CLINICAL PROTOCOL

STUDY NIDA-CTO-0012

PHASE *2*, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF TIAGABINE FOR THE TREATMENT OF COCAINE DEPENDENCE

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Additional study sites may be added if needed to facilitate enrollment

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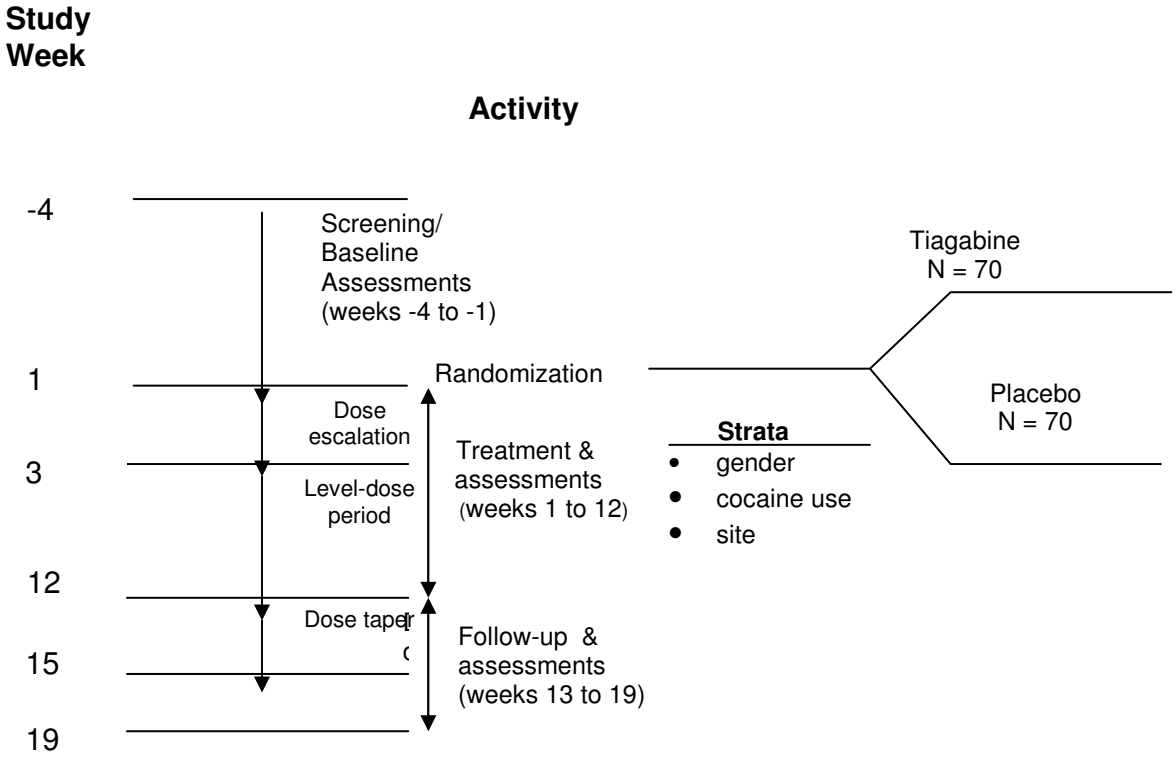
1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ASI-Lite	Addiction Severity Index-Lite
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminse
BE	benzoylecgonine
BP	blood pressure

BSCS	Brief Substance Craving Scale
BUN	blood urea nitrogen
CA	classification accuracy
CAP	College of American Pathologists
CBT	cognitive behavioral therapy
CCQ-NOW	Cocaine Craving Questionnaire-Now
CGI-O	Clinical Global Impression Scale – Observer
CGI-S	Clinical Global Impression Scale – Self
CLIA	Clinical Laboratory Improvement Amendment of 1988
CNS	Central Nervous System
CPDD	College on Problems of Drug Dependence
CRF	Case Report Form
CSEQ	Cocaine Subjective Effects Questionnaire
CSSA	Cocaine Selective Severity Assessment
CYP3A	cytochrome P450, isoform 3A
DA	dopamine
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DTR&D	Division of Treatment Research and Development
ECG	electrocardiogram
GABA	gamma aminobutyric acid
GGT	gamma glutamyltranspeptidase
HAM-D	Hamilton Depression Rating Scale
HR	heart rate
HIV	human immunodeficiency virus
HRBS	HIV Risk-Taking Behavior Scale
IRB	Institutional Review Board
LAAM	levo-alpha-acetylmethadol
LFT	liver function tests
mL	milliliter
NIDA	National Institute on Drug Abuse
PCP	phencyclidine
PI	principal investigator
PPD	purified protein derivative (tuberculin test)
RPR	rapid plasma reagin (test for syphilis)
SAE	serious adverse event
SCID	structured clinical interview for DSM-IV
SFQ	State of Feelings Questionnaire
SUI	substance use inventory
ULN	upper limit of normal

2 STUDY SCHEMA



Treatment period consists of:
- dose escalation (weeks 1 to 3) with tiagabine dose escalating from 4 mg to 20 mg daily or matched placebo
- level-dose period (weeks 4 to 12) with 20 mg tiagabine daily or matched placebo

Follow-up period consists of:
- dose taper (weeks 13 to 15) with tiagabine dose tapering off or matched placebo
- Final follow-up at week 19

3 ABSTRACT

STUDY OBJECTIVES. To assess the efficacy and safety of tiagabine in reducing cocaine use in subjects with cocaine dependence. It is hypothesized that tiagabine treatment, compared to placebo, will be associated with fewer days of cocaine use as assessed by self-report confirmed with urine assays for benzoylecgonine (BE).

STUDY DESIGN. This is a double-blind, placebo-controlled, parallel-group design study in which, after screening and a 2-week baseline assessment period, subjects will be equally randomly assigned to one of two treatment groups, tiagabine or matched placebo. All patients will receive manual-guided cognitive behavioral therapy (CBT). Medication dosing will occur over 15 weeks with the first three weeks being dose escalation and the last three weeks being dose taper. Follow-up will consist of assessments once each week during weeks 13, 14, 15, and 19. Randomization strata include study site, gender and frequency of cocaine use in the 30 days prior to screening.

STUDY POPULATION. One hundred forty (140) subjects with Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for cocaine dependence determined by structured clinical interview (SCID) will be randomized into one of two treatment groups (70 per group). Males and females, at least 18 years-of-age, with at least 1 urine BE positive specimen provided during the 2-week baseline period prior to randomization, and with the ability to understand and provide written informed consent, will be included.

TREATMENTS. Dosage of tiagabine starts at 4 mg each morning and is increased gradually (see Table 8 in section 11.2) until the maximum dose of 20 mg per day (in two divided doses) is reached at the end of study week 3. This dosage regimen will continue until the end of week 12, at which point there will be a three-week taper (see Table 8 in section 11.2). All subjects will take study agents (tiagabine or matched placebo) daily and receive once weekly manual-guided CBT during the 12-week treatment period. Subjects will be asked to return to the clinic for four (4) follow-up assessments (during the weeks 13, 14, 15 and 19) and will receive once weekly manual-guided CBT on week 13 and week 15.

SAFETY ASSESSMENTS. A physical examination will be conducted during screening and during week 12. A 12-lead electrocardiogram (ECG), clinical laboratory studies (blood chemistry, hematology, urinalysis, and pregnancy test, if female) will be completed during screening and during weeks 4, 8 & 12. The HAM-D will be administered during baseline and during weeks 4, 8 and 12. Assessment of vital signs will be performed at each visit during baseline and during the first three weeks of treatment; vital signs will be checked weekly during the remainder of the treatment period. Concomitant medication use will be assessed weekly during baseline and treatment, and at each follow-up visit. Adverse events (AEs) will be assessed at each study visit and recorded weekly. At treatment week 12 or at the time of study discontinuation, subjects will be evaluated by AE assessment, vital signs, physical examination, ECG, HAM-D and clinical laboratory studies (including pregnancy test if female).

EFFICACY ASSESSMENTS. Success in reduction of cocaine use will be determined by comparing cocaine non-use days (self-report confirmed or disproven by urine BE levels) expressed

as the weekly proportion of non-use days to the total number of non-missing study days that week. Secondary assessments include overall proportion of cocaine non-use days, proportion of successful subjects, the largest number of consecutive cocaine non-use days, weekly log of median quantitative urine BE levels and reduction in human immunodeficiency virus (HIV) risk-taking behavior hypothesized to be associated with drug use and assessed by HIV Risk-Taking Behavior Scale (HRBS). Severity of cocaine dependence will be assessed by Addiction Severity Index (ASI)-Lite, Brief Substance Craving Scale (BSCS), Cocaine Craving Questionnaire (CCQ-NOW), and Clinical Global Impression as assessed by the subject (CGI-S) and an observer (CGI-O). Substance Use Inventory (SUI) and urine for BE and creatinine measurements are collected at each visit starting at baseline. Urine toxicology screens are done weekly starting at baseline. ASI-Lite is assessed at screening while ASI-Lite Follow-up is assessed during weeks 4 and 8, and during week 12. The BSCS, CGI-S, and CGI-O, State of Feelings Questionnaire (SFQ) and a Cocaine Subjective Effects Questionnaire (CSEQ) are assessed weekly during baseline and during the treatment period. The CCQ-NOW questionnaire is assessed once at baseline and week 12. A Cocaine Selective Severity Assessment (CSSA) interview will be conducted three times during baseline and weekly during the treatment period. HRBS interview and HIV counseling will be performed at baseline, week 12 and week 19. The assessments performed if patient leaves study prior to week 12 are listed in section 13.3.

ANALYSIS. Each primary and secondary outcome variable will be analyzed using appropriate statistical methods for the intent-to-treat population and for the evaluable population. The intent-to-treat population is defined as the subjects who are randomized to treatment and who receive the first day's study agent. The evaluable study population is defined as the subjects who are randomized and properly qualify to participate in the study in accordance with the inclusion and exclusion criteria and who contribute at least six (6) usable urine samples and 28 days of self-report during the first four weeks of the treatment period, and who reach the full dose of study agent and do not have dose adjustments made during the first four weeks of the treatment period due to side effects. The individual effects, if any, of gender, site, and prior cocaine use on the primary treatment effects will be determined where numbers permit. It is hypothesized that tiagabine treatment, compared to placebo, will be associated with fewer days of cocaine use as assessed by self-report confirmed with urine assays for benzoylecgonine (BE). Therefore, statistical tests will be one-sided at a 5% Type I error rate. Confidence intervals will be one-sided with a 95% confidence coefficient.

Summaries of the characteristics of the subject population in both treatment arms at baseline will be prepared for both the intent-to-treat and evaluable subjects. A summary will be prepared to show dropouts/retention over time in each treatment group and for *a priori* defined subgroups. The number of missing observations will be compared between treatments and for *a priori* defined subgroups. Weekly treatment compliance will be summarized. All adverse events will be reported in tabular form indicating the frequency and severity of each type of event.

Some data are being collected for scientific use and population descriptive purposes such as the CSSA, SFQ, and CSEQ.

4 INTRODUCTION AND RATIONALE

Cocaine dependence is a significant public health problem associated with serious medical, psychiatric, social, and economic consequences. Although many compounds have been evaluated for the treatment of cocaine dependence, none have been approved by the Food and Drug Administration (FDA) for this indication. Psychosocial and behavioral therapy are currently the treatments of choice for cocaine dependence. Unlike methadone or naltrexone treatment for heroin addiction, disulfiram

for alcohol dependence, and bupropion (Zyban) for cigarette smoking, no pharmacological agent is currently approved for the treatment of cocaine dependence. NIDA's goal is to identify and/or develop pharmacological agents to treat cocaine dependence in conjunction with psychosocial interventions. Current strategies to treat cocaine dependence include: 1) blocking its effects, 2) restoration of central nervous system homeostasis, 3) reducing craving or enhancing the addict's ability to manage his/her response to craving, and 4) treating underlying conditions (or consequences of use) that may predispose targeted subpopulations toward dependence (Lavori *et al.,* 1999).

The drug to be studied in this clinical trial is tiagabine. Tiagabine (Gabitril®) was recently approved by the U. S. FDA as an adjunct therapy for the treatment of partial seizures in adults and children 12 years and older. It was discovered by the pharmaceuticals division of Novo Nordisk in Denmark in the late 1980s as part of a synthesis program to develop inhibitors of gamma-aminobutyric acid (GABA) reuptake based on the known GABA reuptake inhibitor nipecotic acid (Andersen *et al.,* 1993). As predicted, this drug is effective in reducing convulsions in animal models of epilepsy (Loscher, 1985) and in man (Adkins and Noble, 1998), and also has anxiolytic activity (Nielsen, 1998).

4.1 RATIONALE FOR USING TIAGABINE FOR TREATING COCAINE DEPENDENCE

Tiagabine increases GABA concentration in the synaptic cleft by blocking its reuptake by presynaptic terminals and glial cells. This action, which causes a potentiation of GABA-mediated inhibitory transmission, is thought to be the mechanism for tiagabine's anticonvulsant effect (Adkins and Noble,1998). This same mechanism may also indirectly lead to a decreased effectiveness of cocaine in augmenting dopamine concentrations in the nucleus accumbens. Such a cocaine-dependent increase in dopamine in the mesolimbic reward centers of the central nervous system (CNS) is thought to be responsible for its reinforcing properties. This phenomenon has been studied in rodents (Fontana *et al.,* 1993). It has been shown that GABAergic neurons in the ventral pallidum inhibit dopaminergic neurons in the nucleus accumbens and striatum. Potentiating the inhibitory action of these GABAergic neurons by tiagabine should lead to a decrease in dopaminergic transmission in the target dopaminergic neurons of the nucleus accumbens. Such a strategy has already been tested using a different GABAergic drug, gamma-vinyl-GABA (vigabatrin). This medication, which is not currently FDA approved, potentiates the inhibitory effects of GABA by irreversibly inhibiting GABA-transaminase, the principal catabolic enzyme of GABA. It has been shown that vigabatrin attenuates cocaine-induced increases in extracellular dopamine in the nucleus accumbens and striatum of cocaine-naïve and cocaine-dependent rats (Dewey *et al*.,1997; Morgan and Dewey, 1998). These same investigators have shown that vigabatrin decreases cocaine self-administration (Kushner *et al*.,1997a) and attenuates the cocaine-induced decrease in brain stimulation reward thresholds in rodents in a dose-dependent manner (Kushner *et al.,* 1997b). They also performed a PET scan study on non-human primates (baboons) using [^{11}C]-raclopride and showed that cocaine increased the dopamine concentration in the striatum and pre-treating the animals with vigabatrin blocked this increase (Dewey *et al*.,1998). It would be very interesting to test vigabatrin directly in clinical trials on cocaine-dependent individuals. However, this medication has significant side effects (principally, irreversible visual field defects) and is currently not available for study. It seems reasonable that tiagabine, which potentiates the inhibitory effect of GABA by a different mechanism, might also be effective in blocking the cocaine-induced increases in extracellular dopamine in the nucleus accumbens, leading to a decrease in cocaine self-administration.

4.2 PHARMACOKINETICS OF TIAGABINE

Tiagabine is well absorbed (> 95%) through the oral route (fasting) reaching peak concentrations within about 45 min (T_{max}) with absolute oral bioavailability of 90%. A high-fat meal decreases the rate (T_{max} = 2.5 hours) and reduces the C_{max} by about 40%, but not the extent (AUC) of tiagabine absorption. In clinical trials, tiagabine was given with meals. The elimination $t_{1/2}$ is 7 to 9 hours in normal volunteers; it is only 4-7 hours in patients receiving hepatic enzyme cytochrome P450 (CYP)-inducing drugs. In clinical trials, most patients were induced.

The pharmacokinetics of tiagabine are linear in the dose range 2 to 24 mg; following multiple dosing, steady state is achieved within two days (Adkins and Noble, 1998). Tiagabine is 96% bound to human plasma proteins over the concentration range from 10 ng/mL to 10,000 ng/mL. The relationship between tiagabine plasma concentration and clinical response is not currently understood; trough plasma concentrations of tiagabine observed in controlled clinical trials at doses from 30 to 56 mg/day ranged from < 1 ng/mL to 234 ng/mL.

Tiagabine is extensively metabolized in the liver by CYP3A, although contributions to the metabolism of tiagabine from CYP1A2, CYP2D6 or CYP2C19 have not been excluded. Less than 2% of an orally administered dose is excreted unchanged, with 25% and 63% of the remaining dose excreted into the urine and feces, respectively, primarily as metabolites. A diurnal effect on the pharmacokinetics of tiagabine was observed. Mean steady-state C_{min} values were 40% lower in the evening than in the morning. Steady-state AUC values were also found to be 15% lower following the evening dose compared to a morning dose.

The pharmacokinetic profile of tiagabine is similar in subjects with normal renal function compared to subjects with moderate or severe renal impairment. The pharmacokinetic profile is also similar in health young versus elderly adults. Although no specific pharmacokinetic studies have been performed that specifically address the issue of gender, race and cigarette smoking, retrospective analysis of pharmacokinetic data does suggests no clinically important differences in these populations.

Since the liver is the prime organ for the elimination of tiagabine, one must be cautious with patients with impaired liver function. In patients with moderate liver impairment the clearance of unbound tiagabine was reduced by about 60%. Thus, the dosage may need to be adjusted downward in patients with impaired liver function. In this study, liver function tests (LFTs) will be checked at weeks 4, 8 and 12, and tiagabine dosage will need to be adjusted in patients with LFTs increasing relative to baseline. The medication would then discontinue if either of these tests (ALT, AST) increased to twice of the upper limit of normal (ULN).

4.3 SAFETY OF TIAGABINE

A total of 2531 patients have been investigated in 5 blinded placebo-controlled clinical trials and 6 non-blind long term trials of tiagabine as adjunct therapy in patients with refractory epilepsy. A summary of the safety of tiagabine as documented in seizure disorder studies may be found in Section 10.6.

Tiagabine has been investigated in a pilot clinical study for the treatment of cocaine dependence. A Cocaine Rapid Efficacy Screening Trial (CREST) was conducted at one of NIDA's medications research units and completed in 2001. This 67-subject four-arm study compared the safety and

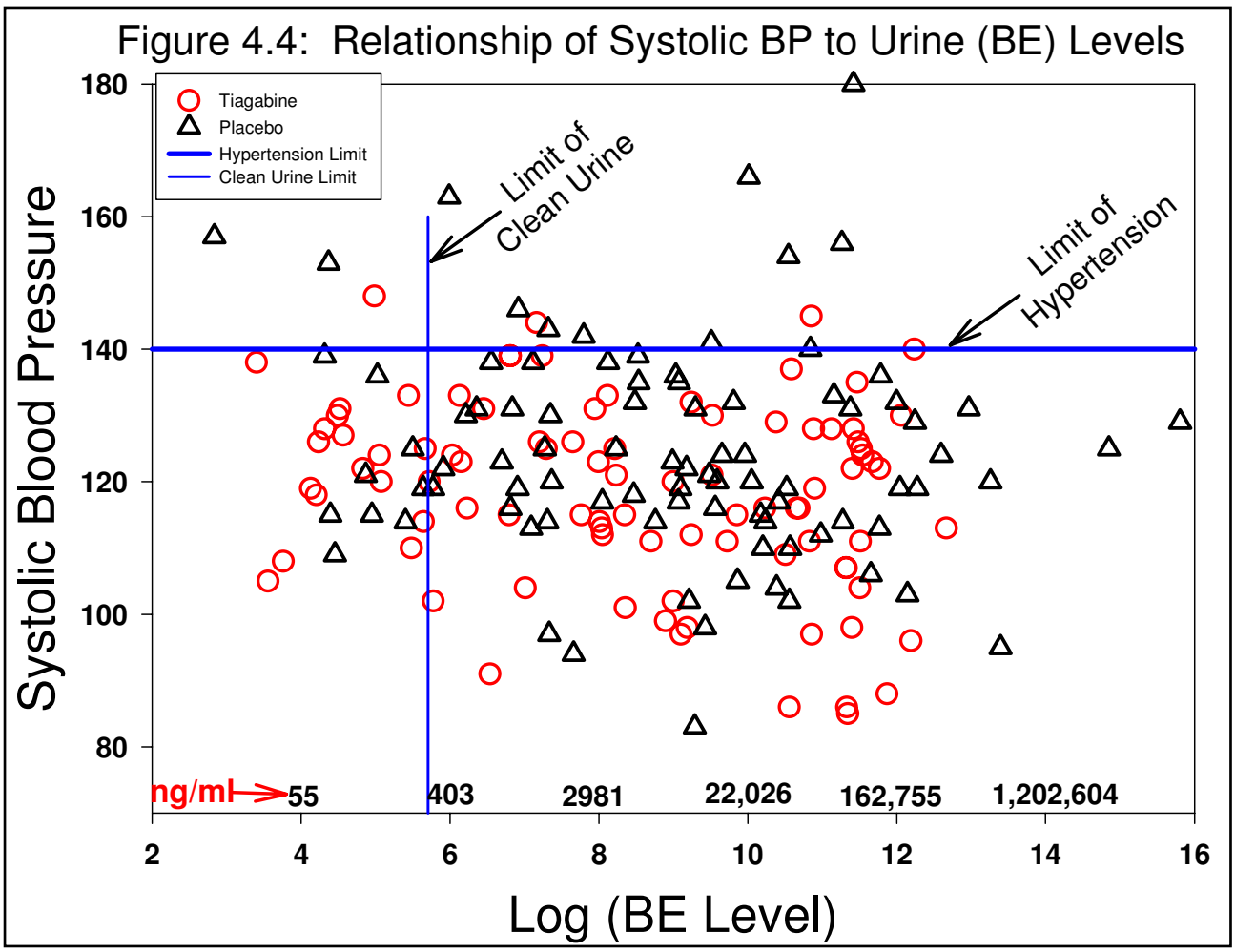
efficacy of tiagabine (at the same dosage regime to be used in the present protocol), together with two additional drugs, donepezil and sertraline, against a single unmatched placebo (17 subjects per group). Analysis of self-report of cocaine use and interviewer-administered instruments suggested that all four study groups decreased their cocaine use and craving. However, only the subjects in the tiagabine and sertraline groups showed a trend toward decreased cocaine use as assessed by urine BE levels at endpoint when compared to baseline ($p = 0.16$; BE levels were normalized by natural logarithm transformation). Although the tiagabine group decreased their urine BE levels compared to their baseline values, the tiagabine group's urine BE levels were not significantly different from the placebo group's BE levels at endpoint (analysis of variance $p = 0.16$). However, this study was not powered to detect statistically significant differences given the large variance in urine BE measurements and the small sample sizes (17 subjects per group). The results of this study were reported by (Somoza *et al.,* 2001).

4.4 SAFETY OF TIAGABINE IN THE PRESENCE OF COCAINE

As mentioned above, tiagabine has been studied by Somoza and colleagues in a small outpatient CREST clinical trial (Somoza *et al.,* 2001), in which 17 patients were randomized to tiagabine and 17 to placebo. This was an eight-week outpatient study during which the patients in both groups frequently used cocaine. During the medication period, urine BE levels were measured three times per week, and vital signs once per week. The relationship between each of the three cardiovascular measures (systolic blood pressure, diastolic blood pressure, and heart rate) and urine BE levels measured on the same visit was examined. Although vital signs were scheduled to be measured at baseline and once per week while patients were on the medication phase of the study (i.e., the enrollment phase), for various reasons vital signs were occasionally measured more than (or less) than once per week. The maximum number of times that vital signs were measured during the medication (enrollment) phase of the study was nine. Note that in the following analysis, we only included data for which both vital signs and urine BE levels were measured during the same visit.

The graph below shows the relationship between the systolic blood pressure and the logarithm of the urine BE level of all 34 patients who were on tiagabine (circles) or on placebo (triangles) during the visits when these two measurements were made simultaneously. Note that along the x-axis we have superimposed a second scale which gives the BE levels directly in ng/mL rather than in the form of the logarithm. The vertical line at the x=300 ng/mL is the limit used to distinguish clean from dirty urines, while the horizontal line at y=140 is the limit of systolic hypertension. Note that the urine BE concentration was found to be very high at a large number of patient visits.

A correlation analysis of these data indicates that for tiagabine the systolic blood pressure actually decreases with increasing BE levels (Table 1). The correlation coefficient is negative and statistically significant (r = -0.24, p=0.0221, N=91, see row ALL in Table 1), while in the case of



placebo there is a very small, non-significant decrease of systolic blood pressure with BE level (r = -0.123, p = 0.247, N=90, see row ALL in Table 1). Table 1 also includes a correlation analysis for each patient for whom four or more data points were available to see if there was a relationship between systolic blood pressure and urine BE levels for specific individuals who participated in this study. Note that in the case of three patients on tiagabine (DSTA, MWIL, and RMAT in Table 1), there were statistically significant correlations. In the case of DSTA, the systolic blood pressure decreased with increasing urine BE levels, but in the case of MWIL and RMAT the systolic blood pressure increased with increasing urine BE levels. However, in the latter two cases, the systolic blood pressure never exceeded 145 mm of Hg. The main point of Figure 4.4 is to show graphically that, based on the

results of this study, there is no evidence to suggest that patients on tiagabine developed higher systolic blood pressures than patients on placebo, even when both populations were exposed to moderate to high concentrations of cocaine.

Table 1. Effect of Tiagabine on Systolic Blood Pressure

TIAGABINE						PLACEBO				
NAME CODE	**N**	**MAX BP**	**r**	**p-value**		**NAME CODE**	**N**	**MAX BP**	**r**	**p-value**
ALL	91	148	-0.24	0.022		ALL	90	180	-0.123	0.247
ADAV	7	140	0.563	0.188		ACOO	6	120	0.042	0.94
DSTA	7	131	-0.755	0.05		DCLA	6	139	0.445	0.376
HALL	7	122	0.211	0.65		DHXX	5	120	-0.875	0.052
JSTA	8	122	0.226	0.59		DKIN	5	132	-0.642	0.243
LMCC	8	137	-0.206	0.625		GFLO	8	130	-0.357	0.386
MSMI	5	133	-0.431	0.468		HDAV	8	180	-0.689	0.059
MWIL	5	124	0.941	0.017		HMOS	8	125	-0.463	0.249
PTAY	9	148	-0.555	0.121		IYAR	5	140	0.735	0.157
PTIP	8	126	0.184	0.662		OMCG	8	131	-0.522	0.185
RMAT	7	145	0.905	0.005		SJON	8	163	-0.545	0.163
SGAR	5	138	-0.782	0.118		TPOW	8	146	-0.035	0.935
VSIM	6	116	-0.647	0.165						
WGRE	4	99	-0.532	0.468						

Table 2 shows the results of a similar analysis for diastolic blood pressure. Again, when the entire medication groups are considered, patients on tiagabine showed a statistically significant negative correlation between diastolic blood pressure and urine BE levels (r=-0.28, p=0.007), whereas in the case of the placebo group there was no statistically significant relationship between these two variables. Again, all individuals for which four or more simultaneous blood pressure and urine BE levels were available were analyzed separately to determine if there was a correlation between these variables. None were identified for the tiagabine group and two for the placebo group, DCLA and DHXX, both of which had maximum diastolic blood pressures within the normal range (85 and 81 mm of Hg for DCLA and DHXX, respectively) (Table 2).

This analysis and similar ones on the relationship between BE levels and heart rate (see Appendix V) suggest that, from a safety perspective, tiagabine showed no significant cardiovascular effects in patients that were actively smoking crack cocaine.

Table 2. Effect of Tiagabine on Diastolic Blood Pressure

TIAGABINE						PLACEBO				
NAME CODE	**N**	**MAX BP**	**r**	**p-value**		**NAME CODE**	**N**	**MAX BP**	**r**	**p-value**
ALL	91	105	-0.28	0.007		ALL	90	115	-0.025	0.816

ADAV	7	89	0.282	0.541		ACOO	6	81	0.302	0.561
DSTA	7	89	-0.72	0.07		DCLA	6	85	0.924	0.008
HALL	7	88	0.137	0.77		DHXX	5	81	-0.9	0.04
JSTA	8	79	-0.67	0.07		DKIN	5	93	-0.683	0.203
LMCC	8	94	-0.205	0.6265		GFLO	8	97	-0.17	0.687
MSMI	5	92	-0.655	0.23		HDAV	8	115	-0.592	0.122
MWIL	5	73	0.764	0.133		HMOS	8	79	0.105	0.804
PTAY	9	99	0.196	0.614		IYAR	5	89	0.33	0.588
PTIP	8	77	-0.205	0.63		OMCG	8	79	-0.384	0.347
RMAT	7	89	-0.373	0.409		SJON	8	114	0.204	0.628
SGAR	5	105	0.756	0.139		TPOW	8	97	-0.03	0.942
VSIM	6	767	-0.635	0.176						
WGRE	4	73	-0.864	0.136						

Clearly this analysis has a significant shortcoming in that the time at which the BE levels were measured (which was during the same visit in which the blood pressure was measured) may have been hours to days after the crack cocaine was actually smoked. Thus, we do not have measures of blood pressures taken at the same time that the cocaine was smoked. However, we do know that the blood pressure readings of patients on tiagabine were never very high and were no worse than those on placebo. Thus, Tables 3 and 4 show all instances in which systolic hypertension was noted in any patient on either tiagabine or placebo during any of the three phases of the study (screening, enrollment, and transition). In the case of tiagabine, note that of the seven patients who had instances of systolic hypertension, three had increased systolic blood pressure only during screening (ADAV, LMCC, and RWI2), two of them had increased systolic blood pressure both during screening and enrollment (JRI2 and RMAT), one of them (SGAR) only during enrollment, and another (PTAY) during all three phases of the study: screening, enrollment, and transition (follow-up).

Table 3. All Instances of Systolic Blood Pressure Readings >140 mm Hg in Patients on Tiagabine

Name Code	Medication Group	Age	Sex	Race	Phase*	Visit	Systolic BP
ADAV	Tiagabine	46	Male	Afr-Am	S	3	155
ADAV	Tiagabine	46	Male	Afr-Am	S	6	143
JRI2	Tiagabine	29	Male	Afr-Am	S	5	144
JRI2	Tiagabine	29	Male	Afr-Am	E	1	154
JRI2	Tiagabine	29	Male	Afr-Am	E	8	155
JRI2	Tiagabine	29	Male	Afr-Am	E	15	145
JRI2	Tiagabine	29	Male	Afr-Am	E	19	147
LMCC	Tiagabine	30	Male	Afr-Am	S	1	159

LMCC	Tiagabine	30	Male	Afr-Am	S	5	150
PTAY	Tiagabine	59	Male	Afr-Am	S	5	146
PTAY	Tiagabine	59	Male	Afr-Am	S	6	150
PTAY	Tiagabine	59	Male	Afr-Am	E	7	144
PTAY	Tiagabine	59	Male	Afr-Am	E	16	148
PTAY	Tiagabine	59	Male	Afr-Am	T	1	141
RMAT	Tiagabine	41	Male	Afr-Am	S	1	147
RMAT	Tiagabine	41	Male	Afr-Am	S	2	145
RMAT	Tiagabine	41	Male	Afr-Am	S	3	144
RMAT	Tiagabine	41	Male	Afr-Am	S	4	146
RMAT	Tiagabine	41	Male	Afr-Am	E	6	145
RWI2	Tiagabine	31	Male	Afr-Am	S	1	147
RWI2	Tiagabine	31	Male	Afr-Am	S	3	144
RWI2	Tiagabine	31	Male	Afr-Am	S	4	148
SGAR	Tiagabine	43	Male	Afr-Am	E	19	159
*Note: symbols for Phase are S=Screening, E=Enrollment, T=Transition							

The slight discrepancy between Figure 4.4 and Table 3 on the number of instances of systolic hypertension in patients taking tiagabine (four in Figure 4.4, eight in Table 3) is due to the fact that on some occasions, the BE levels were not measured at the visit where blood pressure was taken and thus are not represented in Figure 4.4.

Table 4. All Instances of Systolic Blood Pressure Readings >140 mm Hg in Patients on Placebo

Name Code	Medication Group	Age	Sex	Race	Phase*	Visit	Systolic BP
DCLA	Placebo	42	Male	Afr-Am	S	6	143
DJON	Placebo	50	Male	Afr-Am	S	1	153
DJON	Placebo	50	Male	Afr-Am	S	2	143
DJON	Placebo	50	Male	Afr-Am	S	5	148
DJON	Placebo	50	Male	Afr-Am	S	6	154
DJON	Placebo	50	Male	Afr-Am	E	1	142
DJON	Placebo	50	Male	Afr-Am	E	13	158
DJON	Placebo	50	Male	Afr-Am	E	16	153
DJON	Placebo	50	Male	Afr-Am	E	22	150
DKIN	Placebo	50	Female	Afr-Am	S	2	141
DKIN	Placebo	50	Female	Afr-Am	S	6	143
DREL	Placebo	42	Male	Afr-Am	S	3	150
HDAV	Placebo	49	Female	Afr-Am	S	1	144
HDAV	Placebo	49	Female	Afr-Am	S	2	158

HDAV	Placebo	49	Female	Afr-Am	E	6	180
HDAV	Placebo	49	Female	Afr-Am	E	10	156
HDAV	Placebo	49	Female	Afr-Am	E	16	154
HDAV	Placebo	49	Female	Afr-Am	E	21	166
HDAV	Placebo	49	Female	Afr-Am	T	1	181
HDAV	Placebo	49	Female	Afr-Am	T	3	144
HDAV	Placebo	49	Female	Afr-Am	T	4	162
HMOS	Placebo	44	Male	Afr-Am	T	2	147
OJOH	Placebo	33	Male	Afr-Am	E	1	141
SJON	Placebo	44	Male	Afr-Am	S	1	146
SJON	Placebo	44	Male	Afr-Am	S	2	144
SJON	Placebo	44	Male	Afr-Am	S	3	142
SJON	Placebo	44	Male	Afr-Am	E	4	163
SJON	Placebo	44	Male	Afr-Am	E	13	157
SJON	Placebo	44	Male	Afr-Am	T	1	141
SJON	Placebo	44	Male	Afr-Am	T	2	148
TPOW	Placebo	37	Male	Afr-Am	S	3	144
TPOW	Placebo	37	Male	Afr-Am	S	6	141
TPOW	Placebo	37	Male	Afr-Am	E	5	146
TPOW	Placebo	37	Male	Afr-Am	E	14	143
*Note: symbols for Phase are S=Screening, E=Enrollment, T=Transition							

Note that of the nine patients on placebo who had instances of systolic hypertension (Table 4), four (DCLA, DKIN, DREL, and HMOS) had increased systolic blood pressure only during screening or transition, four of them had it when they were in active and non-active phases of the study (DJON, HDAV, SJON, and TPOW), and one of them (OJOH) only on one occasion during the active phase of the study. Note that the patient on placebo with the highest systolic blood pressure (HDAV, Table 4) did not satisfy criteria for hypertension during the screening phase of the study and was, thus, enrolled. She was a very thin (100 lbs) African American woman who would frequently use cocaine long into the night and then would come for her visits in the morning in a very hyperactive state. The physician felt that her increased blood pressure was directly related to her cocaine runs.

Additional analyses on diastolic blood pressure and heart rate gave similar results (see Appendix V). The safety of tiagabine from the perspective of the adverse events encountered during the previous pilot project (CREST-II) is discussed in Section 10.6.

4.5 SAFETY OF OTHER GABAERGIC AGENTS IN THE PRESENCE OF COCAINE

A phase 1 interaction study between cocaine and baclofen, a GABAergic agent, is in progress (Childress, 2001). In this study, patients are randomized to baclofen or placebo and then administered cocaine. So far, only five patients have been studied (two on baclofen and three on placebo) and there is no evidence that baclofen is less safe than placebo in the presence of cocaine. In a recent open label, 18-week outpatient trial, in which baclofen (at a dose of 20 mg three times per day) was used on ten patients, many of whom were using cocaine, the authors reported that baclofen was safe and well tolerated by the patients (Ling and Shoptaw, 1998).

A pre-clinical cocaine interaction study has been conducted for vigabatrin, another GABAergic agent. This study, which was conducted in rats, examined the safety of administering 5 mg/Kg cocaine in rats who had been injected with either saline or 60 mg/Kg of vigabatrin. There was no mortality in the study, and the study authors concluded that the interaction between cocaine and vigabatrin was sufficiently safe to allow for future clinical trials (Molina *et al*.,1999).

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVES

The primary objective of this study is to assess the efficacy of tiagabine in reducing cocaine use in subjects with cocaine dependence using DSM-IV criteria (American Psychiatric Association, 1994). The hypothesis is that tiagabine will increase the weekly mean proportion of cocaine non-use days over the treatment period when compared to placebo as determined by self-report of cocaine use confirmed with urine assays for BE.

5.2 SECONDARY OBJECTIVES

Secondary objectives include:

1. Determining the safety of tiagabine in the study population.
2. Assessing the efficacy of tiagabine in reducing the weekly proportion of cocaine use-days as determined by self-report alone.
3. Assessing the efficacy of tiagabine in increasing the proportion of subjects that achieve measured reductions in cocaine use (25 and 50% reductions in the number of use-days compared to baseline use).
4. Assessing the efficacy of tiagabine in reducing the weekly median urine BE level.
5. Assessing the efficacy of tiagabine in the reduction in the severity of cocaine dependence (assessed by ASI-Lite and ASI-Lite Follow-up and self and observer scored CGI) and craving (assessed by BSCS and CCQ-NOW).
6. Assessing the efficacy of tiagabine in reducing the proportion of self-reported use-days of drugs of abuse (alcohol, nicotine, marijuana, amphetamines, methamphetamine, opiates, PCP, propoxyphene, barbiturates, benzodiazepines, opiates) and percentage of urines positive for other drugs of abuse (amphetamines, barbiturates, benzodiazepines, opiates).
7. Assessing the efficacy of HIV counseling in combination with tiagabine and CBT in the reduction of HIV risk-taking behavior (assessed by HRBS) hypothesized to be associated with drug use.

6 STUDY SPONSOR

Eugene Somoza, M.D., Ph.D., Cincinnati Addiction Research Center, University of Cincinnati, 3210 Jefferson Avenue, Cincinnati, OH 45220 is the study sponsor.

7 STUDY SITES

This study will be conducted at four sites, the Veterans Administration Medical Center, Cincinnati, Ohio; the Veterans Administration Medical Center, Dayton, Ohio; the Boston University Medical Center, Boston, Massachusetts; and the University of Texas Health Sciences Center, Houston, Texas. It is anticipated that Boston and Cincinnati will enroll 35 subjects, Dayton will enroll 30 and Houston will enroll 40.

8 STUDY DESIGN

8.1 EXPERIMENTAL DESIGN

This protocol is a double-blind, placebo-controlled, parallel-group study design. After screening and a 2-week baseline period, subjects will be randomly assigned equally to dosing with placebo or tiagabine for 15 weeks. During the weeks 1 to 3, the study agent dose is escalated, and after remaining at a full dose level during weeks 4 to 12, it is tapered (weeks 13 to15). Manual-guided cognitive behavioral therapy will be provided once weekly during treatment period (weeks 1-12). Four follow-up assessments will be performed during weeks 13, 14, 15 and 19 (see Study Schema in section 2). Manual-guided cognitive behavioral therapy will be provided once weekly on week 13 and week 15 of the follow-up period.

8.2 OUTCOME/RESPONSE MEASURES

Primary Outcome Measure. The principal outcome measure is the cocaine use or non-use day. Cocaine use and non-use days will be defined by subject's self-report of use, confirmed or disproved by quantification of urine BE. For the primary efficacy response, each day of the nine weeks of full dose treatment (weeks 4 to 12) will be coded as either a "use" or a "non-use" day based on the self-reports and on the urine BE data. Because of the pharmacokinetics of cocaine and BE, carryover from previous cocaine use may be difficult to distinguish from new use. The rules formulated by (Preston *et al.,* 1997 a, b) and modified to meet the conditions of this study will be used as described in section 15 to facilitate classification of each assessment day as "use" or "no-use". The weekly mean proportion of non-use days for weeks 4 through 12 (when the subjects are treated with the full dose of study agent) will be compared between treatment groups by Generalized Estimating Equations (GEE).

Secondary Outcome Measures. Secondary outcome measures include other measures of the pattern of cocaine use (overall proportion of non-use days, proportion of successful subjects, and weekly median urine BE levels), measures of severity of cocaine dependence (assessed by ASI-Lite and self- and observer-scored CGI (Tracy *et al*., 2002) and craving (assessed by BSCS (Mezinskis *et al*, 1998), and CCQ-NOW (Tiffany *et al.,* 1993), use and non-use days of other substances of abuse (alcohol, nicotine, marijuana, amphetamines, methamphetamine, opiates, PCP, propoxyphene, benzodiazepines, and barbiturates) as determined by self report, percentage of negative urines by drug (amphetamines, opiates, benzodiazepines and barbiturates), and reduction in HIV risk-taking behavior (assessed by HRBS).

Other Measures. Several measures will be included for population descriptive purposes and other scientific use. These include CSSA, CSEQ and SFQ.

8.3 BLINDING PLAN

The investigational agents, tiagabine and matching placebo, will be supplied by the research pharmacist in high density polyethylene bottles with child resistant caps. The bottles will be labeled with a product label and a subject label. Bottles will be labeled on site with the following information Caution: New Drug – Limited by federal law to investigational use, the subject name, study physician's name, number of tablets dispensed, directions for use and will be labeled "Tiagabine 2 mg or placebo", thus identifying the drug but preserving the blind. It will also contain the name and address of the dispensing institution.

8.4 RANDOMIZATION PLAN

Stratified randomization will be used in order to distribute non-random characteristics known to influence outcomes in substance abuse trials equally across groups. The treatment groups within sites will be balanced with respect to gender and historical self-report of cocaine use (< 18 or ≥ 18 days of use in the 30 days prior to screening).

8.5 CONCURRENT CONTROLS

As the study design is double-blind (neither the investigator nor the subject know the treatment assignment), subjects in the control arm will be given matching placebo agent along with cognitive behavioral therapy according to the same schedule as those in the test agent arm.

8.6 DEFINITION OF STUDY POPULATIONS (INTENT-TO-TREAT AND EVALUABLE)

The intent-to-treat study population is defined as the subjects who are randomized and receive the first day's study investigational agent. The evaluable study population is defined as the subjects who are randomized and properly qualified to participate in the study in accordance with the inclusion and exclusion criteria and who contribute at least six (6) usable urine samples and 28 days of self-report during the first four weeks of the treatment period, and who reach the full dose of study agent, and do not have dose adjustments made during the first four weeks of the treatment period due to side effects.

9 SUBJECT SELECTION

A total of 140 male and female subjects with cocaine dependence will be enrolled in the study (70 per treatment group). Entry into this study is open to both men and women and to all racial and ethnic subgroups. At least 30% female subjects will be enrolled. Subjects will be recruited from a variety of sources. The primary source will be subjects seeking treatment for cocaine dependence at the site's hospital/outpatient clinic. Additional subjects will be recruited from the community by means of referrals from local treatment providers, advertising in local media, and word of mouth among subjects themselves. Recruitment advertisements will be approved by the site's Institutional Review Board (IRB).

9.1 INCLUSION CRITERIA

Potential subjects must:

1. Be at least 18 years-of-age.

2. Have a DSM-IV diagnosis of cocaine dependence as determined by SCID.

3. Be seeking treatment for cocaine dependence.

4. Have at least 1 positive urine BE specimen (> 300 ng/mL) within the two-week baseline period prior to randomization with a minimum of 4 samples tested.

5. Have the ability to understand, and having understood, provide written informed consent.

6. If female, agree to use one of the following methods of birth control:

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

9.2 EXCLUSION CRITERIA

Potential subjects must not:

1. Have current dependence, defined by DSM-IV criteria, on any psychoactive substance other than cocaine, alcohol, nicotine, or marijuana or physiological dependence on alcohol requiring medical detoxification.

2. Be mandated by the court to obtain treatment for cocaine-dependence.

3. Have been enrolled in an opiate-substitution program (methadone, LAAM, buprenorphine) within 2 months of screening.

4. Be anyone who in the opinion of the investigator would not be expected to complete the study protocol due to probable incarceration or relocation from the clinic area.

5. Have a psychiatric disorder, as assessed by the SCID, or a neurological disorder, brain disease, dementia or any disorder that, in the opinion of the study physician requires ongoing treatment that would make study participation unsafe or which would make treatment compliance difficult.

6. Have had electroconvulsive therapy within the past 3 months preceding screening.

7. Have current suicidal ideation or plan (within the past 30 days) as assessed by the SCID.

8. Be pregnant or lactating.

9. Have serious medical illnesses including, but not limited to:

- uncontrolled hypertension,
- significant heart disease (including myocardial infarction within one year of enrollment), or any clinically significant cardiovascular abnormality (ECG).
- angina,
- hepatic, renal or gastrointestinal disorders that could result in altered metabolism or excretion of the study agent,
- current or historical diagnosis of chronic disease of the gastrointestinal tract (e.g., ulcerative colitis, regional enteritis, or gastrointestinal bleeding),
- potentially life-threatening or progressive medical illness other than addiction that may compromise subject safety or study conduct.

10. Have clinically significant abnormal laboratory values, per (Appendix I).

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

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

13. Have a diagnosis of adult (i.e., 21 years or older) asthma, or chronic obstructive pulmonary disease (COPD), including those with a history of acute asthma within the past two years, and those with current or recent (past 3 months) treatment with inhaled or oral beta-agonist or steroid therapy (because of potential serious adverse interactions with cocaine).

14. Be actively using albuterol or other beta agonist medications, regardless of formal diagnosis of asthma. (Inhalers are sometimes used by cocaine addicts to enhance cocaine delivery to the lungs). A subject without respiratory disease who will consent to discontinue beta-agonist use, may be considered for inclusion.

15. Have received a drug with known potential for toxicity to a major organ system within 30 day prior to screening (e.g. isoniazid, methotrexate).

17. Have the need or intention to use concurrently with dosing or within two weeks prior to dosing, any of the following medications: carbamazepine, phenytoin, phenobarbital, primidone, valproic acid, and ketoconazole. In addition, other substances, which affect the enzyme CYP3A4 (as inhibitors, substrates, or inducers) should be used with caution. The research physician will decide on this issue. A listing of these substances may be found in Appendix VI.

18. Have participated in any experimental study within 2 months preceding screening.

19. Have known or suspected hypersensitivity to tiagabine.

20. Be taking tiagabine for any reason.

Notes on inclusion/exclusion criterion: Although AIDS is an exclusion criterion, a positive antibody titer to HIV is not. All prospective subjects will be offered HIV testing. This test is offered as a courtesy to the prospective subject along with HIV education.

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

The infectious disease panel for hepatitis is performed as an aid to determine if the prospective subject has been exposed to the hepatitis virus. Positive hepatitis results do not exclude a prospective subject from participation. However, if liver function tests (e.g. ALT and AST) are over three times normal it is presumptive evidence that the subject has active hepatitis and should be excluded from the study (exclusion criterion #10). Tuberculin test (PPD) is performed only on subjects that are intravenous abusers of any drug. A positive PPD result does not exclude a prospective subject from participation, but if diagnostic tests (e.g. chest x-ray) indicate that active disease is present, subjects will be excluded from participation.

10 INVESTIGATIONAL AGENTS

Tiagabine has a chemical name of (-)-(R)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid hydrochloride, a molecular formula of $C_{20}H_{25}NO_2S_2.HCl$ and a molecular weight of 412.0. It is a white to off-white, odorless, crystalline powder. It is soluble in aqueous base, sparingly soluble in water and insoluble in heptane.

Tiagabine as 2 mg tablets and matched placebo tablets will be provided by Cephalon Pharmaceuticals. Tiagabine tablets contain the following inactive ingredients: ascorbic acid, colloidal silicon dioxide, crospovidone, hydrogenated vegetable oil wax, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch, stearic acid and titanium dioxide. Tablets may also contain a coloring agent.

10.1 DISPENSING INVESTIGATIONAL AGENTS

Blinded supplies of tiagabine and/or matched placebo tablets will be dispensed by the research pharmacist weekly for daily self-administration by subjects. The investigational agent will be distributed by the research pharmacist directly to the subject or to the investigator for dispensing to the subject. Dosing information will be included on the label supplied at the study site.

10.2 LABELING

The investigational agents, tiagabine and matching placebo, will be supplied by the research pharmacist in high density polyethylene bottles with child resistant caps. The bottles will be labeled with a product label and a subject label. Bottles will be labeled on site with the following information Caution: New Drug – Limited by federal law to investigational use, the subject name, study physician's name, number of tablets dispensed, directions for use and will be labeled "Tiagabine 2 mg or placebo", thus identifying the drug but preserving the blind. It will also contain the name and address of the dispensing institution.

10.3 STORAGE

Investigational agents will be stored at room temperature in a secure location.

10.4 RECORD OF ADMINISTRATION

Accurate recording of all investigational agent received, dispensed, administered and returned will be maintained on the appropriate forms.

10.5 USED/UNUSED SUPPLIES

During the study, all investigational agents dispensed to but not used by the subject should be returned to the investigator or designee for assessment of subject compliance. At the end of the study, all unused investigational agents should be inventoried. If any investigational agent is lost or damaged, its disposition should be documented. Unused investigational agents will be retained at the clinic site pending instructions for disposition by the Sponsor.

10.6 SAFETY OF TIAGABINE

The most commonly observed adverse events in placebo-controlled, parallel-group, add-on epilepsy trials associated with the use of tiagabine in combination with other antiepilepsy drugs not seen at an equivalent frequency among placebo-treated patients were dizziness/lightheadedness, asthenia/lack of energy, somnolence, nausea, nervousness/irritability, tremor, abdominal pain, and thinking abnormal/difficulty with concentration or attention. Approximately 21% of the 2531 patients who received tiagabine in phase 2/3 clinical trials of epilepsy discontinued treatment because of an adverse event. The adverse events most commonly associated with discontinuation were dizziness (1.7%), somnolence (1.6%), depression 1.3%), confusion (1.1%) and asthenia (1.1%).

Table 6 lists treatment-emergent signs and symptoms that occurred in at least 1% of patients treated with tiagabine for epilepsy participating in parallel-group, placebo-controlled trials and were numerically more common in the tiagabine group. In these studies, either tiagabine or placebo was added to the patient's current antiepilepsy drug therapy. Adverse events were usually mild or moderate in intensity (Mosby's Rx, 2000). Treatment-emergent adverse events not listed on this table include: mouth ulcerations (1% *versus* 0% in the placebo group), myasthenia (1% *versus* 0% for placebo), hostility (2% *versus* 1%), nystagmus (2% *versus* 1%), language problems (2% *versus* 0%), agitation (1% *versus* 0%), itching (2% *versus* 0%).

Table 6. Safety of Tiagabine

Body System/COSTART Term	Tiagabine	Placebo
Body as a Whole		
Abdominal Pain	7	3
Pain (Unspecified)	5	3
Cardiovascular		

Vasodilation	2	1
Digestive		
Nausea	11	9
Diarrhea	7	3
Vomiting	7	4
Increased Appetite	2	0
Nervous System		
Dizziness	27	15
Asthenia	20	14
Somnolence	18	15
Nervousness	10	3
Tremor	9	3
Decreased Concentration	6	2
Insomnia	6	4
Ataxia	5	3
Confusion	5	3
Speech Disorder	4	2
Decreased Memory	4	3
Paresthesia	4	2
Depression	3	1
Emotional Lability	3	2
Abnormal Gait	3	2
Respiratory System		
Pharyngitis	7	4
Cough	4	3
Skin and Appendages		
Rash	5	4

In U.S. studies, 11% percent of tiagabine treated patients and 6% of placebo treated patients had to discontinue therapy because of adverse events. The most common adverse events considered the primary reason for discontinuation were confusion (1.2%), somnolence (1.0%), and ataxia (1.0%). The assessment of adverse events for tiagabine is confounded by the fact that patients had a serious chronic disease and were on multiple other centrally acting medications. Note that all patients in these clinical trials had epilepsy and were on other medications besides tiagabine.

The dosage of tiagabine used in these clinical trials on epilepsy was generally 32 mg or greater; however, it should be pointed out that several of the anti-convulsants used concomitantly with tiagabine decrease the plasma concentration of tiagabine. The maximum dose to be used in the present study is 20 mg.

The investigators that will be conducting the present clinical trial also completed a small pilot study on tiagabine (using a maximum of 20 mg) on 17 cocaine dependent patients (Table 7).

Table 7. Summary of Adverse Events from the CREST-II Study (17 patients/group)							
	TIAGABINE				PLACEBO		
Category	**Mild**	**Moderate**	**Severe**		**Mild**	**Moderate**	**Severe**
Accident	2	1	0		1	0	0
Cardivascular	2	0	0		0	0	0
Gastroenterological	7	1	0		6	2	0
Genitourinary	3	1	0		3	0	0
Miscellaneous	12	2	0		9	1	0
Musculoskeletal	4	1	2		2	1	0
Neurological	29	5	0		17	2	0
Psychiatric	3	1	1		1	0	0
Respiratory	5	1	0		3	2	0
TOTAL	**67**	**13**	**3**		**42**	**8**	**0**

This was part of a larger study (called CREST-II), which also included 17 patients on an unmatched placebo in a double-blind, parallel group design. Table 7 summarizes the adverse events reported for patients on tiagabine and placebo. Note that the three adverse events rated as "severe" were: shoulder pain, hip pain, and suicidal ideations. The suicidal ideations were deemed to be unrelated to the study medication.

There were three serious adverse events (SAEs) experienced by participants in this study. Two of those participants were assigned to tiagabine, and the third was assigned to another study medication being used. Both SAEs of patients on tiagabine resulted when the patients electively entered a rehabilitation program for treatment of their cocaine addiction. These SAEs were deemed unrelated to study medication**.**

Two participants from the tiagabine group were permanently taken off of their medication due to side effects, and an additional five subjects had their medication dose reduced or temporarily discontinued due to side effects.

11 TREATMENT PLAN

11.1 INVESTIGATIONAL AGENTS

Blinded supplies of tiagabine and/or matched placebo tablets will be dispensed by the research pharmacist weekly for daily self-administration by subjects. Subjects will be instructed to take investigational agents with food according to the dosing schedule in section 11.2, Table 8. The investigational pharmacist of the lead site (Cincinnati) will be unblinded. If a subject's adverse event

(AE) is deemed treatment-related, the site research physician will evaluate the AE and if necessary instruct the study pharmacist to make a dose reduction. Likewise, study subjects receiving placebo will also have study agents reduced if complaining of side effects or other symptoms. For more difficult or serious issues, this decision will be made in consultation with the NIDA Medical Monitor. All manipulations of study agents will be done by the research pharmacist in response to a physician's verbal or written order.

11.2 DOSING SCHEDULE AND DOSE ADJUSTMENTS

Subjects are asked to take a prescribed number of tablets of either tiagabine or placebo with food according to the dosing schedule in section 11.2, Table 8. Weeks 1-3 are dose-escalation weeks and weeks 13-15 are dose-tapering weeks. Dose escalation and taper are performed in order to minimize side effects. Please refer to Table 8 for dose escalation and taper. During the level-dose weeks (4-12), subjects randomized to tiagabine will be taking the maximum dose of 20 mg, four 2-mg tablets in the morning and six 2-mg tablets in the evening, while placebo patients will take the same number of placebo tablets (Table 8).

Table 8 shows the number of 2-mg tablets of tiagabine (or identical-appearing tablets of placebo) that are to be taken each morning during the beginning of week 1 and during week 15 of the study, and each morning and evening during the end of week 1 and during weeks 2-14 of the study.

Table 8. Dosing Schedule

Week	Day	Daily amt (if tiagabine)	AM #tabs	PM #tabs	Week	Day	Daily amt. (if tiagabine)	AM #tabs	PM #tabs
1	1	4 mg	2	0	13	1	16 mg	4	4
1	2	4 mg	2	0	13	2	16 mg	4	4
1	3	4 mg	2	0	13	3	16 mg	4	4
1	4	4 mg	2	0	13	4	16 mg	4	4
1	5	8 mg	2	2	13	5	12 mg	2	4
1	6	8 mg	2	2	13	6	12 mg	2	4
1	7	8 mg	2	2	13	7	12 mg	2	4
2	1	8 mg	2	2	14	1	12 mg	2	4
2	2	8 mg	2	2	14	2	12 mg	2	4
2	3	12 mg	2	4	14	3	8 mg	2	2
2	4	12 mg	2	4	14	4	8 mg	2	2
2	5	12 mg	2	4	14	5	8 mg	2	2
2	6	12 mg	2	4	14	6	8 mg	2	2
2	7	12 mg	2	4	14	7	8 mg	2	2
3	1	16 mg	4	4	15	1	4 mg	2	0
3	2	16 mg	4	4	15	2	4 mg	2	0
3	3	16 mg	4	4	15	3	4 mg	2	0
3	4	16 mg	4	4	15	4	4 mg	2	0
3	5	20 mg	4	6	15	5	0 mg	0	0
3	6	20 mg	4	6	15	6	0 mg	0	0

3	7	20 mg	4	6	15	7	0 mg	0	0
4-12	1-7	20 mg	4	6					

On the first day of the study, the subject will be sent home with sufficient medication for study week 1, plus enough additional medication for an extra 3 days of dosing at the same level as the dosing on week 1, day 7. This extra amount will provide a buffer in case the subject misses the next scheduled medication-dispensing visit. The subject will be instructed on how to take the medication during the upcoming days and asked to bring back the empty bottle(s) or any unused medication during the subject's first clinic visit of study week 2.

Subjects will ideally receive medication during the first clinic visit of weeks 2-12. Subjects preferably will receive the medication for week 13 during the last visit of week 12, the medication for weeks 14 and 15 during the week 13 visit. Again, the subject will be asked to bring back the empty bottle(s) or any unused medication during the subject's first clinic visit of the next study week or, in the case of the week 15 medication, during the subject's week 19 visit.

If a subject misses an entire week of consecutive visits, no medication will be given for that week. If the missed week is during dose excalation or dose tapering phases or if there is any other reason to question the level at which dosing should proceed, the research physician will determine the dosage for the week following the missed week.

A subject may miss up to two consecutive weeks of medication and still be retitrated back to the full dose, provided that the subject will be able to be on the full dose for four weeks before the end of the treatment period. If the missed weeks occur during dose excalation or dose taper, or if there is any other reason to question the level at which dosing should proceed, the research physician will determine the dosages following the missed weeks.

If a subject misses more than two consecutive weeks of medication, the subject may not continue to receive study medications.

A subject who is discontinued from receiving the investigational agent for any reason may be allowed to continue psychosocial therapy per the approval of the investigator.

If a subject leaves the study early, the subject will be offered a dose taper which may last up to three weeks at the discretion of the study physician.

Subjects will be told to take the investigational agent with meals and not to discontinue the agent suddenly but to contact the study staff if adverse reactions occur. Subjects will be warned not to perform hazardous tasks that require alertness and coordination until the subject is comfortable with how the medication makes him/her feel.

Dose Adjustments. Every attempt will be made to maintain subjects at the study agent dose specified in this protocol. However, subjects who are unable to tolerate the specified dose will be allowed to continue in the study at a reduced dose (the maximum tolerated dose as determined by the research physician). Such subjects may continue to participate in all other aspects of the study. When tiagabine dose reduction is warranted due to adverse side effects, the principal investigator (PI) or his designee will decrease the number of tablets of study agent from the maximum to the amount that is clinically reasonable. As dose reductions are permissible in both groups, this will not break the blind

for a subject. However, subjects who have dose reductions during the weeks 1-4 will not be included in the evaluable population of the study.

In the case of severe side effects, discontinuation of the study agent altogether may be necessary. In such a situation, the research physician will evaluate the patient to determine whether the study agent should be discontinued immediately, or should be tapered prior to discontinuation.

AEs will be carefully monitored throughout the study: once a week by the study physician, and three times a week by the study coordinator.

11.3 COGNITIVE BEHAVIORAL THERAPY

All subjects will receive standardized, manual-guided individual cognitive behavioral therapy by a certified therapist once per week during the treatment period (weeks 1-12) and once per week on week 13 and week 15 during the follow-up period. The cognitive behavioral manual, to be provided in the study operation manual, is the 2000 version of the Cognitive Behavioral Therapy Manual. These sessions will consist of one session of approximately 1 hour of individualized counseling per week. During these sessions, emergency counseling and referral services will be provided. Additional emergency crisis management sessions will be available up to a maximum of four. These visits will be documented.

The goal of this behavioral treatment intervention is to increase protocol compliance and educate the subject about his/her dependence and factors associated with drug use, and assist study subjects in achieving abstinence from cocaine without obscuring the impact of the pharmacological treatment. There will be no negative consequences based on urine toxicology results or patient revelations regarding use of illicit substances. The primary purpose of using a manual-guided procedure for therapists is to achieve consistency of theoretical orientation, therapeutic style, and behavioral intervention across subjects and sites. Each therapy session should be audiotaped to monitor drift and assure adherence to manual-guided therapy. Original tapes are to be maintained at the site. The Boston Behavioral Treatment Training Center will select a random proportion of these tapes for review. The psychotherapy manual has the procedure for submission and review of tapes. It is expected that at least one session per month will be rated by the training center.

12 STUDY PROCEDURES

12.1 INFORMED CONSENT

Interested candidates who have been determined by telephone or in person interview to be using cocaine, are seeking treatment, and are available to come to the clinic for at least 21 weeks will meet with a qualified investigative staff member and receive an explanation of the study purpose and requirements. During the initial interview, the interviewer should not ask questions in a manner that reveals the eligibility criteria for study entry.

If the candidate meets the basic requirements for the study and continues to show interest in participating, he or she will be invited to go through the informed consent procedure. This is explained in Section 14.4.

12.2 SCREENING/BASELINE ASSESSMENTS

Screening assessments will be conducted according to the Table 9 in Section 13.

12.3 SUBJECT ENROLLMENT

If the prospective subject meets all of the study inclusion, does not meet the exclusion criteria (a checklist will be provided in the CRF package), and has signed the informed consent form, then the subject can be enrolled onto the study. Investigators or study coordinators will submit all subject's information pertinent to stratification to the randomization center or system. The randomization center or system will assign a random dose code number which provides the participant's treatment assignment. The pharmacist will dispense the investigational agent for the subject within the same day of receiving treatment assignment, to minimize the time between completion of screening and baseline assessments and study start.

If any subject does not actually receive any investigational agent after s/he has been randomized, s/he is considered to be a randomization failure. The randomization center/system will be notified of the randomization failure so that the random code number may be reassigned to another participant.

12.4 TREATMENT

At the first clinic visit of the treatment period, subjects will be given instructions on how to self-administer the investigational agent and will be given a sufficient supply of investigational agent to last until the next clinic visit. Complete information on how subsequent weeks of investigational agent administration are handled is found in Section 11. Subjects will be scheduled for treatment and assessments three times per week, usually on a Monday, Wednesday, and Friday, for twelve weeks (week 1 to 12) and once a week during follow-up weeks 13, 14, 15, & 19. Two consecutive days may be scheduled around holidays or other schedule conflicts. All subjects will be offered an opportunity for HIV testing and counseling and HIV/AIDS education (Appendix II). All subjects will be provided with manual-guided cognitive behavioral therapy once per week during the 12-week treatment period and once per week on week 13 and week 15 during the follow-up period. Clinical evaluations are described in detail in Section 13.

12.5 PREVENTING STUDY DROP-OUTS

Subjects will be encouraged to come for treatment and for the evaluation sessions as described in this protocol. To minimize missed sessions, they will be reimbursed for their transportation and time spent in completing study assessments. It will be emphasized to subjects during screening that even if they have a relapse they should come to all scheduled appointments. They will be discouraged from using cocaine, but there will be no penalty for relapsing or for missed sessions.

12.6 DOSE TAPER AND FOLLOW-UP

At the end of study week 12, subjects will be asked to come to the clinic once a week during dose taper (weeks 13, 14, and 15) and once 4 weeks later (week 19) for a final follow-up visit (See Study Schema in Section 2). During follow-up, subjects will have their dose of study agent or placebo reduced according to the schedule given in Table 8. At these follow-up visits the subject will be asked to provide a urine specimen for BE/creatinine and urine toxicology screen, a self-report for cocaine, alcohol, nicotine, marijuana, amphetamines, ethamphetamine, opiates, PCP, propoxyphene,

benzodiazepines and barbiturates, to report any AEs or concomitant medications used, and to have vital signs taken. At the last study visit (during week 19), the same assessments will be performed and the subject will also be asked to provide any current treatments for drug or alcohol abuse and an impression of the study agent. If it is not possible to arrange for the subject to return to the clinic, then the subject should be telephoned and asked to provide a current self-reported cocaine and other drug use, current treatment for drug or alcohol abuse, and an impression of the study agent. If a subject cannot be contacted directly, attempts will be made to reach the individual(s) previously identified by the subject as a contact source.

12.7 MAINTAINING AND BREAKING STUDY BLIND

The decision to break the study blind for an individual subject lies with the site investigator and study principal investigator in consultation with the NIDA medical monitor whenever possible, but should be resorted to only in cases of life-threatening emergency when knowledge of the treatment arm investigational agent will influence clinical management. The principal investigator must inform NIDA Study Director and NIDA Medical Monitor immediately after breaking the blind.

12.8 SUBJECT REIMBURSEMENT

Subjects will be reimbursed for their transportation, inconvenience, and time. During the screening, baseline, treatment, and follow-up periods they will receive $10 or equivalent in retail scrip or vouchers per visit. At the end-of-study evaluation (during week 12 or at study discontinuation), subjects will receive $35 or equivalent in retail scrip or vouchers because they will need to spend a significantly greater amount of time to perform all of the necessary outcome measures. The reimbursement will be $25 or equivalent in retail scrip or vouchersper visit during weeks 13, 14, 15, and 19. The increased reimbursement is meant to keep patients engaged in treatment during dose taper and for the follow-up visit (to assure that the patient had no ill effects from study participation). Since this is an intent-to-treat design, efforts will be made to obtain the full 12 weeks of data even for patients whose attendance or investigational agent compliance is erratic. This remuneration is for time and expenses incurred (e.g., gasoline, public transportation), not for compliance to the protocol.

12.9 STUDY TERMINATION

Subject Termination. An investigator may terminate a subject if s/he deems it clinically appropriate or for any of the following reasons: 1) significant side effects from the investigational agent, 2) serious or unexpected AEs, 3) inability to comply with the study protocol, 4) protocol violation, 5) missing medication for more than two consecutive weeks, or 6) serious intercurrent illness.

A subject may withdraw from the study anytime s/he wishes. A subject who is discontinued from receiving the investigational agent, will be allowed to continue the cognitive behavioral therapy with the approval of the investigator. Any subject who discontinues prematurely, regardless of the reason, will be requested to return for a final visit to perform the necessary procedures listed in Section 13.3 and to obtain data for end of study/early termination.

Study subjects withdrawn from the protocol secondary to a medical or psychiatric concern will be referred for appropriate treatment. Subjects will be asked to sign a general consent for the release of information to the referred health care. Study staff may request transportation for emergency treatment of a subject if medically appropriate (e.g., for acutely psychotic or suicidal subjects).

All study subjects will be encouraged to carry a wallet card that identifies them as a subject in a clinical research study. The card will provide the name and phone number of the investigator (physician) at the site who can be contacted in the event of an emergency. The card will also instruct the non-study physician rendering emergency care to provide information to the study physician with regards to that care.

Trial Discontinuation. NIDA, in collaboration with the study sponsor, has the right to discontinue the investigation at any time.

12.10 CONCOMITANT MEDICATIONS

Any medications (including prescription, over-the-counter, herbal supplements and health store products) to be taken during the study must be approved by the investigator. The following medications should not be used during treatment with tiagabine, as they will decrease the plasma concentration of tiagabine: carbamazepine, phenytoin, phenobarbital, and primidone. Valproic acid may increase plasma tiagabine levels and so should also be avoided. In addition, other medications, which affect the enzyme CYP3A4 (as inhibitors, substrates, or inducers) should be used with caution at the research physician's discretion. A list of these medications may be found in Appendix VI.

13 CLINICAL EVALUATIONS

Table 9 provides an overview of the schedule of assessments to be conducted during the study.

Table 9. Overview of Study Assessments

Assessment	**Screening***	**Baseline***		**Treatment**						**Follow-up**	
Study Week	-4 to -1			1-3	4	5-7	8	9-11	12	13-15	19
Screening											
Informed consent	X										
SCID	X										
Psychiatric evaluation	X										
Medical History	X		**R**								
Prior Mediations	X		**A**								
Infectious disease panel/syphilis test	X		**N**								
HIV test (optional)	X		**D**								
Safety/Other			**O**								
Physical exam	X		**M**						X[b]		
Vital signs**		3X[d]	**I**	3X[c]	X[a]	X[a]	X[a]	X[a]	X[b]	X[e]	X[e]
Hematology	X		**Z**		X		X		X[b]		
Blood chemistry (including LFTs)	X		**A**		X		X		X[b]		
Urinalysis	X		**T**		X		X		X[b]		
ECG	X		**I**		X		X		X[b]		
Pregnancy test	X		**O**		X		X		X[b]		
HAM-D		X	**N**		X		X		X		
Adverse events[d]		3X[d]		3X[d]	3X[d]	3X[d]	3X[d]	3X[d]	3X[d]	X[e]	X
Concomitant medications		Weekly for 2 weeks		X[a]	X[a]	X[a]	X[a]	X[a]	X[b]	X[e]	X

Efficacy											
ASI-Lite***	X										
ASI-Lite Follow-up					X[a]		X[a]		X[b]		
SUI		3 X/week for 2 weeks		3X	3X	3X	3X	3X	3X	X[e]	X
Urine cocaine rapid test		3 X/week for 2 weeks									
Urine BE and creatinine**		3 X/week for 2 weeks		3X	3X	3X	3X	3X	3X	X[e]	X
Urine tox screen**		Weekly for 2 weeks		X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[e]	X
HRBS***	X								X		X
HIV counseling	X								X		X
BSCS		Weekly for 2 weeks		X[a]	X[a]	X[a]	X[a]	X[a]	X[a]		
CCQ-NOW		X							X[a]		
CGI-S		Weekly for 2 weeks		X[a]	X[a]	X[a]	X[a]	X[a]	X[a]		
CGI-O		Weekly for 2 weeks		X[a]	X[a]	X[a]	X[a]	X[a]	X[a]		
CSSA		3X		X[a]	X[a]	X[a]	X[a]	X[a]	X[a]		
SFQ		Weekly for 2 weeks		X[a]	X[a]	X[a]	X[a]	X[a]	X[a]		
CSEQ		Weekly for 2 weeks		X[a]	X[a]	X[a]	X[a]	X[a]	X[a]		
Treatment compliance				3X	3X	3X	3X	3X	3X	X[e]	
Collection of returned study agent				X (wk 2,3)	X	X	X	X	X	X[e]	X
Missed visit log				Completed as a log only when subject misses visits							
Follow-up questionnaire											X

* Screening and baseline may occur simultaneously and both must be completed within the 30 days prior to randomization.
** Vital Signs and Urine Tox/Urine BE are both screening and baseline measures, and will serve as a possible basis for exclusion from study. *** ASI-Lite and HRBS also serve as both screening and baseline measures, but will not be used as a basis for exclusion from study.

X[a] - Once per week preferably at the first visit of the week.
X[b] - During week 12 or if the subject discontinues prematurely.
X[c] - Vital signs are taken at each visit the first three weeks, then weekly thereafter
X[d] - Assessed at each visit; AE CRFs completed weekly
X[e] - Once a week.

13.1 ASSESSMENTS AT SCREENING/BASELINE

Prior to randomization, subjects will be screened to determine if they meet eligibility requirements. In addition, certain baseline assessments that are part of eligibility determinations will also provide physiological, psychological, and disease status information prior to active treatment. Screening and baseline may occur simultaneously, and both must be completed within the 30 days prior to randomization.

13.1.1 SCREENING ASSESSMENTS

1. Informed Consent
2. Complete medical history
3. Physical exam
4. Psychiatric evaluation and SCID evaluation for DSM-IV diagnosis of cocaine dependence and Axis-I disorders
5. Prior medications. All medications (including prescription, over-the-counter, herbal supplements and health store products) taken by the subject for the 30 days prior to screening will be documented on a Prior Medication CRF

6. ASI-Lite
7. Hematology
8. Blood chemistries, including liver function tests
9. Urinalysis
10. Urine cocaine rapid test*
11. Pregnancy test (if female)
12. Infectious disease panel
13. Syphilis test
14. ECG
15. HRBS
16. HIV counseling
17. HIV test (optional)

*During screening each urine specimen (collected on Monday, Wednesday and Friday) will be tested on the site via dipstick test for presence of cocaine, then sent to the central laboratory for analysis.

13.1.2 BASELINE ASSESSMENTS

Baseline assessments to occur over a two-week period, will include the following:

1. Three-times weekly urine BE plus creatinine measurements for two weeks. Subjects must provide at least 4 urine specimens in a consecutive 2-week period, at least one of which must be positive for urine BE (> 300 ng/mL). Ideally, 3 of the specimens will be obtained in one week and 3 in the next week. No more than 4 of the specimens may be obtained in one week of the two-week baseline and no more than two specimens can be collected on consecutive days in one week.

2. Vital signs at each study visit.

3. The following must be obtained weekly for two weeks:
   a. BSCS
   b. Urine toxicology screen
   c. Concomitant Medications
   d. CGI-S and CGI-O
   e. SFQ and CSEQ

NOTE: BSCS, CGI-S, CGI-O, SFQ, and CSEQ scores obtained on the first visit of treatment week 1 before study agent administration will be also included in the baseline mean score calculations.

4. CSSA must be obtained three times.

5. Daily report of use and route of administration of cocaine, alcohol, nicotine, marijuana, amphetamines, methamphetamine, opiates, PCP, propoxyphene, benzodiazepines and barbiturates use will be recorded at each visit on a SUI CRF.

6. CCQ-NOW will be obtained once.

7. HAM-D will be obtained once.

8. AEs assessed at each visit, AE CRFs completed weekly

Screening and baseline may occur simultaneously, and both must be completed within the 30 days prior to randomization.

13.2 ASSESSMENTS DURING TREATMENT (WEEKS 1-12)

Over the 12-week period of treatment, subjects will return to the clinic three times per week (ideally on Monday, Wednesday, and Friday). Assessments will be performed as follows:

At each visit:

1. SUI
2. Urine BE and creatinine
3. Treatment compliance
4. AEs assessed at each visit, AE CRF completed weekly
5. Vital signs (first three weeks, then weekly thereafter)

Once per week, preferably at the first visit each week and last visit of week 12:

1. Urine toxicology screen
2. BSCS
3. CGI-S
4. CGI-O
5. CSSA
6. SFQ
7. CSEQ
8. Vital signs (see note for each visit above)
9. Concomitant medications

Preferably at the first visit of weeks 4 and 8 and last visit of week 12:

1. Hematology
2. Blood chemistries, including liver function tests
3. Urinalysis
4. ECG
5. Pregnancy test (if female)
6. ASI-Lite Follow-up
7. HAM-D

Note: In addition a missed visit log will be maintained for each subject and completed if the subject misses a scheduled visit.

13.3 ASSESSMENTS AT END OF TREATMENT (WEEK 12) OR IF PATIENT LEAVES STUDY PRIOR TO WEEK 12

Urine BE and creatinine, SUI and treatment compliance are to be assessed three times during week 12. All other assessments scheduled for study week 12 should ideally be completed at the final scheduled study visit or if the subject discontinues prematurely, regardless of the reason (request that the subject returns for final assessments).

1. If the subject discontinued prematurely, determine the reason for termination.
2. Physical exam
3. Vital signs
4. SUI
5. Urine BE and creatinine
6. AEs
7. Urine toxicology screen
8. BSCS
9. CCQ-NOW
10. CGI-S
11. CGI-O
12. CSSA
13. SFQ
14. CSEQ
15. Hematology
16. Blood chemistries
17. Urinalysis
18. Pregnancy test (if female)
19. ASI-Lite Follow-up
20. HRBS
21. HIV counseling
22. HAM-D
23. ECG
24. Treatment compliance
25. Concomitant medications

13.4 ASSESSMENTS DURING DOSE TAPER (WEEKS 13, 14, 15)

During the dose taper weeks, subjects will return to the clinic for the following assessments:

1. Urine BE and creatinine
2. Urine toxicology screen
3. SUI
4. AEs
5. Concomitant medications
6. Treatment compliance (in addition, subjects will be asked to return all unused study agent)
7. Vital Signs

13.5 ASSESSMENTS AT FINAL FOLLOW-UP (WEEK 19)

Subjects will be asked to return to the clinic for one follow-up assessment 4 weeks after completion of medication taper. Follow-up assessments include:

1. Urine BE and creatinine
2. Urine toxicology screen
3. SUI
4. HRBS
5. HIV counseling
6. AEs
7. Concomitant medications

8. Vital Signs

In addition, at the last study visit the following will be performed:

1. Questions regarding current treatment for drug or alcohol abuse,
2. Impression of the study treatments.

13.6 ASSESSMENT METHODS

13.6.1 Vital Signs

Vital signs to be assessed include oral temperature, blood pressure, pulse rate, and respiratory rate.

13.6.2 Physical Exam

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

13.6.3 Hematology

Blood will be collected in anticoagulant containing evacuated venous blood collection tubes (e.g., Vacutainer™) for hematologic assessments. Complete blood counts (CBC) with differentials and platelet count will be performed. Quantitative analyses for hemoglobin, hematocrit, red blood cells, platelets, total white blood cells, and percentage of neutrophils, lymphocytes, monocytes, eosinophils, and basophils, will be performed. Analyses will be performed in the institutions clinical laboratory. The laboratory performing these assessments should be either directly regulated by the College of American Pathologist (CAP) or the Clinical Laboratory Improvement Act of 1988 (CLIA) or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

13.6.4 Blood Chemistries

Blood will be collected in serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) and serum separated according to standard procedures. Quantitative analysis will be performed for the following analytes: sodium, potassium, chloride, carbon dioxide, glucose, creatinine, albumin, total protein, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyltranspeptidase (GGT), total bilirubin, and blood urea nitrogen (BUN). The laboratory performing these assessments should be either directly regulated by CAP or CLIA or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

13.6.5 Infectious Disease Panel and Syphilis Test

Blood will be collected in a serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) and serum separated according to standard procedures. Qualitative analysis reporting positive/negative results will be performed for the following analytes: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and hepatitis C virus antibody. A purified protein derivative (PPD) skin test for tuberculosis will be performed only on i.v. drug abusers (any drug) and if positive a chest x-ray is required to assess active tuberculosis. If the subject reports that s/he has been previously positive for the PPD test, the PPD test will not be performed and only a chest x-ray will be required. A rapid plasma reagin test (RPR) for syphilis will be performed.

13.6.6 HIV Test
All subjects will be offered the opportunity to have an HIV test performed. This test is not requisite for study participation. HIV test informed consent must be obtained before collecting blood for this test. An HIV antibody test will be performed on a serum sample collected from the subject after the HIV informed consent form is signed.

13.6.7 Pregnancy Test
A urine pregnancy test designed to measure human chorionic gonodotropin will be used. All female subjects will be tested regardless of their child-bearing capacity.

13.6.8 HAM-D
The HAM-D is an interviewer administered assessment of the subject's level of depression. The questions for items 1 – 21 were developed by Williams (Williams, 1988). The HAM-D for this study includes three additional questions all associated with cocaine dependence (22. Helplessness, 23. Hopelessness, and 24. Worthlessness).

13.6.9 SCID
A SCID to assess the subject's cocaine-dependence according to DSM-IV criteria and Axis-I disorders will be conducted during screening.

13.6.10 ASI-Lite CF Version and ASI-Lite Follow-up
The ASI-Lite will be administered at screening/baseline by a research staff member having at least a bachelor's degree in the social sciences or equivalent training and experience as determined by the site's investigator. The ASI-Lite is the interviewer's estimate of the severity of the subject's status in seven areas (medical, employment, drug use, alcohol use, legal, family/social, and psychological). Composite scores will be calculated according to the procedures described by McGahan *et al*. (1982) and Carroll *et al*. (1994). The Lite version is a shorter version of the ASI that still retains all questions used to calculate the ASI composite scores. ASI-Lite Follow-up will be administered at weeks 4, 8 and 12.

13.6.11 Urine Collection and Analyses
Urine will be collected for five (5) types of analyses as follows:

1. Cocaine rapid test performed at the site
2. BE and creatinine performed at a central laboratory
3. Urine Toxicology Screen (Qualitative Analysis of amphetamines, opiates, benzodiazepines and barbiturates) performed at a central laboratory
4. Urinalysis performed at the local clinical laboratory
5. Pregnancy test

Depending upon the assessment schedule, urine samples will be collected and aliquoted into the appropriate number of specimens. One specimen will be held frozen at the clinical site as a back-up. The others will be frozen (if appropriate – cocaine rapid tests, urinalysis and pregnancy test samples do not need to be frozen) or sent directly to the appropriate laboratory for analysis. Samples to be tested for drugs of abuse and creatinine will be sent to a central laboratory and tested using a validated method. Specimens will be collected and tested as follows:

***BE and Creatinine*.** Urine samples will be collected 3 times a week (generally Monday, Wednesday, and Friday, barring holidays and schedule conflicts). During baseline, three samples will be set aside,

one for freezing and one for shipment to a central laboratory for analysis of BE plus creatinine. In addition a third aliquot will be tested on-site for a rapid cocaine test result.

Urine samples collected during treatment and follow-up will be frozen and sent to a central laboratory to be analyzed for BE and creatinine. The back-up sample retained at the site will be stored frozen until the NIDA data coordinating center has notified the site that it can be disposed. Results will not be provided to the site during the study, and the site is prohibited from analyzing samples locally.

Urine Toxicology Screen (Qualitative Analysis of Substances of Abuse). The first sample of each week taken for BE and creatinine analysis will be analyzed additionally for amphetamines, opiates, benzodiazepines and barbiturates.

Urinalysis. Urine will be collected and analyzed for specific gravity, pH, blood, protein, glucose, ketones, leukocytes, and nitrite. Analysis may be conducted at a local laboratory or by study staff using a qualitative dipstick urinalysis according to the package insert.

13.6.12 Substance Use Inventory (SUI)
The SUI measures the subject's report of days of recent drug use and routes of administration. The use of cocaine, alcohol, nicotine, marijuana, amphetamines, methamphetamine, opiates, PCP, propoxyphene, benzodiazepines and barbiturates will be recorded on this form at each clinic visit.

13.6.13 BSCS
The BSCS is a self-administered assessment that asks the subject to rate his or her craving for cocaine. The BSCS used for this study is a modification of the State of Feelings and Cravings Questionnaire (Mezinskis *et al.*, 1998).

13.6.14 Cocaine Craving Questionnaire (CCQ-NOW)
The CCQ-NOW is a 45 item self-administered questionnaire that asks the subject to rate his or her craving for cocaine (Tiffany *et al*., 1993).

13.6.15 Clinical Global Impression-Observer (CGI-O)
The CGI-O (Tracy *et al*., 2002) requires an RN or a professional with Master's level or higher with experience with this population, who knows the participant, to rate the global severity of the subject's cocaine dependence symptoms and to rate the improvement of the subject's cocaine dependence since the beginning of the study. The severity of the subject's cocaine dependence is rated according to eight specific problem areas often associated with cocaine dependence. The severity of each of the eight specific problem areas is rated first; the global severity is rated second; and the global improvement is rated last.

13.6.16 Clinical Global Impression-Self (CGI-S)
The CGI-Self (Tracy *et al*., 2002) is a self-administered assessment that asks the subject to rate the global severity of his or her cocaine dependence symptoms and to rate the improvement of his or her cocaine dependence symptoms since the beginning of the study.

13.6.17 Cocaine Selective Severity Assessment (CSSA)
The CSSA is administered by properly trained personnel. Questions relate to withdrawal symptoms of cocaine dependence. There are a total of 18 questions and subjects report their responses on a scale of 0 to 7 with 0 being no symptoms at all and 7 being the most extreme symptom. In addition,

there are two self-administered assessments that ask the subject to rate their cravings over the previous 24 hours.

13.6.18 State of Feelings Questionnaire (SFQ)
The SFQ (Mezinskis *et al.*, 1998). is a subject-completed questionnaire reporting on feelings associated with anxiety, depression, restlessness, anger, irritability, frustration, impatience, and difficulty concentrating. Subjects rate their feelings on a 5 point scale from none at all to extreme.

13.6.19 Cocaine Subjective Effects Questionnaire (CSEQ)
The CSEQ is a subject-completed questionnaire reporting on the subjective experience (if cocaine was used) of using cocaine including drug effect, rush, good effects, desire, and liking of the experience. In addition to asking about drug use, the effects are scored on a 7 point scale from none to extreme.

13.6.20 Adverse Events (AEs)
AEs will be assessed at each visit by a member of the investigative team. If an AE is reported that requires medical attention, it should be reported to a study physician immediately. The investigator or study physician will assess subjects weekly for any medical or psychiatric AEs. The physician will assess AEs by asking the participant "How have you been feeling since I saw you last". The type of AE, severity of the AE, and the relationship to the study treatments will be recorded on an AE CRF according to the procedures described in section 14.7. After AEs are assessed, study physician must review with the subjects and assess any AEs unresolved from the previous week.

13.6.21 HIV Risk-Taking Behavior Scale (HRBS)
The HRBS is a brief 12-item interview administered scale that examines the behavior of intravenous drug users in both injecting and sexual behavior.

13.6.22 ECG
Twelve-lead electrocardiograms will be performed according to standard procedures. The results will be reviewed by a board-certified cardiologist for interpretation.

13.6.23 Prior Medications
All medications taken by the subject for the 30 days prior to screening will be documented on a Prior Medications CRF. The reported medications will be reviewed and approved by the principal investigator/study physician.

13.6.24 Concomitant Medications
All medications taken by the subject during the two-week baseline period, while on study, and during follow-up must be pre-approved by the study physician whenever possible to avoid interactions with study drug. All medications taken during the study period (including screening/baseline) will be recorded once per week on a Concomitant Medications CRF.

13.6.25 Treatment Compliance
At each clinic visit, the subject will be asked to provide a report of the number of tablets taken each day. Subjects will be asked to keep a dosing diary to facilitate reporting accuracy. Compliance with cognitive behavioral therapy will be accounted for by recording the length of time the subject spent in attendance at the weekly therapy session.

13.6.26 Missed Visit Log

A CRF is completed as a log that documents the reason that the subject reports for a missed visit during the treatment phase of the study.

14 REGULATORY AND REPORTING REQUIREMENTS

14.1 GOOD CLINICAL PRACTICES

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

14.2 FDA FORM 1572

The investigator at each study site will sign a Statement of Investigator FDA Form 1572 prior to initiating this study.

14.3 IRB APPROVAL

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

14.4 INFORMED CONSENT

A two-part informed consent process will be used consisting of a single informed consent form but with separate signatures for parts 1 and 2 of the consent process. The difference in the two parts of the consent process is that during part 1, the initial interview and study explanation can be conducted by a qualified study staff member but does not have to be a study physician/ investigator. Part 2 of the consent process is an explanation of the study by a study physician/ investigator. If the study is initially explained to the potential subject by a study staff member that is not a physician/investigator, then part 1 of the form will be signed by the subject and the study staff member. If the study is initially explained to the potential subject by a physician/ investigator, then both of the part 1 and part 2 signature sections will be signed by the potential subject and investigator.

During the initial admission interview potential participants are told the study purpose and procedures. All potential candidates for the study will be given a current copy of the two-part Informed Consent Form to read and take home. All aspects of the study will be explained in lay language. After the participant has read the consent form, a short questionnaire will be given to the participant before signing the form. Any participant who has difficulty understanding the information contained in the consent form will reread the misunderstood portion(s) of the consent and discuss with a research staff member until s/he shows complete understanding of the information and may thus give full consent. Research staff will work closely with the participant in an effort to help them understand the requirements of their participation. Persons with literacy problems will be assisted to the extent possible. Any participant who is unable to demonstrate understanding of the

information contained in the informed consent will be excluded from study participation and assisted in finding other sources of treatment. Persons who are excluded, or who decline participation, will be given referrals to other resources in the area.

After determining that the subject is eligible for the study, the study procedures will be reviewed with the subject again, the questionnaire will be given again, and if the subject understands the procedures, the subject will be asked to initial the informed consent form demonstrating their continued willingness to participate in the study.

14.5 DRUG ACCOUNTABILITY

Upon receipt, the investigator/pharmacist is responsible for taking inventory of the investigational agents(s). A record of this inventory must be kept and usage must be documented. The Sponsor, in collaboration with Cephalon Pharmaceuticals, will provide instructions to the sites about disposition of any unused or expired investigational agent(s).

14.6 OUTSIDE MONITORING

Data and Safety Monitoring Board (DSMB): Safety data will be reviewed by a DSMB, which will meet after approximately the first 70 subjects have completed or terminated from the study, or earlier if deemed necessary. Additional meetings will be held on an *ad hoc* basis. The board will be blinded to subjects' actual treatment assignments; however the Board may request that the data center break the blind if safety concerns arise from the blinded data.

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

Clinical Monitors: All investigators will allow NIDA or their representatives to periodically audit, at mutually convenient times during and after the study, all CRFs and corresponding source documents for each subject. These monitoring visits provide NIDA with the opportunity to evaluate the progress of the study and to inform NIDA of potential problems at the study sites. The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that investigational agents are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, monitor source documentation for primary outcome measure, review Serious Adverse Events and assure that all essential documentation required by good clinical practices guidelines are appropriately filed.Monitors will conduct a site initiation visit prior to the start of the study.

At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and good clinical practice's guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

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

14.7 ADVERSE EVENTS REPORTING

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the study investigators or study physicians according to the specific instructions detailed in this section of the protocol and Appendix III. The occurrence of AEs will be assessed at each visit, including screening/baseline visits, and an AE CRF completed weekly. The AEs assessed during the screening/baseline period will be analyzed separately from those obtained during the active clinical trial.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered related to the investigational agent or clinically significant. For this study, AEs will include events reported by the subject, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. All AEs must be recorded on the AE CRF. The AE CRF is also used to record follow-up information for unresolved events reported on previous visits.

Each week, a study investigator must review the AE CRF completed for the previous week for any events that were reported as continuing. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study investigators until satisfactory resolution. AEs should be reported up to 4 weeks following completion of or termination from treatment. At week 19 follow-up visit, AEs will be recorded and followed to resolution only if they are serious, or if the study physician assesses them to be clinically significant.

14.8 SERIOUS ADVERSE EVENTS

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

- results in death;

- is life-threatening; (NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)

- requires inpatient hospitalization or prolongation of existing hospitalization;

- results in persistent or significant disability/incapacity; or

- is a congenital anomaly/birth defect.

An unexpected event is one that is not described with respect to nature, severity, or frequency in the current Investigator's Brochure or product package insert.

Any SAEs due to any cause, that occur during the course of this investigation, whether or not related to the investigational agent, must be reported within 24-hours by telephone to: the NIDA Medical Monitor, the NIDA Study Director, and the sponsor- investigator. The telephone report is to be followed by submission of a completed SAE Form with demographic information and a narrative explanation of the event. Attached to the SAE Form should be photocopies of the AE Form, the Concomitant Medication Form, and the Medical History Form from the subject's CRFs. Any serious medical events are also to be reported to the responsible IRB according to local regulatory requirements. All participating investigators will be notified of any serious and unexpected AE requiring submission to the FDA in an IND safety report from the sponsor- investigator.

Any fatal or life-threatening SAE that is investigational agent related and unexpected must be reported by the sponsor-investigator 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-investigator of the SAE. All other SAEs will be reported in an annual report or more frequently as necessary. Any additional clinical information that is obtained must be reported to the FDA, as it becomes available in the form of an information amendment. The sponsor-investigator will inform NIDA within 24 hours of all SAEs that occur during the study.

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

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

15 ANALYTICAL PLAN

15.1 STATISTICAL HYPOTHESES

The primary objective of this randomized controlled trial is the assessment of the efficacy of tiagabine in reducing cocaine use in subjects with cocaine dependence (DSM-IV criteria). It is

hypothesized that tiagabine will increase the weekly mean proportion of non-use days relative to placebo as determined by self-report of cocaine use confirmed with urine assays for BE.

Secondary objectives include assessing the efficacy of tiagabine in increasing the overall proportion of cocaine non-use days (weeks 4 – 12 combined) and the proportion of subjects that achieve measured reductions in cocaine and other drug use (non-use days on treatment compared to non-use days at baseline), the reduction in the severity of cocaine dependence and craving (ASI-Lite and ASI-Lite Follow-up, BSCS, CCQ-NOW, CGI-S, and CGI-O), the effects of treatment in combination with HIV counseling in reducing HIV risk-taking behavior (HRBS), and the relative safety of tiagabine (AEs, laboratory data, HAM-D, physical exams, and vital signs) in the study population.

There is no generally accepted definition of clinically significant improvement in the treatment of cocaine dependency. The primary and secondary outcome variables are intended to explore various aspects of response to therapy and to help define a clinically meaningful response. The primary outcome has been chosen for its ability to indicate activity of the test product. Some of the secondary outcome variables add a measure of clinical relevance to the reduction of use by requiring either sustained abstinence or a predetermined, substantial overall reduction in use days. Other secondary outcome variables explore the need for laboratory confirmation of the self-report of use. Still others explore the effect of therapy on psychosocial aspects of cocaine dependency.

The primary outcome measure was selected based on a recommendation resulting from a meeting of the College on Problems of Drug Dependence (CPDD) on April 28 – 29, 1999. The consensus from this meeting was as follows:

"The consensus of the group was that the best overall outcome measure was a composite index of abstinence derived from a combination of confidential patients self-report and objective biological testing (typically urinalysis testing). The recommendation was that this composite index of abstinence be used to classify each day as abstinent or non-abstinent and that the primary outcome analysis be based on these classifications."

Some data will be collected in this study for scientific use and not as primary or secondary outcome measures. These include the CSSA, SFQ, and CSEQ.

15.2 OUTCOME MEASURES

15.2.1 Primary Outcome Measure

The primary outcome variable is the weekly proportion of cocaine non-use days. Cocaine use and non-use days will be defined by subject self-report of use, confirmed or disproved by quantification of urine BE. For the primary efficacy response, each day of weeks 4 through12 will be coded as either a use or a non-use day based on the self-reports and on the urine BE data. Three urine collection days are scheduled per calendar week. The last day of week 12 that the subject receives the investigational agent will not be scored as use or non-use days because of the scoring rules. Thus, each subject has a maximum of 62 days of use/non-use data over the nine weeks of level-dose treatment.

Because of the pharmacokinetics of cocaine and BE, carryover from previous cocaine use may be difficult to distinguish from new use. The rules enunciated by Preston *et al*. (1997 a,b) and modified to meet the conditions of this study (Rules 1-5 below) will facilitate classification of each assessment day as use or no-use.

The following will indicate "new use":

RULE 0: Subject reports new use.

The subject self report claims no new use but any of the following applies:

RULE 1: An increase in cocaine metabolite concentration over concentration of preceding urine specimen to any value over 300 ng/mL.

RULE 2: Both of the following occur: 1) cocaine metabolite concentration is greater than 300 ng/mL and 2) cocaine metabolite concentration is greater than one-half of the concentration measured in the preceding urine specimen.

RULE 3: Cocaine metabolite is greater than 300 ng/mL in the first urine specimen collected in the study.

RULE 4: If the previous urine specimen was collected more than 2 calendar days before, urine specimen with cocaine metabolite greater than 300 ng/mL.

RULE 5: Creatinine less than 20 mg/dL and cocaine metabolite/creatinine ratio is increased compared to that of previous specimen. (Cocaine metabolite does not have to be above 300 ng/mL).

Assessment days may be less than 48 hours but must be more than 24 hours apart in this study. For this reason, the Preston rules were modified to delete reference to previous urine specimen collected at least 48 hours earlier.

Self-report gives preliminary determination of each day as a use or non-use day. Non-use days are confirmed or disproved by the urine BE data as follows:

Subject reports no new use since last urine BE or within the preceding 72 hours (whichever is the shorter time frame) but urine BE shows new use, then score the preceding day as a use day.
Self report days of non-use will be considered as missing if not followed by a urine BE assessment within 7 days. In the case of obtaining urine within 7 days, data will also be considered as missing if the concordance rate between self report and urine BE for the individual is < 70 %. Self reports of use are accepted in all cases.

Percentage non-concordance between self-report of use and urine BE data will be calculated for each study subject as the percentage of the number of days that were scored as use days based on urine BE data overruling self-report (according to criteria in #1 immediately above) divided by the total number of urine samples analyzed, as follows:

% non-concordant = # non-concordant use days/total urine samples analyzed * 100%, thus

% concordant = 100 - % non-concordant.

The concordance rate of < 70% was established based on a survey of data sets from recently completed NIDA studies that showed that mean concordance rates ranged from 70-90%.

In addition, the primary outcome measure, the cocaine non-use day, was defined using an additional modification of the Preston rules as demonstrated in Appendix IV. This alternative primary outcome measure will be compared between treatment groups using the same methods as used for the main primary outcome measure but as a separate exploratory analysis.

15.2.2 Secondary Outcome Measures

Measured reductions in cocaine and other drug use

A. The proportion of successful subjects. A successful subject is one who reduces the overall proportion of cocaine use days to 75% or less of his/her baseline rate.

B. The proportion of successful subjects. A successful subject is one who reduces the overall proportion of cocaine use days to 50% or less of his/her baseline rate.

C. The proportion of successful subjects. A successful subject is one who reduces use days to 75% of his/her baseline level according to subject self report without regard to BE levels.

D. The proportion of successful subjects. A successful subject is one who achieves 3 consecutive weeks of abstinence – self report confirmed by urine BE.

E. Weekly proportion of non-use days according to subject self report without regard to BE levels.

F. Weekly proportion of non-use days of other drug use, by drug, according to self-report.

G. Proportion of negative urines for other drug use (the denominator is the total possible urines to be collected while the subject was on study, i.e., 12 if the subject completes treatment, 8 if the subject completed 8 weeks of treatment, etc.).

H. Weekly log of median urine BE.

I. Overall proportion of cocaine non-use days during the 9 week treatment period (weeks 4 through 12, non-use days divided by non-missing study days).

J. The maximum number of consecutive cocaine non-use days.

Reduction in the severity of cocaine dependence and craving

K. CGI-O scores.

L. CGI-S scores.

M. ASI-Lite scores.

N. BSCS scores.

O. Change in CCQ-NOW score over baseline.

Reduction in HIV Risk-taking Behavior

P. Change in HRBS scores since baseline.

Safety of Tiagabine

Q. AEs, laboratory data, HAM-D, physical exams, and vital signs.

15.3 INTENT-TO-TREAT AND EVALUABLE SUBJECT POPULATIONS

The intent-to-treat population is defined as the subjects who are randomized to treatment and who receive the first day's study agents. The evaluable population is defined as the subjects who are randomized and properly qualified to participate in the study in accordance with the inclusion and exclusion criteria, and who contribute at least six (6) usable on-study urine samples and 28 days of self report during the first four weeks of the treatment period, and who reach the full dose of study agent and do not receive adjusted doses of study agent during the first four weeks of the treatment period due to side effects.

15.4 ANALYSIS PLAN

15.4.1 Efficacy Assessments

Each primary and secondary efficacy outcome measure will be analyzed for the intent-to-treat and for the evaluable population. Major differences in the results, if any, will be further explored. While there is every intent to be complete in describing the analyses to be performed, it is not possible to anticipate every contingency and some adjustments may be required to meet constraints posed by the structure of the data.

It is hypothesized that tiagabine treatment, compared to placebo, will be associated with fewer days of cocaine use as assessed by self-report confirmed with urine assays for benzoylecgonine (BE). Therefore, statistical tests will be one-sided at a 5% Type I error rate. Confidence intervals will be one-sided with a 95% confidence coefficient.

Primary Efficacy Outcome

The primary outcome variable for each subject is the weekly proportion of cocaine non-use days during weeks 4 through 12. Each subject's weekly proportion is equal to the number of his/her cocaine non-use days divided by the number of his/her non-missing study days during that week. There is interest in attempting to estimate the actual number of cocaine "use" or "non-use" days by combining the self-reported patterns of use confirmed or disproved by the presence of urinary BE. For this outcome measure, each day of weeks 4 through 12 will be coded as either a use or non-use day based on the self-reports and on the urine BE data. Three urine collections are scheduled per calendar week. The last day of week 12 will not be scored as use or non-use days because of the scoring rules. Thus, each subject has a maximum of 62 days of use/non-use data over the nine (9) weeks of the level-dose treatment.

The weekly mean proportion of cocaine non-use days on study will be compared between treatment groups using Generalized Estimating Equations (GEE). GEE provide a model-based regression methodology applicable for the analysis of the correlated data that will result from this repeated measures longitudinal study. The GEE procedure proposed by (Liang and Zeger, 1986) and (Zeger and Liang, 1986) models the population average and has several useful features:

1. It can be used to analyze different types of outcomes such as continuous, binary, or count.

2. It can be used to analyze an unbalanced design caused by either differing numbers of observations per person or by observations taken at different times.

3. The parameter estimates are consistent even if assumptions about the variance structure are not completely accurate.

As a secondary analysis, prior use in the last 30 days before screening (≤ 18 and > 18 days of cocaine use), site, gender, and their first-order interactions with treatment will also be included in the model. Presentation will include the full model with all terms and a reduced model containing only significant terms.

Secondary Efficacy Outcomes

Unless the primary response analysis implies the need for a more elaborate model, between group comparisons of the secondary outcomes will be performed as follows:

1. Proportion of successful subjects (measures A, B, C, and D) will be assessed by Chi-square tests.

2. Weekly mean proportion of cocaine non-use days, other drug non-use days, and log of weekly median BE (measures E, F, and H), by GEE.

3. The proportion of negative urines for other drug use, and the proportion of cocaine non-use days on study (measures G and I) will be assessed by generalized linear model.

4. The maximum number of consecutive cocaine non-use days (measure J) will be assessed by Wilcox test.

5. The change in the CCQ-NOW and HRBS scores since baseline (measures O and P) will be assessed by t-test or appropriate non-parametric test.

6. Weekly CGI-O, CGI-S, BSCS scores and monthly ASI-Lite Follow-up scores (measures K, L, N, and M) will be assessed by GEE (the CGI-O, CGI-S, BSCS scores obtained on the first visit of treatment week 1 before study agent administration and ASI-Lite obtained at screening/baseline will be also included in the baseline mean score calculations).

7. Adverse events, laboratory data, physical exams, and vital signs will be reported in tabular form. AEs will be listed indicating the frequency of each type of event by various demographic

characteristics such as gender, ethnicity, age, duration of addiction, other medical problems both related to and independent of the addiction, and combinations of these characteristics. The frequencies of adverse events by type will be compared between study arms using Chi-square analyses.

15.4.2 Descriptive Statistics

Summaries of the characteristics of the subject population in both treatment arms at baseline will be prepared for both the intent-to-treat and evaluable subjects. A summary will be prepared to show dropouts/retention over time in each treatment group and for *a priori* defined subgroups. The number of missing observations will be compared between treatments and for *a priori* defined subgroups. Weekly treatment compliance of each group will be summarized. All adverse events will be reported in tabular form indicating the frequency and severity of each type of event.

15.5 SAMPLE SIZE CALCULATION

Because there is little information to determine the effect of tiagabine on the study population (there were only 17 patients in the tiagabine group in the CREST-II study) and because urine BE level was the primary outcome measure in that study, no formal power analysis was performed.

The study sample size of 70 subjects in each treatment arm was selected based on other NIDA studies of substance abuse as a number that is sufficient to provide an estimate of treatment effect, which can then be used in planning a future, pivotal trial should it be warranted.

15.6 CONTROL OF BIAS

Stratified randomization will be performed to balance treatment arms with respect to study site, gender and historical self-report of cocaine use for the last 30 days at the time that informed consent is given (≥18 days of use and < 18 days of use). The randomization process will be performed by computer at the data coordinating center. The research pharmacist will be provided with the treatment assignments. Investigative staff and subjects will remain blind to treatment assignment. Study agents will be prepared in a matched configuration.

15.7 POST HOC ANALYSES

Data will be collected in this study for scientific use and not as primary or secondary outcome measures. Analyses of data from the CSSA, SFQ, and CSEQ are included in this category. This data are being collected to build a database that will help characterize the study population. Additional post hoc analysis may be performed to evaluate other confounding factors on outcomes such as patterns of cocaine use at baseline and after treatment.

16 DATA MANAGEMENT AND CASE REPORT FORMS (CRF)

Data management activities and statistical analytical support will be coordinated through the NIDA data coordinating center.

16.1 DATA COLLECTION

Data will be collected at the study sites onto source documents and then transferred onto Case Report Forms (CRFs), or directly onto CRFs where possible. The completed CRFs will be sent to the Data Coordinating Center. CRFs will be supplied by the NIDA Data Coordinating Center. CRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. CRFs should be completed according to the instructions in the study operations manual. The principal investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. The principal investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

16.2 DATA EDITING AND CONTROL

Data received at the NIDA data coordinating center will be reviewed. If incomplete or inaccurate data are found, a data clarification request will be forwarded to the clinical site for a response. The site will resolve data inconsistencies and errors prior to returning data to the data coordinating center. All corrections and changes to the data will be reviewed prior to being entered into the main study database. NIDA/DTR&D and the participating sites will receive reports at least monthly regarding the quality and quantity of data submitted to the data coordinating center.

The principal investigator agrees to routine data audits by the staff of the NIDA data coordinating center and by NIDA's programmatic staff. The study monitors will routinely visit the study site to assure that data submitted on the appropriate forms are in agreement with source documents. They will also verify that the investigational agents have been properly stored and accounted for, subject informed consent for study participation has been obtained and documented, all essential documents required by Good Clinical Practice regulations are on file, and sites are conducting the study according to the research protocol. Any inconsistencies will be resolved, and any changes to the data forms will be made using the data coordinating center procedures.

16.3 DATA ENTRY, PROCESSING AND ANALYSES

Data will be collected at the study sites onto source documents and then transferred onto CRFs, or directly onto CRFs where possible. When the study is completed and all data have been entered into the clinical database and the database has been checked by Quality Assurance and is locked, statistical analysis of the data will be performed by the Data Coordinating Center's statisticians in collaboration with NIDA statisticians, in accordance with the analytical plan section of this protocol. Periodically, during the investigation, data sets will be submitted to the NIDA DTR&D central data repository according to procedures specified in the study operations manual.

16.4 STUDY DOCUMENTATION AND RECORDS RETENTION

Study documentation includes all CRFs, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, NIDA-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, IRB correspondence and approved consent form and signed informed consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, patient/patient diaries, biopsy reports, ultrasound photographs, patient/patient progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

Government agency regulations and directives require that the investigator must retain all study documentation pertaining to the conduct of a clinical trial. These documents must be kept for a minimum of two years after discontinuation of the IND or 2 years after the approval of an NDA.

16.5 CONFIDENTIALITY

16.5.1 Confidentiality of Data

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

By signing this protocol the investigator affirms to NIDA that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

16.5.2 Confidentiality of Patient Records

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

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

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

17 PUBLICATIONS OF THE STUDY RESULTS

NIDA and the investigative group agree that clinical database will be made available to individual investigators to encourage other publications, either by a group or by an individual investigator provided that: manuscripts based on the use of tiagabine for the treatment for cocaine dependence may not be submitted for publication until the main findings of the study have been published. Review of manuscripts resulting from this study or from data generated during this study must occur

according to the NIDA DTR&D Publications Policy prior to submission for publication. Authorship shall be consistent with NIDA and DTR&D policies.

18 SIGNATURES

NIDA REPRESENTATIVES

Typed Name	Signature	Date
Ann Montgomery, R.N. Study Director	_____	_____
Roberta Kahn, M.D.. Study Medical Monitor	_____	_____
Jurij Mojsiak, M.S. Project Officer	_____	_____
Ahmed Elkashef, M.D. CMB Branch Chief	_____	_____

INVESTIGATOR (S)

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in section 14.7 of this protocol.

Typed Name	Signature	Date
Eugene Somoza, M.D., Ph.D. Principal Investigator	_____	_____
Maryann Afshar, M.D. Medical Monitor	_____	_____
R. Jeffery Goldsmith, M.D Subinvestigator	_____	_____
Judy Harrer, Ph.D Subinvestigator	_____	_____
Theresa Winhusen, Ph.D. Subinvestigator	_____	_____
Florence Coleman, M.D.	_____	_____

Subinvestigator

Domenic Ciraulo, M.D.__ _____ _____
Subinvestigator

John Grabowski, Ph.D_ _____ _____
Subinvestigator

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APPENDIX I: CRITERIA FOR IDENTIFYING LABORATORY VALUES AS CLINICALLY SIGNIFICANTLY OUTSIDE NORMAL LIMITS

Analyte	Abnormal Values	
Fasting Glucose (mg/dL)	<40	>140
Non-fasting Glucose (mg/dL)		>200
AST (SGOT)	> 3X ULN*	
ALT (SGPT)	> 3X ULN	
Alkaline Phosphatase	> 3X ULN	
Lactate Dehydrogenase	> 3X ULN	
Gamma Glutamyltranspeptidase	> 3X ULN	
Creatinine (mg/dL)	>1.7	
Bilirubin (total) (mg/dL)	>1.5	
Hemoglobin (g/dL)		
Male	<11.0	
Female	< 9.5	
Red Blood Cells (mill/mm^3)	<3.5	
White Blood Cells (per mm^3)	<2,800	>16,000
Neutrophils (%)	<35	>80
Eosinophils (%)		>10
Basophils (%)		>5
Lymphocytes (%)	<10	>50
Monocytes (%)		>15
Platelet Count (per mm^3)	<75,000	>700,000

*ULN = upper limit of normal

APPENDIX II: HIV/AIDS EDUCATION

Education should be performed by trained staff and should include the following topics:

Modes of transmission
High risk behaviors
Prevention behaviors
stop drug use
don't share needles
clean "works" before using
use of condoms

HIV Testing
What test is for
Confidential *versus* anonymous
Optional
What +/- test results mean
Anxiety related to waiting for results

Demonstration of:
Use of alcohol swipes
Use of bleach kits

Subject wishes to be tested?
If yes, talk through the consent
Obtain signature
Offer outside referrals

APPENDIX III: INSTRUCTIONS FOR EVALUATING AND REPORTING ADVERSE EVENTS

A. GENERAL INSTRUCTIONS

Adverse Events (AEs) will be assessed and recorded starting from the time the informed consent is signed, at each study visit by study staff. A study physician must meet with each subject once a week to assess all medical and psychiatric AEs since the previous physician evaluation, including those recorded by other study staff.

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

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

B. DEFINITIONS – SEVERITY OF EVENTS

Mild:	Awareness of symptom, but easily tolerated.
Moderate:	Discomfort enough to cause interference with usual activity.
Severe:	Incapacitating with inability to work or do usual activity.

C. DEFINITIONS – RELATEDNESS OF EVENTS

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

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

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

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

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

Response to discontinuation of the study drug/placebo.

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

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

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

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

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

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

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

D. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

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

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

E. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24 hour Reporting Requirements

Any serious adverse event, including death due to any cause, which occurs to any subject from the time of admission through discharge whether or not related to the study drug/placebo, must be

reported ***within 24 hours*** to the NIDA Medical Monitor, the NIDA Project Officer, and the principal investigator (IND sponsor).

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

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

3-day Supporting Documentation Requirements

Written documentation for all SAEs/unexpected AEs must be received by the NIDA Medical Monitor/Alternate and the IND sponsor within 3 days of reporting the event. Required documents that must be submitted include the following:

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

Follow-Up of All Adverse Events/Serious Adverse Events

All adverse medical events must be followed until they are resolved, or until all attempts to determine the resolution of the AE/SAE are exhausted. This may require an extended inpatient period or a change in status from outpatient to inpatient. All treatments, outcomes and information regarding whether or not the subject was referred to their Primary Care Provider for additional follow-up must be recorded in the source document. All serious and unexpected adverse events occurring 30 days after administration of the last dose of study drug/placebo must be reported. All follow-up week 19 AEs will be recorded and followed to resolution only if they are serious, or if the study physician assesses them to be clinically significant.

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

Reporting to the FDA

The principal investigator, who is the IND sponsor, is required to report SAEs to the FDA:

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

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

- in an annual report in all other cases.

APPENDIX IV: ALTERNATIVE DEFINITION OF PRIMARY OUTCOME MEASURE FOR EXPLORATORY ANALYSIS

Primary Outcome Measure

The primary outcome variable is the weekly proportion of cocaine non-use days. As defined in section 3 (Efficacy Assessments), a subject's weekly proportion is equal to the number of his/her cocaine non-use days divided by the number of his/her non-missing study days during that week. Cocaine use and non-use days will be defined by subject self-report of use, confirmed or disproved by quantification of urine BE. For the primary efficacy response, each day of weeks 4 through12 will be coded as either a use or a non-use day (or as an unknown day) based on the self-reports and on the urine BE data. Three urine collection days are scheduled per calendar week. The last day of week 12 that the subject receives the investigational agent will not be scored as use or non-use day because of the scoring rules. Thus, each subject has a maximum of 62 days of use/non-use data over the nine weeks of level-dose treatment.

Because of the pharmacokinetics of cocaine and BE, carryover from previous cocaine use may be difficult to distinguish from new use. The rules enunciated by Preston *et al*. (1997) and modified to meet the conditions of this study (Rules 1-5 below) will facilitate classification of each assessment day as use or no-use.

The following will indicate "new use":

RULE 0: Subject reports new use.

The subject self report claims no new use but any of the following applies:

RULE 1: An increase in cocaine metabolite concentration over concentration of preceding urine specimen to any value over 300 ng/mL.

RULE 2: Both of the following occur: 1) cocaine metabolite concentration is greater than 300 ng/mL and 2) cocaine metabolite concentration is greater than 1/N of the concentration measured in the preceding urine specimen, where N depends as follows on the number of days that have elapsed since the last specimen.

Number of Days Elapsed	N
1	2
2	4
3	8

Note that this is a revision of RULE 2 as it is found in Section 15.2.1 of this document.

RULE 3: Cocaine metabolite is greater than 300 ng/mL in the first urine specimen collected in the study.

RULE 4: This version of this rule as it is found in Section 15.2.1 of this document has been superseded by RULE 2 above.

RULE 5: Creatinine less than 20 mg/dl and cocaine metabolite/creatinine ratio is increased compared to that of previous specimen. (Cocaine metabolite does not have to be above 300 ng/mL).

Cocaine use for each day is determined via two mechanisms. The first is self-report; the second utilizes urine BE levels as described below. Any day for which one or both of the two mechanisms indicates use is considered to be a use day. Any day for which both of the two mechanisms indicate non-use is considered to be a non-use day. Any day for which both mechanisms indicate that use is unknown, or one indicates unknown and one indicates non-use, is considered to be an unknown day. This algorithm is summarized in the following table:

		Self Report of Use		
		Use	Non-Use	Unknown
Urine BE Levels	Use	Use	Use	Use
	Non-Use	Use	Non-Use	Unknown
	Unknown	Use	Unknown	Unknown

BE levels from urine collected on a given day are used to determine the use/non-use/unknown status for any previous days for which a status has not already been determined via BE level results. A BE-based status value is determined as follows:

If all of the appropriate rules (excluding Rule 0, which is only used for self report) indicate that no new use has occurred, mark up to three previous days (those not already marked) as Non-Use. Mark any still-unmarked previous days (more than three days ago) as Unknown.
If any appropriate rule (excluding Rule 0) indicates that a new use has occurred, mark the previous day as a Use day, and mark any other previous days for which a BE status has not been entered as Unknown.

Percentage non-concordance between self-report of use and urine BE data will be calculated for each study subject as the percentage of the number of days that were scored as use days based on urine BE data overruling self-report (according to criteria in (2) immediately above) divided by the total number of urine samples analyzed, as follows:

% non-concordant = # non-concordant use days/total urine samples analyzed * 100%, thus

% concordant = 100 - % non-concordant.

The false negative percentage will also be calculated as the number of days that were scored as use days based on self-report overruling urine BE data, divided by the total number of urine samples analyzed.

Examples of Scoring Use/Non-Use Days

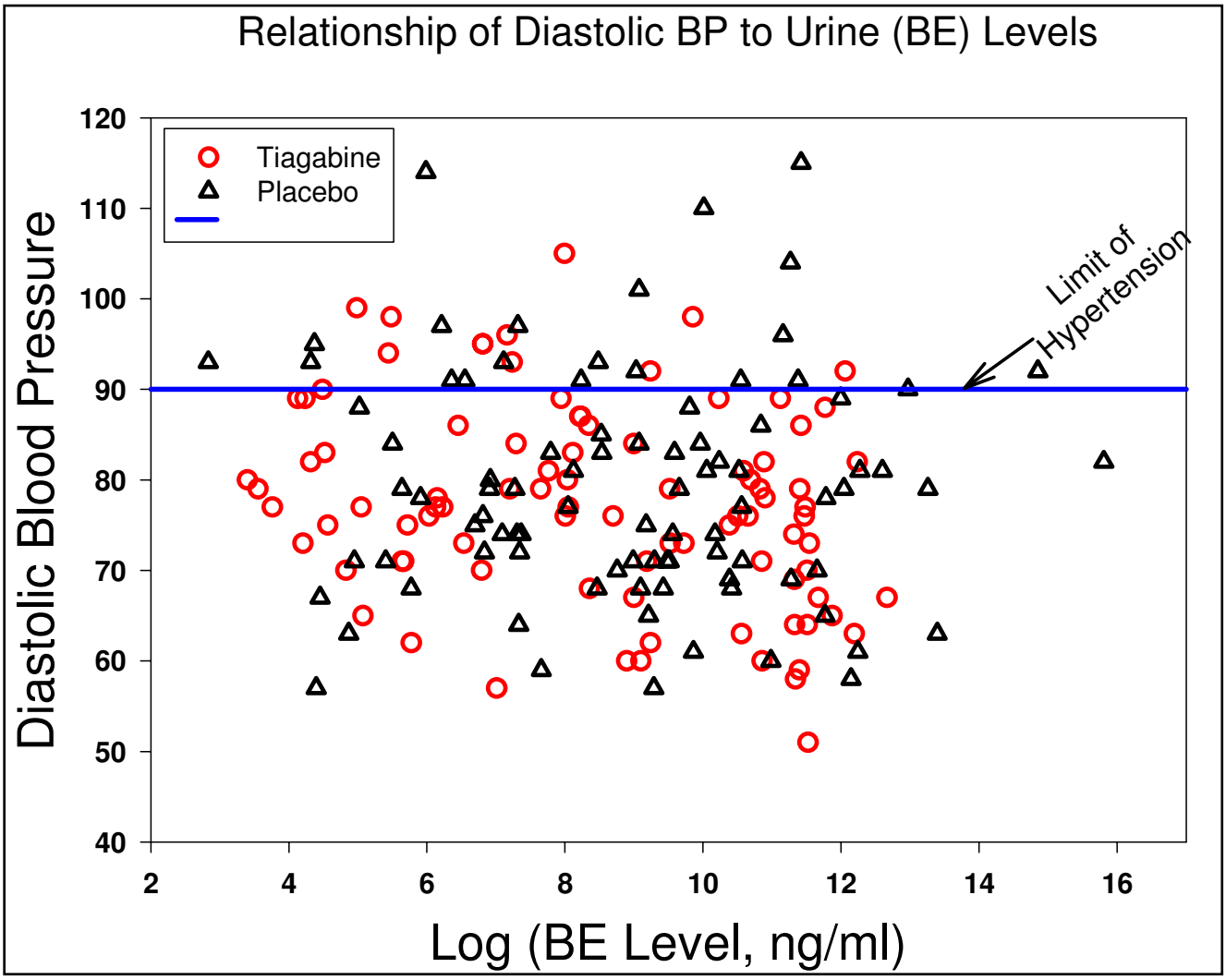
Example I: Subject reports no new use over 12 days, all urine BE data are available and two urine BE's suggest new use. Using the procedure described above, 2 use days are scored, 7 non-use days are scored, and 3 unknown days are scored.

Day	M	T	W	Thu	F	Sat	Sun	M	T	W	Thu	F
SUI	0	0	0	0	0	0	0	0	0	0	0	0
BE	0		1		0			0		0	1	
Score	U	1	0	0	0	0	0	0	0	1	U	U

0 = No use or no new use; 1 = use or new use, M = missing, U=unknown; SUI = self report of use; BE = urine BE results 0 = no new use, 1 = new use; Score = assignment of use or non-use day.

Example II: Subject reports no new use over 12 days; 8 days elapse between urine samples, and the next two urine samples after the missing samples show new use. Using the procedure described above, 2 use days are scored, and 10 Unknown days are scored.

Day	M	T	W	Thu	F	Sat	Sun	M	T	W	Thu	F
SUI	0	0	0	0	0	0	0	0	0	0	0	0
BE	0		M		M			M		1		1
Score	U	U	U	U	U	U	U	U	1	U	1	U


Relationship of Diastolic BP to Urine (BE) Levels
Diastolic Blood Pressure
120
110
100
90
80
70
60
50
40
2
4
6
8
10
12
14
16
Log (BE Level, ng/ml)
Tiagabine
Placebo
Limit of Hypertension

APPENDIX V: SAFETY OF TIAGABINE VERSUS PLACEBO IN THE PRESENCE OF COCAINE: DIASTOLIC BLOOD PRESSURE AND HEART RATE

All Instances of Diastolic Blood Pressure ≥90 mm Hg in Patients on Tiagabine

Name Code	Medication Group	Age	Sex	Race	Level*	Visit	Diastolic BP
DSTA	Tiagabine	42	Male	Afr-Am	S	2	94
DSTA	Tiagabine	42	Male	Afr-Am	S	3	94
DSTA	Tiagabine	42	Male	Afr-Am	S	5	95
FBAI	Tiagabine	42	Male	Afr-Am	E	1	98
JRI2	Tiagabine	29	Male	Afr-Am	S	3	97
JRI2	Tiagabine	29	Male	Afr-Am	S	4	94
JSTA	Tiagabine	37	Male	Afr-Am	T	1	105
LMCC	Tiagabine	30	Male	Afr-Am	S	5	113
LMCC	Tiagabine	30	Male	Afr-Am	E	8	94
LMCC	Tiagabine	30	Male	Afr-Am	T	2	109
MSMI	Tiagabine	36	Male	Afr-Am	S	1	97
MSMI	Tiagabine	36	Male	Afr-Am	S	5	93
MSMI	Tiagabine	36	Male	Afr-Am	E	9	92
PTAY	Tiagabine	59	Male	Afr-Am	S	1	108
PTAY	Tiagabine	59	Male	Afr-Am	S	2	110
PTAY	Tiagabine	59	Male	Afr-Am	S	4	98
PTAY	Tiagabine	59	Male	Afr-Am	S	5	93
PTAY	Tiagabine	59	Male	Afr-Am	S	6	112
PTAY	Tiagabine	59	Male	Afr-Am	E	7	96
PTAY	Tiagabine	59	Male	Afr-Am	E	11	92
PTAY	Tiagabine	59	Male	Afr-Am	E	13	98
PTAY	Tiagabine	59	Male	Afr-Am	E	16	99
PTAY	Tiagabine	59	Male	Afr-Am	E	19	95
PTAY	Tiagabine	59	Male	Afr-Am	E	19	95
PTAY	Tiagabine	59	Male	Afr-Am	E	19	95
PTAY	Tiagabine	59	Male	Afr-Am	E	19	95
PTAY	Tiagabine	59	Male	Afr-Am	E	23	93
PTAY	Tiagabine	59	Male	Afr-Am	T	2	94
RMAT	Tiagabine	41	Male	Afr-Am	S	5	92
RWI2	Tiagabine	31	Male	Afr-Am	S	1	101
RWI2	Tiagabine	31	Male	Afr-Am	S	3	96
RWI2	Tiagabine	31	Male	Afr-Am	E	7	92
SGAR	Tiagabine	43	Male	Afr-Am	E	19	94
SGAR	Tiagabine	43	Male	Afr-Am	E	22	105
VSIM	Tiagabine	34	Female	Afr-Am	S	1	97

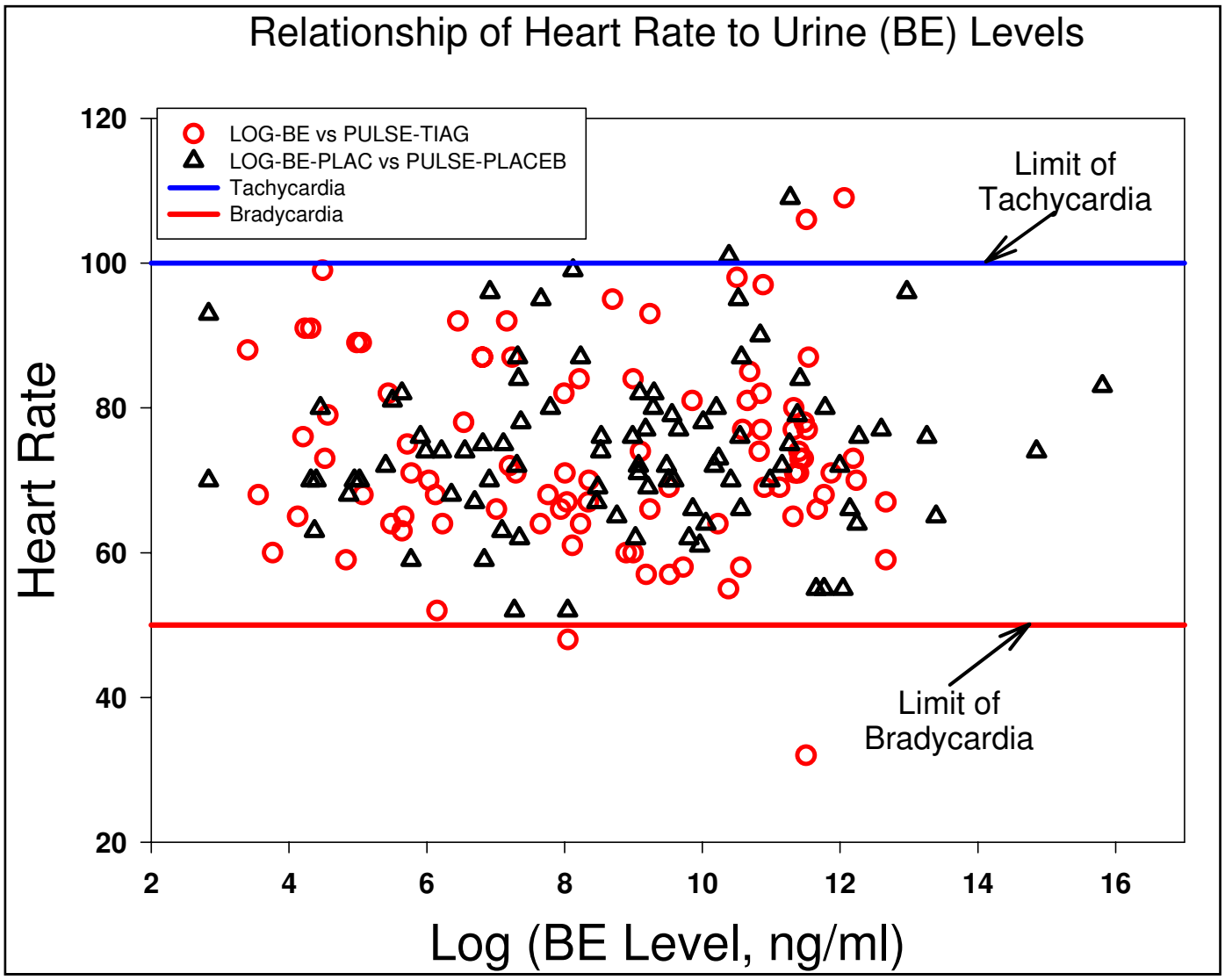
*Note: symbols for Level are S=Screening, E=Enrollment, T=Transition

Diastolic Hypertension - Placebo

Name	Medication	Age	Sex	Race	Level*	Visit	Diastolic

Code	Group						BP
DCLA	Placebo	42	Male	Afr-Am	S	3	92
DJON	Placebo	50	Male	Afr-Am	S	1	96
DJON	Placebo	50	Male	Afr-Am	S	2	103
DJON	Placebo	50	Male	Afr-Am	S	4	103
DJON	Placebo	50	Male	Afr-Am	S	5	97
DJON	Placebo	50	Male	Afr-Am	S	6	97
DJON	Placebo	50	Male	Afr-Am	E	7	92
DJON	Placebo	50	Male	Afr-Am	E	13	99
DJON	Placebo	50	Male	Afr-Am	E	16	95
DJON	Placebo	50	Male	Afr-Am	E	22	95
DKIN	Placebo	50	Female	Afr-Am	S	1	94
DKIN	Placebo	50	Female	Afr-Am	S	2	95
DKIN	Placebo	50	Female	Afr-Am	S	6	100
DKIN	Placebo	50	Female	Afr-Am	E	1	91
DKIN	Placebo	50	Female	Afr-Am	E	17	93
DKIN	Placebo	50	Female	Afr-Am	E	21	91
GFLO	Placebo	36	Male	Afr-Am	E	13	97
HDAV	Placebo	49	Female	Afr-Am	S	1	97
HDAV	Placebo	49	Female	Afr-Am	S	2	94
HDAV	Placebo	49	Female	Afr-Am	E	6	115
HDAV	Placebo	49	Female	Afr-Am	E	7	92
HDAV	Placebo	49	Female	Afr-Am	E	10	104
HDAV	Placebo	49	Female	Afr-Am	E	16	91
HDAV	Placebo	49	Female	Afr-Am	E	21	110
IYAR	Placebo	36	Male	Afr-Am	S	1	93
JGRE	Placebo	41	Male	Afr-Am	S	3	101
SJON	Placebo	44	Male	Afr-Am	S	1	106
SJON	Placebo	44	Male	Afr-Am	S	2	98
SJON	Placebo	44	Male	Afr-Am	S	3	96
SJON	Placebo	44	Male	Afr-Am	S	6	100
SJON	Placebo	44	Male	Afr-Am	E	1	91
SJON	Placebo	44	Male	Afr-Am	E	4	114
SJON	Placebo	44	Male	Afr-Am	E	7	101
SJON	Placebo	44	Male	Afr-Am	E	10	93
SJON	Placebo	44	Male	Afr-Am	E	13	93
SJON	Placebo	44	Male	Afr-Am	E	16	93
SJON	Placebo	44	Male	Afr-Am	E	22	96
SJON	Placebo	44	Male	Afr-Am	T	1	101
SJON	Placebo	44	Male	Afr-Am	T	2	101
SJON	Placebo	44	Male	Afr-Am	T	3	104
TPOW	Placebo	37	Male	Afr-Am	S	1	95
TPOW	Placebo	37	Male	Afr-Am	E	14	97
TPOW	Placebo	37	Male	Afr-Am	E	17	91

*Note: symbols for Level are S=Screening, E=Enrollment, T=Transition



TIAGABINE HEART RATE						PLACEBO HEART RATE				
NAME	**N**	**MAX HR**	**r**	**p-value**		**NAME**	**N**	**MAX HR**	**r**	**p-value**
ALL	90	109	-0.04	0.708		ALL	89	109	0.109	0.307
ADAV	7	97	0.0377	0.936		ACOO	5	109	0.253	0.682
DSTA	7	106	0.578	0.173		DCLA	6	76	0.099	0.852
HALL	7	77	0.413	0.358		DHXX	5	95	-0.204	0.742
JSTA	8	76	0.212	0.614		DKIN	5	79	0.621	0.263
LMCC	7	84	0.224	0.63		GFLO	8	82	0.273	0.513
MSMI	5	109	0.559	0.327		HDAV	8	96	0.037	0.931
MWIL	5	87	0.45	0.394		HMOS	8	72	0.104	0.806

PTAY	9	99	-0.567	0.111		IYAR	5	90	0.169	0.785
PTIP	8	78	0.142	0.737		OMCG	8	76	-0.172	0.683
RMAT	7	82	0.268	0.562		SJON	8	75	0.412	0.31
SGAR	5	91	-0.407	0.497		TPOW	8	99	-0.079	0.853
VSIM	6	81	0.492	0.322						
WGRE	4	78	-0.51	0.49						

Heart Rate - Tiagabine

Name Code	Medication Group	Age	Sex	Race	Level*	Visit	Heart Rate
DSTA	Tiagabine	42	Male	Afr-Am	E	13	106
EMUR	Tiagabine	44	Male	Afr-Am	S	2	43
EMUR	Tiagabine	44	Male	Afr-Am	S	3	45
EMUR	Tiagabine	44	Male	Afr-Am	E	2	57
EMUR	Tiagabine	44	Male	Afr-Am	E	5	55
HALL	Tiagabine	54	Male	Afr-Am	S	3	58
HALL	Tiagabine	54	Male	Afr-Am	E	1	57
HALL	Tiagabine	54	Male	Afr-Am	E	16	50
JRI2	Tiagabine	29	Male	Afr-Am	S	2	59
JRI2	Tiagabine	29	Male	Afr-Am	S	3	43
JRI2	Tiagabine	29	Male	Afr-Am	S	5	53
JSTA	Tiagabine	37	Male	Afr-Am	E	1	59
JSTA	Tiagabine	37	Male	Afr-Am	T	1	58
JSTA	Tiagabine	37	Male	Afr-Am	T	2	55
LMCC	Tiagabine	30	Male	Afr-Am	S	5	44
LMCC	Tiagabine	30	Male	Afr-Am	T	2	46
LMCC	Tiagabine	30	Male	Afr-Am	T	4	37
MSMI	Tiagabine	36	Male	Afr-Am	E	9	109
PTAY	Tiagabine	59	Male	Afr-Am	S	1	112
PTAY	Tiagabine	59	Male	Afr-Am	T	2	45
PTAY	Tiagabine	59	Male	Afr-Am	T	3	102
PTAY	Tiagabine	59	Male	Afr-Am	T	4	48
PTIP	Tiagabine	30	Female	Afr-Am	S	2	54
PTIP	Tiagabine	30	Female	Afr-Am	E	1	48
PTIP	Tiagabine	30	Female	Afr-Am	E	9	59
PTIP	Tiagabine	30	Female	Afr-Am	E	15	32
SGAR	Tiagabine	43	Male	Afr-Am	S	6	52
SGAR	Tiagabine	43	Male	Afr-Am	E	1	52
WGRE	Tiagabine	42	Male	Afr-Am	S	3	56
WGRE	Tiagabine	42	Male	Afr-Am	S	4	53
WGRE	Tiagabine	42	Male	Afr-Am	E	7	58

*Note: symbols for Level are S=Screening, E=Enrollment, T=Transition

Heart Rate - Placebo

Name Code	Medication Group	Age	Sex	Race	Level*	Visit	Heart Rate
ACOO	Placebo	42	Male	Afr-Am	E	10	101
ACOO	Placebo	42	Male	Afr-Am	E	17	109
DHXX	Placebo	37	Female	Afr-Am	S	2	32
DHXX	Placebo	37	Female	Afr-Am	S	5	101
DHXX	Placebo	37	Female	Afr-Am	T	2	107
DJON	Placebo	50	Male	Afr-Am	E	10	57
DREL	Placebo	42	Male	Afr-Am	S	3	108
DREL	Placebo	42	Male	Afr-Am	S	4	106
DREL	Placebo	42	Male	Afr-Am	S	6	101
GFLO	Placebo	36	Male	Afr-Am	S	2	56
HMOS	Placebo	44	Male	Afr-Am	S	1	50
HMOS	Placebo	44	Male	Afr-Am	S	3	58
HMOS	Placebo	44	Male	Afr-Am	S	4	59
HMOS	Placebo	44	Male	Afr-Am	E	22	52
JGRE	Placebo	41	Male	Afr-Am	S	5	59
OJOH	Placebo	33	Male	Afr-Am	S	1	50
OJOH	Placebo	33	Male	Afr-Am	S	2	56
OJOH	Placebo	33	Male	Afr-Am	S	3	54
OJOH	Placebo	33	Male	Afr-Am	S	4	57
OJOH	Placebo	33	Male	Afr-Am	S	6	53
OJOH	Placebo	33	Male	Afr-Am	E	6	59
OMCG	Placebo	43	Male	Afr-Am	S	1	54
OMCG	Placebo	43	Male	Afr-Am	S	6	58
OMCG	Placebo	43	Male	Afr-Am	E	1	55
OMCG	Placebo	43	Male	Afr-Am	E	6	55
OMCG	Placebo	43	Male	Afr-Am	E	8	55
OMCG	Placebo	43	Male	Afr-Am	E	10	59
OMCG	Placebo	43	Male	Afr-Am	E	13	52
OMCG	Placebo	43	Male	Afr-Am	T	1	41
OMCG	Placebo	43	Male	Afr-Am	T	2	59

*Note: symbols for Level are S=Screening, E=Enrollment, T=Transition

APPENDIX VI: CYP3A4 Interaction Information

Many drugs use CYP 3A4 as a metabolic pathway and it is impossible to study each and every interaction. A few important ones have been studied and they are listed in the package insert. Cimetidine 800 mg/day did not effect tiagabine levels. Tiagabine (low dose) did not effect prothrombin times when used in combination with warfarin and did not appear to effect oral contraceptive levels (no mention of what these drugs did to tiagabine plasma levels). There was some concern mentioned about use in combination with other sedating drugs like ethanol and benzodiazepines.

If an inhibitor of CYP3A4 (or a substrate--a drug that uses the same metabolic pathway) were given concomitantly with tiagabine, one might expect to see an increase in tiagabine plasma levels with the potential for an increase in the side effect profile. For example, Valproic acid is a substrate and can increase tiagabine plasma levels by as much as 40% (valproic acid is an excluded med for this study).

Enzyme inducers can increase the metabolism of tiagabine and thus may decrease plasma levels of tiagabine. There may not be any side effects of this, but the subject would essentially be getting less drug. Primidone, phenobarbital, phenytoin and carbamazepine are all enzyme inducers and can decrease plasma levels of tiagabine by as much as 60%. Most patients with epilepsy, the population in which tiagabine is most often used, are usually taking at least one enzyme inducing drug concomitantly with tiagabine. Our subjects in this study will not be on enzyme inducers.

Besides the epilepsy drugs that are listed as exclusionary in the protocol, (carbamazepine, phenytoin, phenobarbital, primidone, valproic acid, ketoconazole) there have been no documented contraindications between CYP 3A4 inducers/inhibitors and tiagabine.

Since this is a study where the goal is to look at the effects of a particular dose of tiagabine, it would be prudent to avoid the use of ANY drug that is an inhibitor, inducer or substrate of CYP 3A4. At the least, these drugs should be used with caution.

Documents are included in this appendix to assist the clinician in identifying inhibitors, inducers and substrates of CYP3A4: 1) a copy of the sortable Excel file which was provided to each site; 2) a chart of common medications by category; and 3) the Tiagabine package insert.

The Excel file is adapted from the Drug Information Handbook, 9th Edition 2001-2002, Lacy CF, Armstrong LL, Goldman, MP Lance LL eds. Lexi-comp's Clinical Reference Library, APhA Press. This Excel file is provided just as a guideline; it does not separate out drugs as inducers, substrates or inhibitors. In using this list, clinicians can sort by drug indication and then by deduction choose a drug that is not on the list. Or if a patient reports being on a listed drug, the clinician can sort by drug name and perhaps discontinue the drug if it is not absolutely necessary. The drugs listed in **bold italics** in the Excel file are those that are more likely to interfere with the enzyme and thus be more likely to cause a drug interaction, even though there has been no documented interaction with tiagabine; the bolded drugs should probably (but not necessarily) be avoided.

Unfortunately, CYP 3A4 is the most common metabolic pathway, as suggested by this exhaustive list of drugs. Apart from looking up each individual drug and making a determination whether or not it should be listed, all are listed. Few drugs have specifically been tested in vitro or in vivo for drug interactions with tiagabine itself.

The chart of common medications by category is provided just to assist in identifying some common drugs as inhibitors, inducers or substrates. No drugs are bolded in the printed list.

APPENDIX VI: inducers, inhibitors and substrates of CYP3a4

Inhibitors of CYP3A4

	Acitretin		Methylprednisolone
	Amiodarone		Mibefradil
	Cimetidine		Miconazole (Monistat)
	Ciprofloxacin		Mifepristone
	Clarithromycin (Biaxin)		Nefazodone (Serzone)
	Cyclosporine		Nelfinavir (Viracept)
	Danazol		Nicardipine
	Delavirdine		Nifedipine
	Diltiazem		Norethindrone
	Diethyl-dithiocarbamate		Norfloxacin
	Efavirenz		Norfluoxetine
	Erythromycin		Omeprazole (Prilosec)
	Ethinyl estradiol		Oxiconazole
	Fluconazole (Diflucan)		Paroxetine (Paxil)
	Fluoxetine (Prozac)		Prednisone
	Fluvoxamine (Luvox)		Quinine
	Gestodene		Ritonavir (Norvir)
	Grapefruit juice		Roxithromycin
	Grepafloxacin		Saquinavir (Fortovase, Invirase)
	Indinavir (Crixivan)		Sertraline (Zoloft)
	Isoniazid		Troleandomycin
	Itraconazole (Sporanox)		Verapamil
	Ketoconazole (Nizoral)		Zafirlukast
	Metronidazole (Flagyl)		Zileuton (Zyflo)

Inducers of CYP3A4

	Barbiturates		Primidone (Mysoline)
	Carbamazepine (Tegretol)		Rifabutin (Mycobutin)
	Ethosuximide (Zarontin)		Rifampin (Rifadin)
	Nelfinavir (Viracept)		Troglitazone (Rezulin)
	Phenobarbitol		
	Phenytoin (Dilantin)		

Substrates of CYP3A4

	Amitriptyline		Venlafaxine
	Fluoxetine		Diazepam
	Nefazodone		Alprazolam
	Paroxetine		Zolpidem
	Sertraline		Rifapin
	Trazodone		Buspirone
	Ondansetron		Sildenafil
	Ciprofloxacin		Tramadol

Generic name	Brand name	Drug Class	Usual indication
Acetaminophen	Tylenol		Analgesic
Alfentanil		Opioid agonist	Analgesic--anesthesia
Alprazolam	Xanax	Benzodiazepine	anxiety
Amiodarone	Cordarone	antiarrythmic agent	abnormal heart rythmn
Amitriptyline	Elavil	Antidepressant-tricyclic	depression/pain
Amlodipine		Calcium channel blocker	blood pressure
Amoxapine			
Amprenavir	Agenerase	antiretroviral-protease inhibitor	HIV/AIDS
Anastrozole	Arimidex	antineoplastic agent	Cancer-breast
Atorvastatin	Lipitor	antilipemic agent	Cholesterol
Azithromycin	Zithromax	Antibiotic	infection
Bepridil	Vascor	Calcium channel blocker	Angina
Bexarotene	Targretin	Vit. A derivative	cancer-lymphoma
Bromocriptine	Parlodel	Anti-Parkinson's agent	Parkinson's Disease
Bupropion	Wellbutrin/Zyban	Antidepressant	Depression/smoking cessation
Buspirone	BuSpar	Antianxiety agent	anxiety
Busulfan	Myleran	antineoplastic agent	cancer-leukemia
Caffeine		CNS stimulant	
Cannabinoids			
carbamazepine	Tegretol	Anticonvulsant	seizures/pain/bipolar disorder
Cerivastatin	Baycol	antilipemic agent	Cholesterol
Cevimeline	Evoxac	Cholinergic Agent	Alzheimer's disease/dry mouth
chlordiazepoxide	Librium	Benzodiazepine	anxiety/ETOH withdrawal
Chlorpromazine	Thorazine	Antipsychotic	psychosis/hiccups
Cilostazol	Pletal	Platelet aggregation inhibitor	Periperal vascular disease
Cimetidine	Tagamet	Histamine H2 blocker	stomach acid
Cisapride	*Propulsid*	*Cholinergic agent*	*stomach acid*
Citalopram	Celexa	Antidepressant-SSRI	Depression
Clarithromycin	Biaxin	Antibiotic	Infection
Clindamycin	Cleocin	Antibiotic	Infection
Clofibrate	Atromid-S	antilipemic agent	Cholesterol
Clomipramine	Anafranil	Antidepressant-tricyclic	Depresseion/OCD/panic attacks
Clonazepam	Klonopin	Benzodiazepine	seizures/anxiety
Clorazepate	Tranxene	Benzodiazepine	anxiety/ETOH withdrawal
Clozapine	Clozaril	Antipsychotic	schizophrenia
Cocaine			
Codeine		Opioid agonist	analgesic/cough suppressant
Cortisone		Steroid	anti-inflammatory
cyclobenzaprine	Flexeril	muscle relaxant	musle spasm
cyclophosphamide	Cytoxan	antineoplastic agent	cancer-
Cyclosporine	Sandimmune	Immunosuppressant	organ transplants/rheumatoid arthritis
Danazol	Danocrine	steroid-androgen	endometriosis
Dapsone		Antibiotic	Leprosy/mycobacterium
Delavirdine	Rescriptor	antiretroviral-NNRTI	HIV/AIDS
dexamethasone		steroid	anti-inflammatory/antiemetic
dextromethorphan	Robitussin-DM	cough suppressant	cough
Diazepam	Valium	Benzodiazepine	anxiety/muscle relaxer
Digitoxin		cardiac glycoside	Congestive heart failure

Drug

Diltiazem	Cardizem	Calcium channel blocker	hypertension/angina
Disopyramide	Norpace	antiarrythmic agent	abnormal heart rythmn
docetaxel	Taxotere	antineoplastic agent	Cancer-breast
dofetilide	Tikosyn	antiarrythmic agent	abnormal heart rythmn
dolasetron	Anzemet	antiemetic-serotonin antagonist	nausea/vomiting
donepezil	Aricept	Cholinergic Agent	Alzheimer's disease
doxorubicin	Adriamycin	antineoplastic agent	cancer-leukemia
doxycycline	Vibramycin	Antibiotic	Infection
dronabinol	Marinol	THC	nausea/vomiting
enalapril	Vasotec	ACE-inhibitor	Hypertension/CHF
erythromycin		Antibiotic	Infection
ethinyl estradiol		estrogen	replacement/prostate CA
ethosuximide	Zarontin	Anticonvulsant	seizure disorder
etoposide	VePesid	antineoplastic agent	cancer
examestane	Aromasin	antineoplastic agent	Cancer-breast
felodipine	Plendil	Calcium channel blocker	antihypertensive
fentanyl	Duragesic	Opioid agonist	analgesic
fexofenadine	Allegra	antihistamine	allergy
finasteride	Proscar/Propecia	antiandrogen	benign prostatic hyperplasia/male patter
fluconazole	Diflucan	antifungal	fungal infection
fluoxetine	Prosac/Sarafem	Antidepressant-SSRI	depression/PMS
flutamide	Eulexin	antiandrogen	cancer-prostate
fluvoxamine	Luvox	antidepressant-SRI	depression/OCD/panic
gemfibrozil	Lopid	antilipemic agent	cholesterol-hypertriglyceridemia
glyburide	DiaBeta/Micronase	hypoglycemic agents	diabetes
granisetron	Kytril	antiemetic-serotonin antagonist	nausea/vomiting
grapefruit/grapefruit juice			
griseofulvin		antifungal	fungal infection
haloperidol	Haldol	Antipsychotic	psychosis/agitation
hydrocortisone		Steroid	anti-inflammatory
Ifosfamide	Ifex	antineoplastic agent	cancer
imipramine	Tofranil	Antidepressant-tricyclic	depression/pain
indinavir	Crixivan	antiretroviral-protease inhibitor	HIV/AIDS
isoniazid		antitubercular agent	TB infection
isradipine	DynaCirc	Calcium channel blocker	hypertension/migraines
itraconazole	Sporanox	antifungal	fungal infection
ketoconazole	Nizoral	antifungal	fungal infection
lansoprazole	Prevacid	Proton pump inhibitor	stomach acid/GERD
loratadine	Claritin	antihistamine	allergy
lovastatin	Mevacor	antilipemic agent	cholesterol
methadone		Opioid agonist	analgesic
metronidazole	Flagyl	antibiotic	infection
midazolam	Versed	Benzodiazepine	preoperative sedation
mifepristone	Mifeprex	hormone antagonist	abortifacient
modafinil	Provigil	CNS stimulant	ADHD/fatigue
montelukast	Singulair	Leukotriene receptor antagonist	asthma
nafcillin		Antibiotic	Infection
nefazodone	Serzone	antidepressant	depression
nelfinavir	Viracept	antiretroviral-protease inhibitor	HIV/AIDS
nevirapine	Viramune	antiretroviral-NNRTI	HIV/AIDS

nevirapine	Viramune	antiretroviral-NNRTI	HIV/AIDS
Nicardipine	Cardene	Calcium channel blocker	Antihypertensive/angina
nifedipine	Procardia/Adalat	Calcium channel blocker	Antihypertensive/angina
nimodipine	Nimotop	Calcium channel blocker	brain hemorrage
nisoldipine	Sular	Calcium channel blocker	hypertension
norfloxacin	Noroxin	Antibiotic	infection
omeprazole	Prilosec	Proton pump inhibitor	stomach acid/GERD
ondansetron	Zofran	antiemetic-serotonin antagonist	nausea/vomiting
oral contraceptives-estrogen			
orphenadrine	Norflex	muscle relaxant	musle spasm
oxcarbazepine	Trileptal	Anticonvulsant	seizures
paclitaxel	Taxol	antineoplastic agent	Cancer-breast
pantoprazole	Protonix	Proton pump inhibitor	stomach acid/GERD
paroxetine	Paxil	antidepressant-SRI	depression/OCD/panic/anxiety
phenobarbital	Luminal	barbiturate	seizures
phenytoin	Dilantin	Anticonvulsant	seizures
pimozide	Orap	Antipsychotic	Tourette's disorder
pioglitazone	Actos	hypoglycemic agents	diabetes
pravastatin	Pravachol	antilipemic agent	Cholesterol
prednisone		Steroid	many conditions
primidone	Mysoline	Barbiturate	seizures
progesterone		steroid-progestin	contraception/endometriosis
propoxyphene	Darvon/Darvocet-N	Opioid agonist	analgesic
quetiapine	Seroquel	Antipsychotic	schizophrenia
quinidine		antiarrythmic agent	abnormal heart rythmn
quinine/tonic water		antimalarial	leg cramps
ranitidine	Zantac	Histamine H2 blocker	stomach acid/GERD
repaglininde	Prandin	hypoglycemic agents	diabetes
rifabutin	Mycobutin	Antibiotic	infection-mycobacterium
rifampin	Rifadin	Antibiotic	TB infections
rifapentine	Priftin	Antitubercular agent	TB infections
risperidone	Risperdal	Antipsychotic	schizophrenia
ritonavir	Norvir	antiretroviral-protease inhibitor	HIV/AIDS
rofecoxib	Vioxx	NSAID-Cox-2 inhibitor	analgesic
saquinavir	Invirase	antiretroviral-protease inhibitor	HIV/AIDS
sertraline	Zolf	Antidepressant-SSRI	depression/PTSD
sibutramine	Meridia	anorexiant	obesity/weight loss
sildenafil	Viagra	PDE inhibitor	erectile disfunction
simvastatin	Zocor	antilipemic agent	cholesterol
St.John's wort		Herbal	depression/mood
sufentanil	Sufenta	general anesthetic	anesthesia
sulfinpyrazone	Anturane	Uricosuric agent	gout
tamoxifen	Nolvadex	antineoplastic agent	Cancer-breast
temazepam	Restoril	Benzodiazepine	sleep
testosterone		steroid-androgen	replacement/breast CA
theophylline		bronchodilator	asthma/chronic bronchitis
tiagabine	Gabitril	anticonvulsant	seizures
tolcapone	Tasmar	COMT inhibitor	Parkinson's disease
tolterodine	Detrol	anticholinergic agent	overactive bladder
trazodone	Desyrel	antidepressant	depression/sleep

tretinoin	Vesanoid	antineoplastic agent	cancer
triazolam	Halcion	Benzodiazepine	sleep
troleandomycin	Tao	Antibiotic	Infection
valproic acid	Depakene	anticonvulsant	seizures/mania/migraines
venlafaxine	Effexpr	antidepressant	depression
verapamil	Calan/Isoptin	Calcium channel blocker	angina/irregular heart rhythmn
warfarin	Coumadin	anticoagulant	embolism/thrombosis
yohimbine		alpha 2 antagonist	herbal--aphrodsiac
zaleplon	Sonata	hypnotic	sleep
zidovudine	Retrovir	antiretroviral-NRTI	HIV/AIDS
zileuton	Zyflow	lipoxygenase inhibitor	asthma
ziprazidone	Geodon	Antipsychotic	schizophrenia
zolpidem	Ambien	hypnotic	sleep
zonisamide	Zonegran	Anticonvulsant	seizures

A copy of the package insert, as contained in the study Operations Manual should follow these pages in the protocol Appendix VI.

APPENDIX VII: PROCEDURE FOR APPLYING FOR A CERTIFICATE OF CONFIDENTIALITY

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

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

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

Applying for a Certificate of Confidentiality

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

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

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

Accordingly, this special privacy protection can be granted only to research (i.e., a systematic investigation, designed to develop or contribute to generalizable knowledge). It is granted only when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives.

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

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

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

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

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

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

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

or

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

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

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

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