender differences in CLAV PK will be explored.
3. ***PD. Pupil diameter*** (over time) after Cocaine infusion alone (with PBO) will be compared with pupil diameter (over time) after Cocaine infusion with CLAV at both doses (250 mg, 500 mg).

Exploratory:

1. ***Subjective effects of cocaine alone (PBO) will be compared with subjective effects of cocaine and CLAV (250 mg, 500 mg, 750 mg)*** using both the Visual Analog Questionnaire (VAQ) and the Visual Analog Scales (VAS) for each condition (COC+PBO vs. COC+CLAV). *The perceived value* of cocaine alone (PBO) will be compared with the perceived value of cocaine in combination with CLAV (250 mg, 500 mg, 750 mg) using the Drug Value Questionnaire (DVQ) for each condition (COC+PBO vs. COC+CLAV). *Cocaine craving* associated with cocaine alone (PBO) will be compared with the craving associated with cocaine and CLAV (250 mg, 500 mg, 750 mg) using measured by Cocaine Craving Questionnaire-Brief (CCQ-Brief).

2. ***The subjective effects of clavulanic acid without cocaine*** (250 mg, 500 mg, and 750 mg) on mood and personality will be assessed using the Profile of Mood States (POMS) score for each dose of CLAV compared with the score on PBO. The effects of CLAV on the abuse liability using the Addiction Research Center Inventory (ARCI) will be compared at each dose of CLAV (250 mg, 500 mg, and 750 mg) compared with PBO score.

3. ***Safety of clavulanic acid and buprenorphine in combination with cocaine.*** Safety and toleration as assessed by the rates of occurrence of adverse events across the three study periods within each subject with comorbid cocaine and opiate use disorder. In addition, the following cardiovascular measures will be assessed during the three study periods: supine vital signs measurements (BP, HR) and ECG standard 12-lead monitoring (QTc prolongation).

4. ***Safety of 750 mg clavulanic acid dose.*** Safety and toleration as assessed by the occurrence of adverse events compared with adverse events on placebo. In addition, the following cardiovascular measures will be assessed and compared with placebo: supine vital signs measurements (BP, HR) and ECG standard 12-lead monitoring (QTc prolongation).

STUDY DESIGN: This is a randomized, double-blind, placebo-controlled inpatient cross-over study of CLAV for Cocaine Use Disorder (CUD). The crossover study will involve acute oral administration of two (2) doses of CLAV (250 mg/day; 500 mg/day); (low and medium) and matched oral placebo in 12 (12 completers, 21 enrolled) healthy non-treatment seeking CUD adult subjects for each drug. The study is performed in an inpatient medical unit (Centennial 6)

at Temple-Episcopal Hospital (T-EH) to determine the safety of the CLAV in combination with cocaine (COC).

STUDY DURATION: Study duration will include up to six (6) days on an inpatient unit in addition to the pre-intake screening and follow up visit. The pre-intake screening will last up to 30 days. The inpatient period will include:

- One (1) outpatient day of intake and admission screening (Day # -30 – 0)
- One (1) inpatient day of screening cocaine infusions (Day #1)
- Four (4) days of inpatient treatment with CLAV or placebo with i.v. cocaine infusions of 40 mg (Days #2 through #5)

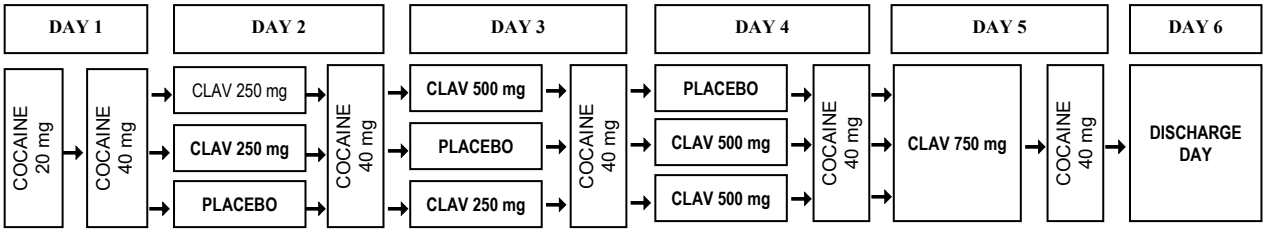
Clinic discharge is on Day #6 unless subject safety precludes them from completing Study Day #5. Liver function test results, hematology studies, CPK results, vital signs, and occurrence/severity of adverse events (AEs) will be reviewed after Study Day #4 to determine eligibility for Study Day #5 at 750 mg.

Subjects will be requested to return for follow-up at 5-8 days after the day of discharge. If subjects have a positive urine for cocaine on inpatient admission, they have the option of being admitted for observation for 24 hours and commencing Study Day #1 on the next day. Subjects with severe cocaine use disorders have difficulty not using cocaine in their community to obtain a negative urine for cocaine. Subjects with combined cocaine and opiate use disorder must have a positive urine test for buprenorphine on admission and a negative test for other opiates to be eligible for Day #1 screening that day. Subjects with a positive test for buprenorphine as well as other opiates will be evaluated on a case by case basis for commencing Study Day #1 after being observed for 24 hours in the hospital.

SAMPLE SIZE: Twenty-one (21) subjects are estimated to enroll, with 12 expected to complete the study. Study subjects who complete the inpatient phase of the study will be considered completed subjects. Subjects will continue to be screened until the total number (n=12) have completed the study.

POPULATION: Volunteer experienced cocaine users, 18-to-65 years of age, who have used cocaine by the smoked or i.v. route at least twice a week for at least four (4) of the past six (6) weeks and provided a positive urine test for cocaine within two weeks of entering the study.

Figure 1. Schedule for Inpatient CLAV Study



TREATMENTS: The initial crossover study will involve acute oral administration of 2 doses of CLAV (250 mg/day; 500 mg/day); (low and medium) and matched oral placebo. Subject will potentially have four (4) cocaine infusions after randomization, one with CLAV 250 mg, one with CLAV 500 mg (always given after 250 mg dose) and one with placebo (See Figure 1). If subjects tolerate the low and medium dose of cocaine with mild adverse effects, have stable vital signs and bloodwork results that indicate it is safe for them to proceed, they are given 750 mg/day dose on study day #5 on a single blind basis. Subjects will be randomized after the screening cocaine infusion of 40 mg i.v. (Day #1) to one of the following arms:

Treatment Arm 1: Day #2: CLAV 250 mg (low dose); Day #3: CLAV 500 mg; Day #4: Placebo; Day #5: CLAV 750 mg.

Treatment Arm 2: Day #2: CLAV 250 mg (low dose); Day #3: Placebo; Day #4: CLAV 500 mg; Day #5: CLAV 750 mg.

Treatment Arm 3: Day #2: Placebo; Day #3: CLAV 250 mg (low dose); Day #4: CLAV 500 mg; Day #5: CLAV 750 mg.

Table 1. Cocaine Infusion Session Schedule

Study Phase	Infusion Number	Study Day	Infusion
Screening Stage II	Safety Infusion #1	1	Single-blind infusion of COC 20 mg IV
Screening Stage II	Safety Infusion #2	1	Single-blind infusion of COC 40 mg IV at least 2 hours 45 minutes after initial infusion
Treatment	Treatment Infusion #1	2	Single-blind infusion of COC 40 mg IV 60 minutes post CLAV/placebo administration
Treatment	Treatment Infusion #2	3	Single-blind infusion of COC 40 mg IV 60 minutes post CLAV/placebo administration
Treatment	Treatment Infusion #3	4	Single-blind infusion of COC 40 mg IV 60 minutes post CLAV/placebo administration
Treatment	Treatment Infusion #4	5	Single-blind infusion of COC 40 mg IV 60 minutes post single-blind CLAV 750 mg administration

STATISTICAL ANALYSIS PLAN

5.1 Outcome Measures

5.1.1 Primary Outcome Measures

The primary outcome measures are adverse events and cardiovascular responses (HR, BP, ECG (QTc prolongation). Safety and toleration as assessed by the **rates of occurrence of adverse events across the three study periods (250 mg, 500 mg, PBO) within each subject.**

5.1.2 Secondary Outcome Measures

Secondary outcome measures are intended to determine if there are any changes in cocaine pharmacokinetics in the presence of clavulanic acid (250 mg, 500 mg) after acute dosing of

CLAV. The pharmacokinetics of clavulanic acid at 2 doses (250 mg, 500 mg) will be determined in non-treatment seeking adults with cocaine use disorder. The pharmacodynamic effects of clavulanic acid in combination with cocaine will be determined by measuring the diameter of the subject's pupil after the cocaine infusion.

5.1.3 Exploratory Outcome Measures

Exploratory outcome measures are intended to evaluate whether if there are any changes in the subjective effects of cocaine in the presence of clavulanic acid (250 mg, 500 mg, 750 mg) after acute dosing of CLAV. The subjective effects of clavulanic acid without cocaine in non-treatment seeking adults with cocaine use disorder will be assessed at all doses (250 mg, 500 mg, 750 mg).

5.2 Data Analysis Plan

5.2.1 Primary Outcome Measures

The primary objective of this study is to assess the safety and tolerability of CLAV in combination with cocaine to generate data regarding the safety of the combination of CLAV and cocaine in relevant doses of both drugs. This is required prior to an outpatient efficacy study of CLAV for cocaine use disorders. Secondary objectives are to assess whether cocaine alters serum levels of CLAV and to assess serum levels of CLAV at both doses of CLAV in study subjects. Exploratory objectives are to assess the subjective ratings of drug effects with regard to craving and mood. Summary statistics will be provided for all safety, tolerability and subjective data. In addition to the analyses specified below, listings of all data for each patient will be provided.

5.2.1.1 Demographic and Baseline Comparability Analyses

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

5.2.1.2 Primary, Secondary, and Exploratory Analyses

5.2.1.2.1 Primary Analyses: Safety is a primary assessment variable. The number of patients reporting each AE by treatment group and severity will be presented. Adverse events will be tabulated by body system and organ class. 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 at all doses (250 mg, 500 mg, 750 mg) and placebo and presented as summary statistics by organ system. Our primary analyses will compare the rates of occurrence of adverse events across the three-periods within each person. The data are gathered using a 3-period 3-treatment crossover design. Safety concerns constrain us to restrict the order of administration of the 2 study drug doses of CLAV, so each subject receives the doses in increasing order. Thus, we have three sequences: {PBO, Low (250 mg), Medium (500 mg)}, {Low, PBO, Medium}, and {Low, Medium, PBO}. One third of the subjects are randomized to each of these sequences. Each period is a 1 day session and the periods correspond to days 2, 3, and 4, providing 24 half-lives between administrations. The main explanatory variables in the models are: 1) a 3 level within-

subject factor representing drug condition (PBO, study drug low dose (SDlow), study drug medium dose (SDmedium), and 2) a three level factor representing period (1, 2, and 3). We use standard mixed effects (repeated measures) ANOVA models for binary responses in three-period three-treatment crossover designs to test our hypotheses.[73] An overall F-test of the condition effect will test for differences in response across the three drug doses, and contrasts will determine the pattern of differences (if any). Mixed effects models can allow for different error variances for different sessions, and other complex error structures as needed. As this study has only three repeated measures, a relatively simple covariance structure model (e.g. heterogeneous compound symmetry model) should be sufficient to account for within-subject correlations.

Pharmacodynamic parameters (systolic and diastolic blood pressure, heart rate and QT_C interval, expressed as AUC, 2-minute values and maximal values) will be similarly analyzed. The COC infusions occur on the day of each session, providing three repeated sets of measures of each COC related response (change in HR, change in SBP, change in DBP, change in QT_c interval,).

HR and BP (systolic BP (SBP) and diastolic BP (DBP)) and QT_C induced by cocaine infusion will be compared to HR and BP and QT_C measurements before the cocaine infusion to assess change. BP and HR and QT_C changes after infusion given after CLAV (250 mg, 500 mg, 750 mg) will be compared to those without CLAV. We will compare the distribution of Area Under Curve (AUC) summaries of the within-period repeated measures of changes in vital signs (heart rate, systolic blood pressure, diastolic blood pressure) across the three-periods within each person as described above.

QT_C interval measured by the ECG induced by cocaine infusion will be compared to *QT_C interval* before the cocaine infusion to assess change. *QT_C interval* changes after infusion given after CLAV (250 mg, 500 mg, 750 mg) will be compared to those without CLAV. We will compare the distribution of Area Under Curve (AUC) summaries of the within-period repeated measures of changes in QTc interval across the three-periods within each person as described above.

5.2.1.2.2 Secondary Analyses: The pharmacokinetic parameters will be statistically analyzed using a repeated measure analysis of variance model.

5.2.1.2.3 Exploratory Analyses: Subjective effects of cocaine, as measured by check lists, visual analog and rating scales, will be listed for each patient and summarized for each group. Adverse events for the CLAV 750 mg group will be analyzed as described above for the lower CLAV doses. Adverse events for the subset of subjects stabilized on Buprenorphine will be analyzed as described above.

5.2.2 Secondary Outcome Measures

Secondary outcome measures are intended to determine if there are any changes in cocaine pharmacokinetics and pharmacodynamics in the presence of clavulanic acid (250 mg, 500 mg). The pharmacokinetics of clavulanic acid will be determined in non-treatment seeking adults with cocaine use disorder. The COC infusions occur on the day of each session, providing four repeated sets of measures of each COC related response (PK, PD as determined by change in

pupil diameter from baseline). PK curves for single dose CLAV at 250 mg and 500 mg will be constructed for all subjects and then for men and women, separately.

5.2.3 Exploratory Outcome Measures

Data regarding CLAV's effect on subjective effects and motivation for COC will be considered exploratory regarding efficacy, as subjects receive acute treatment.