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AFQ056

Clinical Trial Protocol CAFQ056X2201

A randomized, subject and investigator blinded, placebo-controlled, parallel group study to investigate whether AFQ056 reduces cocaine use in patients diagnosed with Cocaine Use Disorder (CUD)

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct.

Note: The SOM does not form part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Chief Medical Office and Patient Safety (CMO & PS) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the SOM.

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List of abbreviations

AA	anonym alcoholic
ACR	albumin-creatinine ratio
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase

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BE	Benzoylecgonine
BID	twice a day
BMI	Body Mass Index
C-SSRS	Columbia Suicide Severity Rating Scale
CFR	U.S. Code of Federal Regulation

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CK	creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety
CNS	Central nervous system
CO_2	carbon dioxide
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSF	Clinical Service Formulation
CUD	Cocaine Use Disorder
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition.
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
eSource	Electronic Source
EtG	Ethyl Glucuronide
FDA	Food and Drug Administration

FXS	Fragile X Syndrome
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	hour
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
i.v.	intravenous
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	lactate dehydrogenase
LFT	Liver function test

mAIMS	modified Abnormal Involuntary Movement Scale
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MTD	maximum tolerated dose
p.o.	oral
PA	posteroanterior
PCR	protein-creatinine ratio
PD	pharmacodynamic(s)
PD-LID	Parkinson’s disease - L-dopa induced dyskensia
PIP	pediatric investigation plan
PK	pharmacokinetic(s)

PPND	pre- and post-natal development
PSD	Premature subject discontinuation
PT	prothrombin time
RBC	red blood cell(s)
RO	receptor occupation
SAE	serious adverse event
sCR	serum creatinine
SD	standard deviation
SOM	Site Operations Manual
SSRI	Selective serotonin reuptake inhibitors

SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TLFB	Timeline Follow-Back
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Pharmacokinetic definitions and symbols

Ae0-t	Amount of drug (or defined metabolite) excreted into the urine from time zero to time 't' where t is a defined time point after administration [mass units or % of dose]
AUC0-t	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUCinf	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume]
AUClast	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
AUCtau	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau [mass x time / volume]
AUCtau,ss	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau at steady state [mass x time / volume]
Cav,ss	The average steady state plasma (or serum or blood) concentration during multiple dosing
CL	The systemic (or total body) clearance from plasma (or serum or blood) following intravenous administration [volume / time]
CL/F	The apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration [volume / time]
CLr	The renal clearance from plasma (or serum or blood) [volume / time]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Cmax,ss	The observed maximum plasma (or serum or blood) concentration following drug administration at steady state [mass / volume]
Cmin,ss	The lowest plasma (or serum or blood) concentration observed during a dosing interval at steady state [mass / volume]
F	Bioavailability of a compound. Fabs is the absolute bioavailability, i.e. the fraction (or percentage) of the administered extravascular dose systemically available. Frel is the relative bioavailability, i.e. the bioavailability relative to a reference
MRT	Mean residence time determined as AUMCinf/AUCinf following intravenous administration [time]
Racc	The accumulation ratio
T1/2	The terminal elimination half-life [time]

T1/2,acc	The effective half-life based on drug accumulation at steady state [time]
Tmax	The time to reach the maximum concentration after drug administration [time]
Vss	The volume of distribution at steady state following intravenous administration [volume]
Vss/F	The apparent volume of distribution at steady state following extravascular administration [time]
Vz	The volume of distribution during the terminal elimination phase following intravenous administration [volume]
Vz/F	The apparent volume of distribution during the terminal elimination phase following extravascular administration [volume]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up) which applies across all arms of a study.
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance”
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest

Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Run in Failure	A subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject's medications or other intervention)
Screen Failure	A subject who is screened but is not treated or randomized
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

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Protocol summary

Protocol number	CAFQ056X2201
Full Title	A randomized, subject and investigator blinded, placebo-controlled, parallel group study to investigate whether AFQ056 reduces cocaine use in patients diagnosed with Cocaine Use Disorder (CUD).
Brief title	Study to investigate whether AFQ056 reduces cocaine use in patients diagnosed with Cocaine Use Disorder (CUD).
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Drug
Study type	Interventional
Purpose and rationale	The main purpose of this study is to evaluate whether AFQ056 can have a beneficial effect by reducing cocaine use in Cocaine Use Disorder (CUD) patients as assessed by Timeline Follow-Back (TLFB) cocaine self-report (TLFB, Sobell and Sobell 1996). Commercially Confidential Information
Primary Objective(s)	• To evaluate treatment effect of 98-day AFQ056 administration in reducing cocaine use.

Secondary Objectives	• To assess the effects of 98-day AFQ056 administration versus placebo on:
	  • other measures of cocaine use
	  • alcohol use
	• To assess the safety and tolerability of multiple bid oral doses of AFQ056.
	• To evaluate the pharmacokinetics of AFQ056.

Study design	This is a randomized, subject and investigator blinded, parallel group, placebo-controlled study. The total duration for each patient in the study is up to approximately 20-weeks including periods of: screening, baseline, treatment, observational follow-up and end of study. The entire study is to be run in outpatient setting.
Population	Male and female subjects, 18 to 65 years of age (inclusive) diagnosed with Cocaine Use Disorder according to DSM 5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Ed.).
Key Inclusion criteria	• Understand the study procedures and provide written informed consent before any assessment is performed. • Male and female subjects, 18 to 65 years of age (inclusive) and diagnosed with Cocaine Use Disorder according to DSM 5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Ed.). • Must use cocaine through snorting (intranasally) as primary route of administration. • Recent cocaine use confirmed by positive urine screen for 1 or more benzoylecgonine (BE). • Must be seeking treatment for cocaine dependence and have a desire to reduce or cease cocaine use.

Key Exclusion criteria	• Has current diagnosis of Substance Use Disorder (according to the DSM 5) on alcohol, cannabis or other stimulants, except cocaine. • Meets current or lifetime DSM 5 criteria for schizophrenia or any psychotic disorder, or organic mental disorder. Notes: Subjects diagnosed with other psychiatric disorders may be included at the discretion of the PI provided that the concurrent treatment for the comorbid psychiatric condition will not interfere with completion of the study or place the patient at heightened risk through participation in the trial. • Have current treatment for Substance Use Disorder (e.g.: disulfiram, acamprosate, methyl phenidate, modafinil, topiramate, immediate release dexamfetamine,or baclofen). • Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test • Have a history of any illness, condition, and use of medications that in the opinion of the investigator or designee might confound the results of the study or pose additional risk in administering the investigational agents to the subject or preclude successful completion of the study • Current or/and previous treatment with concomitant medications that are strong or moderate inducers/inhibitors of CYP3A4 (e.g., clarithromycin, ketoconazole, ritonavir, etc.) • History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result. • Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). • Score “yes” on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months, or “yes” on any item of the Suicidal Behavior section, except for the “Non-Suicidal Self-Injurious Behavior” (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years. • Controlled hypertension
Study treatment	• AFQ056 50 mg bid for 7 days followed by AFQ056 100 mg bid for next 7 days and then fixed dose of 200 mg bid for 84 days. • Placebo - matched for 98 days.
Pharmacokinetic assessments	• AFQ056 plasma concentrations (pre- and 3 h post-dose levels).
Key Efficacy/PD assessments	• Proportion of cocaine use days delivered from TLFB cocaine self-report. • Cocaine Benzoylecgonine (BE) as delivered from urinalysis. • Alcohol consumption as delivered from TLFB alcohol self-report.
Key safety assessments	Vital signs, ECG parameters, clinical safety laboratory parameters (chemistry/hematology/urinalysis), (serious) adverse events reporting, suicidal ideation (Columbia Suicide Severity Rating Scale (C-SSRS).
Other assessments	Commercially Confidential Information

	Commercially Confidential Information
Data analysis	**Primary variable:** a Bayesian analysis will be conducted on the proportion of cocaine use days. Commercially Confidential Information
Key words	*Cocaine Use Disorder; cocaine dependence*

1 Introduction

1.1 Background

Cocaine use in the United States is a significant public health concern, leading to loss of income, use of public services, and mortality. The results from the 2012 National Survey on Drug Use and Health (2013) shows that 1.6 million Americans aged 12 or older were current cocaine users (including crack cocaine), comprising 0.6% of the population. Despite this widespread use, there are currently no approved medications for the treatment of cocaine use disorder, therefore there is a high medical need.

AFQ056 (mavoglurant) is a structurally novel, subtype-selective, non-competitive antagonist at the mGlu5 receptors. It is an allosteric modulator, an emerging class of orally available small molecule therapeutic agents. Cocaine Use Disorder (CUD) is associated with dysregulated glutamate neurotransmission. Preclinical studies indicate that the modulation of glutamate signaling through the antagonism of the mGlu5 receptor can attenuate cocaine mediated drug induced behaviors such as drug seeking, self-administration and re-instatement (relapse) (Lee et al 2005).

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AFQ056 has been demonstrated to be generally safe and well tolerated in several Phase I and II/III studies in Fragile X Syndrome (FXS); Levodopa-induced dyskinesia in Parkinson's disease (PD-LID) and in Obsessive Compulsive Disorder (OCD). While the full development programs for FXS and PD-LID were discontinued due to lack of efficacy in these indications, the compound was found to have good tolerability and due to its mechanism of action, remains of high interest in other CNS disorders associated with excessive glutamatergic transmission.

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure.

1.2 Nonclinical data

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1.2.1 Teratogenicity and reproductive toxicity data

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1.2.2 Summary of non-clinical pharmacokinetics and metabolism

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1.2.3 Nonclinical abuse and dependence potential

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1.3 Clinical data

1.3.1 Human safety and tolerability data

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1.3.1.1 Abuse and dependence potential – human data

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1.3.2 Human pharmacokinetic data

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1.3.3 Human pharmacodynamics data

Efficacy in patients with PD-LID

The efficacy of AFQ056 in PD patients with LID was assessed in six patient studies, five using the IR formulation and one (CAFQ056A2223) using the MR formulation. Efficacy on LIDs, as measured by the mAIMs, was shown in three of the six studies as summarized below. Studies with similar designs are grouped.

Proof of Concept studies (CAFQ056A2203 and CAFQ056A2206): In a pooled analysis of the efficacy data for these two PoC studies , reduction of LIDs was observed using the mAIMS, UPDRS-Part IV, and the activities of daily living using the Lang- Fahn Scale Activities of Daily Living Dyskinesia Scale (LFADLDS). The difference in mean change from baseline to day 16 for AFQ056 treated patients vs placebo was -5.4 points (improvement) on the mAIMs total score (Berg et al 2011).

Dose finding study (CAFQ056A2208): The primary efficacy objective in study CAFQ056A2208 was to compare the antidyskinetic effect of five fixed doses of AFQ056 (10, 25, 50, 75, and 100 mg bid.) vs. placebo (Stocchi et al 2013). The primary analysis (mAIMS) showed statistical significance vs. placebo at the dose of AFQ056 100 mg bid. (p=0.007) and there was a trend for significant improvement in patients treated with AFQ056 at 25 mg bid. Analysis of the mAIMS by final actual dose of AFQ056 demonstrated a monotonic ascending dose-response relationship with highest change from baseline at the AFQ056 100 mg bid. dose. For the 100 mg bid dose, the adjusted change from baseline (standard error [SE]) was -5.7 (0.75) points and difference vs placebo was -2.8; Secondary assessments: the overall F-test for dyskinesia duration (item 32 of UPDRS part IV) was significant and pair-wise comparisons for dyskinesia duration were significant for the AFQ056 25 mg and 100 mg bid treatment groups vs. placebo. There were no statistically significant differences on any other secondary assessments including the Clinical Global Impression of Change (CGIC), Patient Global Impression of Change, patient diary or disability due to dyskinesia (26-Item Parkinson Disease Dyskinesia Scale).

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Efficacy in patients with Fragile X Syndrome

Study CAFQ056A2204 was a placebo controlled crossover study evaluating AFQ056 150 mg .i.d. (n=30). The primary efficacy variable (ABC-C) was assessed at Day 19. No beneficial effect of AFQ056 over placebo on ABC-C total score and sub scores was observed at Day 19.

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Study CAFQ056A2212 was a large double blind parallel group randomized controlled trial comparing three doses of AFQ056 (25, 50, and 100 mg bid.) to placebo in a total of 175 adult patients aged 18 to 45 years with FXS. The study population was stratified based on the extent of methylation of the FMR1 gene (methylation status). The primary objective was to assess the efficacy of the three doses of AFQ056 versus placebo in reducing the ABC-C Total score (using the FXS specific algorithm - ABC-CFX) after 12 weeks of treatment in FXS patients with FM FMR1 gene. The study was considered to have achieved its primary objective if at least one of the AFQ056 doses was statistically significantly better than placebo in FXS patients with FM FMR1 gene after adjustment for multiplicity. Of note, the baseline values of the efficacy variables were after 4 weeks of placebo run-in and an improvement in ABC-CFX is indicated by a lower post-baseline score. The LS mean changes from baseline were -11.4 for the placebo group, -14.3 for the AFQ056 25 mg bid treatment group, +1.8 for the AFQ056 50 mg bid treatment group, and -1.8 for the AFQ056 100 mg bid treatment group. Hence, the greatest improvement in ABC-CFX total score was seen in the AFQ056 25 mg bid treatment group. However, no statistical significance was reached in favor of any of the three AFQ056 treatment groups over placebo at the significance level with multiplicity adjustment. Even though the p-value of comparing AFQ056 50 mg bid to placebo reached statistical significance in favor of placebo, the positive change in ABC-CFX total score for the 50 mg bid. AFQ056 treatment group was small and should not be viewed as worsening of symptoms, especially since the final score for the AFQ056 50 mg bid dose group was lower than the mean score at Screening.

Study CAFQ056A2214 was a large double blind parallel group randomized controlled trial comparing three doses of AFQ056 (25, 50, and 100 mg bid.) to placebo in a total of 139 adolescent patients with FXS, aged 12 to 17 years inclusive. The study population stratification and study methodology were similar to those in the adult study (CAFQ056A2212). In FM patients, the LS mean changes from baseline were –9.4 for the placebo group, -11.8 for the AFQ056 25 mg bid treatment group, -3.4 for the AFQ056 50 mg bid treatment group, and +8.6 for the AFQ056 100 mg bid treatment group. Hence, the greatest improvement in ABC-CFX total score was seen in the placebo group. In comparing the AFQ056 100 mg bid to placebo on change from baseline at Week 12 for the ABC-CFX total score, a statistically significant difference was observed at the significance level of multiplicity adjustment in the FM stratum (p=0.004). However, it was not in favor of AFQ056 100 mg bid.

1.4 Study purpose

Background

Cocaine use has become the third most common reason (after opiate and cannabis use) for patients in Europe to enter drug abuse treatment. Currently, no pharmacological treatment of proven efficacy exists for cocaine addiction. AFQ056 is a mGlu5 receptor antagonist and has shown to reduce cocaine-seeking behavior in animal models.

Purpose

The main purpose of this study is to evaluate whether AFQ056 can have a beneficial effect by reducing cocaine use in Cocaine Use Disorder (CUD) patients as assessed by Timeline Follow-Back (TLFB) cocaine self-report (TLFB, Sobell and Sobell 1996), a validated and widely employed method in stimulant abuse trials.

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2 Objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	***Endpoints related to primary objective(s)***
• To evaluate treatment effect of 98-day AFQ056 administration in reducing cocaine use.	• Proportion of cocaine use days by TLFB cocaine self-report.

2.2 Secondary objective(s)

Secondary objective(s)	***Endpoints related to secondary objective(s)***
• To assess the effects of 98-day AFQ056 administration versus placebo on: a) other measures of cocaine use b) alcohol use	• a) Urinalysis (cocaine Benzoylecgonine (BE) b) TLFB alcohol self-report
• To assess the safety and tolerability of multiple bid oral doses of AFQ056.	• Vital signs, ECG parameters, clinical safety laboratory parameters (chemistry/hematology/urinalysis), (serious) adverse events reporting, suicidal ideation (Columbia Suicide Severity Rating Scale (C-SSRS).
• To evaluate the pharmacokinetics of AFQ056.	• AFQ056 plasma concentrations (pre- and post-dose levels).

2.3 Exploratory objective(s)

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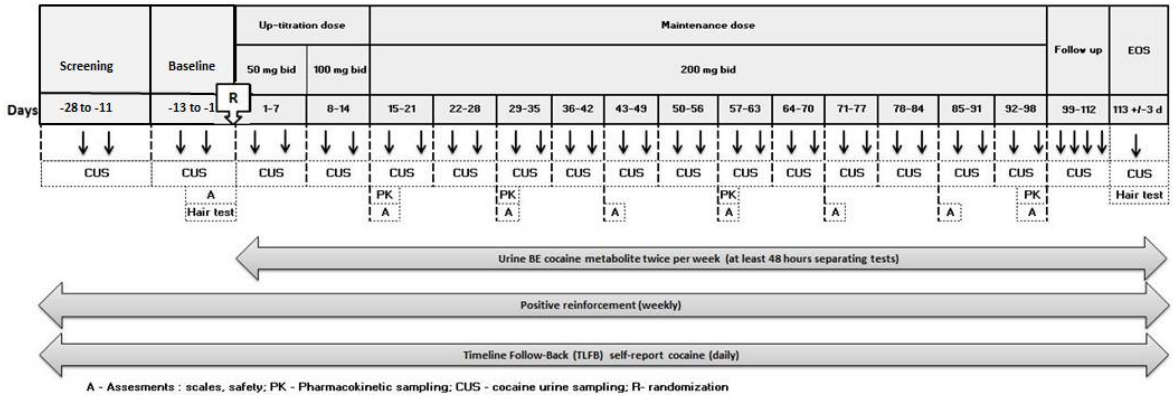
3 Investigational plan

3.1 Study design

This is a randomized, subject and investigator blinded, parallel group, placebo-controlled study in approximately 60 patients with CUD. The study consists of: about 17-day screening period followed by a 12-day baseline; a 98-day out-patient treatment period (14-day up-titration dose regimen followed by 84-day maintenance dose) and finally an end of study visit evaluation approximately 14-days after the last study drug administration. The total duration for each patient in the study is up to approximately 20-weeks including screening and baseline. The study design is summarized in Figure 3-1 below.

Figure 3-1 Study Design



Study visits: (days 1-113): study visits will be performed in an ambulatory setting of frequency twice per week. During these visits the urine samples will be collected for cocaine's metabolite benzoylecgonine (BE) and other illicit drug, as applicable, along with safety/efficacy assessments as specified in the Assessment schedule.

Screening (days -28 to -11): includes safety examinations and other clinical tests, determines patients' initial eligibility. Patients who meet the eligibility criteria at screening will be admitted to the baseline evaluation. For all examinations to be done at screening, refer to the Assessment schedule.

Baseline (days -13 to -1): includes, in addition to the safety evaluations, a patient's self-assessment on various scales and questionnaires (see Section 8.5.1). During baseline, a history of self-reported cocaine use (TLFB) and two urine samples collected on two different days with second sample collected 3 days prior randomization must demonstrate the abstinence

from cocaine use. For all examinations to be done at baseline, refer to the Assessment schedule.

Treatment (days 1-98): following baseline, on Day 1, approximately 60 eligible patients will be randomly assigned in a 1:1 ratio to either AFQ056 or placebo

- Group A - AFQ056: up-titration regimen for the first 2 weeks (14 days): 50 mg bid from Day 1 to Day 7 , 100 mg bid from Day 8 to Day 14 , followed by dosing at 200 mg bid for 84-days
- Group B: matching placebo.

Study drug: must be taken twice daily (bid) in the morning and evening (separated by approximately 12 hour intervals) with food. For all ambulatory morning visits that involve any study assessments or PK/urine sample collection, study medication will be self-administered by patient at study center and supervised by study personnel. On these days, standard breakfast should be served at study center and consumed by the patient during his/her medication intake.

During treatment period, patients will also undergo assessments with various scales and questionnaires, as well as safety assessments and pharmacokinetic sampling at pre- and 2 ± 1-hour post dose per SoA. For a detailed outline of all study assessments and time points refer to the Assessment schedule.

Urine samples (days1-113): samples will be collected at study center twice per week, with at least 48 hours separating tests. The sample collection will be assayed quantitatively for the presence of cocaine's metabolite (benzoylecgonine (BE), as well as, other illicit drugs may be assayed. It is expected that a total of approximately 33 urine samples will be collected during study conduct: 28 samples from patients who remain in treatment for the 14 weeks (total of 4 samples: weeks 1–2 of up-titrations); 24 samples in weeks 3–14 (maintenance dose); 4 samples in weeks 15–16 (follow up) and finally 1 last sample at end of study visit. If a patient fails to attend the clinic or refuses to provide a sample on a scheduled testing day, samples will be considered positive unless an excused absence is granted (e.g.. illness, other personal reason). In cases of missed or refused samples, samples should be collected on the next day whenever possible.

Clinical support to ensure medication and protocol's adherence:

- **Positive Reinforcement (PR):** on top of study treatment, all patients will receive weekly at site the Positive Reinforcement (PR) with the focus on patients' adherence to the medication and study procedures. Detailed description of PR techniques will be provided to the participating sites in a separate document.
- **Medication compliance:** patients will be at the study site at time of study drug administration for the morning dose on PK collection days and on all other days that involves urine sampling assessments. On these days study medication self-administration will be supervised by study personnel. It is recommended to the site personnel to check patient's mouth to ensure that the medication(s) has(ve) been swallowed. To monitor medication adherence, patients will be provided with individual Medication Diary (booklet) to record administration of study medication. Medication compliance will be monitored by the Investigator and/or study personnel at least on a weekly basis using tablet(s) counts. Dosage adherence will be verified by comparing the patient's Medication

Diary self-reported data against the total number of tablets in the returned bottle or blister (depends on the packaging form). Adherence will be calculated as the total amount of tablets taken divided by the scheduled total amount to be taken during the treatment phase. If the Investigator feels it is appropriate, the patient may also be contacted during the out-patient periods to confirm compliance.

3.2 Rationale of study design

The design of this trial has been selected to adequately assess the primary objective and follows the similar design of trials for substance use disorders (American Psychiatric Association (APA) Practice Guidelines, 2006). Furthermore, randomized subject and investigator blinded control design are considered as "validated method in stimulant abuse trials" and parallel treatment group design was selected due to the long duration of treatment.

The entire study treatment duration of 98 days will be conducted in an outpatient treatment setting, which is a commonly used setting in treatment of substance use disorders (UNODC-WHO, 2016) and appropriate for the purpose of this study. The outpatient setting in this study includes frequent visit schedule (twice/week) in conjunction with urine sample collection; weekly monitoring of medication and study assessment adherence and safety adverse event monitoring. As an outpatient setting may increase the likelihood of patients dropping out of treatment, weekly interventions of Positive Reinforcement techniques are introduced with the focus on patient's adherence to the protocol's procedures and medication compliance.

For primary objective, daily cocaine use will be determined using TLFB self-report, which is a "gold standard" for measurement of substance use (Robinson et al 2012). For secondary objective, cocaine use will be determined twice/week by urine drug screen

Commercially Confidential Information Frequency of urine sample collection was scheduled in accordance with the halflife of cocaine metabolites BE in urine (3-4 days).

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3.3 Rationale for dose/regimen, route of administration and duration of treatment

The dose selected (200 mg bid with modified release formulation) for evaluation in this study has been chosen based on the safety, tolerability of dose, regimen and pharmacokinetic data from completed healthy volunteers and patient studies including modeling and simulation of PK and RO profiles. A total of 2159 study subjects have been enrolled in a total of 42 completed human studies with AFQ056. Dosage of 200 mg bid have been shown to be safe and tolerable.

During clinical development, majority of the studies were conducted using immediate release (CSF, MF) capsule formulations for oral administration. Nevertheless, there were some challenges experienced with the immediate release formulation as most of the AFQ056-mediated AEs (dizziness, insomnia, and headache) appear to be peak plasma concentration dependent. As a result, a modified release (MR) formulation of AFQ056 has been developed

with the goal of reducing peak plasma concentrations while maintaining optimal exposure (i.e. reducing Cmax/AUC ratio).

The maximum anticipated therapeutic dose levels of AFQ056 are 150 mg bid. (CSF formulation – immediate release), 100 mg bid. (MF- IR formulation) or 200 mg bid. (MR formulation).

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In the proposed CUD study it is assumed that patients will have certain levels of cocaine when receiving AFQ056. Chronic cocaine administration has been reported to induce CYP3A4 in rodents (Pellinen et al 1996) and P-glycoprotein, an efflux transporter. AFQ056 is primarily eliminated via metabolism catalyzed by multiple CYP isoenzymes (incl. CYP1A1, 2C9, 2C19, 3A4) and possibly by UGT isoenzymes. Thus one cannot rule out that the AFQ056 levels may be altered (lowered) in subjects with long term cocaine use. Thus lowering of AFQ056 levels may affect efficacy rather than posing a safety risk.

Up-titration regimen: Data from three patients studies (CAFQ056A2203, CAFQ056A2206 and AFQ056A2225) indicated that the up-titration period will allow patients to adapt towards any side effects and thus have a better chance of tolerating the target dose of 200 mg bid..

3.4 Rationale for choice of comparator

As there are currently no approved medications for the treatment of Cocaine Use Disorder, placebo is the only relevant comparator to be used in this study. .

3.5 Rationale for choice of background therapy

Not applicable.

3.6 Purpose and timing of interim analyses/design adaptations

Due to the small sample size for this type of population, no IA planned for this trial.

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3.7 Risks and benefits

The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring. Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the Section 4.2 (Exclusion Criteria). If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

Sexually active males must be informed of the requirement to wear a condom for the following reasons:

- Prevent pregnancy in a female partner

AND

- Prevent delivery of investigational drug via seminal fluid to their partner as study treatment may involve unknown risks to the fetus if pregnancy were to occur

Although, AFQ056 has been tested in more than 2000 subjects, and it has been shown to be safe and well tolerated it may be unknown risk associated to AFQ056.The most frequent side effects of the study medicine include: headache, dizziness, initial insomnia, feeling drunk and euphoric mood. In addition visual hallucinations have been reported after single intakes of high doses of the study drug (3 to 4 times of the highest dose used in this study) and in chronic smokers. The different studies performed in healthy volunteers and patients showed that AFQ056 is well tolerated also when given over a period of several weeks.

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3.7.1 Blood sample volumes

A maximum of up to 500 mL of blood is planned to be collected over a period of 14 weeks of treatment, from each subject as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment schedule (Section 8.1).

A summary blood log is provided in the Site Operations Manual. Instructions for all sample collection, processing, storage and shipment information is also available in the Bioanalytics Study Specifications (BSS) and Central Laboratory Manual.

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3.7.2 Risks associated with study procedures

In this study the tests done at each visit are standard medical tests. The most unpleasant is often having blood samples taken. The risks of taking blood may include fainting, pain and/or bruising at the site of needle or canula insertion. Rarely, a small blood clot or infection could occur that would require treatment. at the site of the needle puncture. The blood pressure cuff may also cause discomfort or bruising to the upper arm. There is also a chance for redness or irritation of the skin where the sticky electrode patches are placed during the heart tracing test (electrocardiogram).

4 Population

CUD patients

A total of approximately 60 patients, aged of 18-65 inclusive with a diagnosis of CUD who use cocaine through snorting (intranasally) will be enrolled in the study.

The investigator must ensure that all subjects being considered for the study meet the following eligibility criteria(s). No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all eligibility criteria at screening and baseline. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a subject from enrollment into the study.

4.1 Inclusion criteria

CUD patients eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Understand the study procedures and provide written informed consent before any assessment is performed.
2. Male and female subjects, 18 to 65 years of age (inclusive) and diagnosed with Cocaine Use Disorder according to DSM 5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Ed.).
3. Must use cocaine through snorting (intranasally), as primary route of administration.

4. Recent cocaine use confirmed by positive urine screen for 1 or more benzoylecgonine (BE).
5. Must be seeking treatment for cocaine dependence and have a desire to reduce or cease cocaine use as per goals assessed at baseline.
6. Must be abstinent from cocaine use for at least 3 days preceding 1st dosing (Day 1) as assessed by self-report TLFB. The two urine drug screen samples at v2 and v3 must show a decrease in BE level or both must be negative.

7. Must be in good health as determined by medical history, physical examination, at screening.
8. At screening and baseline, vital signs (systolic and diastolic blood pressure and pulse rate) must be within the acceptable ranges by the investigator considering the cocaine's increasing effect on pulse rate in order for the subject to qualify. The investigator may be guided to use the below ranges:
   - systolic blood pressure, 90-150 mmHg
   - diastolic blood pressure, 50-90 mmHg

   Three readings are acceptable. At least the one of three readings must be within the acceptable ranges.
9. Patients must be able to:
   - communicate well verbally with the Investigator and to understand written instructions.
   - verbalize a willingness to complete all study procedures.
   - verbally acknowledge that she/he will be able to attend each scheduled visit, and that she/he does not have any already scheduled events or activities that may substantially interfere with study participation.

4.2 Exclusion criteria

CUD patients fulfilling any of the following criteria are <u>not</u> eligible for inclusion in this study:

1. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes.
2. Has current diagnosis moderate or severe Substance Use Disorder (according to the DSM 5) on alcohol, cannabis, opioids or other stimulants, except cocaine.
3. Meets current or lifetime DSM 5 criteria for schizophrenia or any psychotic disorder or organic mental disorder.

   Notes: Subjects diagnosed with other psychiatric disorders may be included at the discretion of the PI provided that the concurrent treatment for the comorbid psychiatric condition will not interfere with completion of the study or place the patient at heightened risk through participation in the trial.
4. Have current treatment for Substance Use Disorder (e.g.: disulfiram, acamprosate, methyl phenidate, modafinil, topiramate, immediate release dexamfetamine, or baclofen).
5. Requires treatment with any psychoactive medications, including any anti-seizure medications (with an exception of medications used for short-term treatment of insomnia)

   Note:

- SSRI's are allowed if they have adequate stable dose for at least 1 month prior to study treatment dosing

6. Use of other investigational drugs at the time of screening, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations.
7. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
8. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using **effective methods*** of contraception during dosing and for 30 days after last dosing of study medication.

   *Effective contraception methods include:

   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. Note: In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
   - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner must be the sole partner for that subject
   - Barrier methods of contraception: Condom or Occlusive cap (diaphragm orcervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository; Placement of an intrauterine device (IUD) or
   - intrauterine system (IUS)

   Hormonal contraceptives that are injected or implanted or administered orally or transdermally **cannot** be considered as effective methods of contraception if taken with study medication.

   Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms)

   Note: In case the local requirement differs from the contraception methods listed above, local regulations would apply and it will be described in the ICF.
9. History of Porphyria.
10. History or presence of malignancy of any organ system, (other than localized basal cell carcinoma of the skin or in-situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
11. Have a history of any illness, condition, and use of medications that in the opinion of the investigator or designee might confound the results of the study or pose additional risk in administering the investigational agents to the subject or preclude successful completion of the study
12. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in

case of participation in the study. The Investigator must make this determination in consideration of the subject's medical history and/or clinical or laboratory evidence of the following, at screening:

- Clinical laboratory values (including AST, ALT, total bilirubin or creatinine) considered as not clinically acceptable for CUD population, in the opinion of the Investigator, at screening:
  - ALT, serum bilirubin must not exceed 2 x ULN
  - GGT, AST and alkaline phosphatase must not exceed 5 x ULN.

In the case where a safety laboratory assessment at screening is outside of the range specified above, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the subject is excluded from the study.

13. Current or/and previous treatment with concomitant medications that are strong or moderate inducers/inhibitors of CYP3A4 (e.g., clarithromycin, ketoconazole, ritonavir, etc.).

    Note: Concomitant medications that are strong or moderate inducers/inhibitors of CYP3A4 should have been stopped at least 5 half-lives prior to first dosing.
14. Concomitant use of agents known to prolong the QT interval unless these can be permanently discontinued for the duration of study.
15. History or current diagnosis of ECG abnormalities, at screening or baseline, indicating significant risk of safety for subjects participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    - History of familial long QT syndrome or known family history of Torsades de Pointes
    - QTcF > 450 msec (males) ; QTcF > 460 msec (females)

    Note : sinus tachycardia, left axis deviation, and nonspecific ST or T wave changes are not exclusionary
16. Known history or presence of cardiovascular or cerebrovascular disease such as: angina pectoris, myocardial infarction, stroke, transient ischemic attack, peripheral vascular disease.
17. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
18. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV).
19. Score "yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months, or "yes" on any item of the Suicidal Behavior section, except for the "Non-Suicidal Self-Injurious Behavior" (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years.
20. Patient cannot :
    - anticipate any significant problems with transportation arrangements or available time to travel to the study site and have any plans to move within the next months to a location which would make continued participation in the study impractical
    - be involved in any unresolved legal problems that could jeopardize continuation or completion of the study

21. Patients with controlled hypertension i.e. patient diagnosed for hypertension and taking anti-hypertensive treatment must be excluded from this study.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Restrictions for Study Subjects

For the duration of the study, the subjects should be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirement outlined in the Section 4.2 (Exclusion Criteria). If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

5.2 Prohibited treatment

Use of the following treatments/therapies are NOT allowed during the study:

- **Cognitive Behavioral Therapy (CBT)** or other similar interventional behavioral therapy(ies). Group therapies and support groups (such as AA) are allowed, provided the patients have been on such therapies for at least 3 months before screening, and therapies are continuing during the conduct of the study.
- **Glutamatergic drugs** due to potential mechanistic interactions with AFQ056
- **Moderate or strong inducers/inhibitors of CYP3A4** – potential for increased/decreased metabolism of AFQ056 (see Section 17)
- **Lithium**– narrow therapeutic windows and not enough data regarding potential interactions between AFQ056 and these compounds
- **Unstable** treatment (unstable dose) with domperidone, antidepressants, and anxiolytics (see below *) – multiple potential interactions confounding the safety of AFQ056, especially when doses are adjusted
- Typical or atypical neuroleptic agents – risk of malignant neuroleptic syndrome when dopaminergic medication is adjusted
- Any pharmacotherapy with a potentially effective drug for cocaine dependence (i.e. disulfiram, acamprosate, methyl phenidate, modafinil, topiramate, immediaterelease dexamfetamine, or baclofen) – potential for confounding the safety and/or efficacy of AFQ056

Notes:

SSRI are not allowed unless patients are on stable dose regimen and this dose is maintained over Screening and Baseline and being maintained stable during the treatment period.

Short-acting benzodiazepines used occasionally (e.g. against insomnia) are permitted

5.3 Dietary restrictions

- Cruciferous vegetable consumption (e.g. Brussel sprouts, broccoli, cabbage, cauliflower) should be limited to 1-2 times per week (due to the potential interaction with CYP 450 enzymes (Nakajima et al 2001).
- No grapefruit or grapefruit juice is to be consumed for 14 days prior to dosing until 7 days following the last dose.
- In order to avoid wide variations in urine volumes, patients should be encouraged to have a fluid intake of approximately 240 mL every 4 hours during their waking hours, in addition to the fluid taken with meals and medication.

Dosing regimen:

Study medication will be provided in bottles. Patients should take one tablet in the morning with solid food (i.e. breakfast/morning meal) and one tablet in the evening with solid food (i.e. dinner/evening meal). The morning and evening doses should be taken at approximately 12-hour intervals. Study medication should be administered with a glass of water, and taken with a meal as described above. Patients should not chew the medication, but swallow it whole. Patients should avoid drinking grapefruit juice during the study.

Missed doses:

- If a patient misses a dose of study medication for any reason, the patient should not make up the missed dose with the next scheduled dose.
- If a patient misses a dose and realizes it within 3 hours, he/she should take the missed doses immediately; if a patient realizes it after 3 hours and more the doses is missed and a patient should take the next planned doses.
- The dosing regimen should be overseen by a caregiver, where appropriate, to ensure the dosing regimen is correctly followed.

5.4 Other restrictions

Not applicable.

6 Treatment

6.1 Study treatment

The investigational drug AFQ056 50mg, 100mg tablets and placebo will be prepared by Novartis and supplied to the Investigator as single blind patient specific medication pacs.

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the SOM.

6.1.1 Investigational treatment and control drug(s)

Table 6-1 Overview of study medication

Study drug name	Formulation	mg per tablet	Packaging	Provided by
AFQ056 50mg	Tablet	50mg	Single blind patient specific kits	Novartis
AFQ056 100mg	Tablet	100mg	Single blind patient specific kits	Novartis
Placebo	Table	0mg	Single blind patient specific kits	Novartis

6.1.2 Additional study treatment

No additional treatment beyond investigational drug and control drug are included in this trial.

6.2 Treatment arms

Subjects will be assigned to one of the following 2 treatment arms in a ratio of 1:1.

- AFQ056 arm:: up-titration bid regimen followed by fixed-dose bid regimen (50 mg bid from Day 1 to Day 7 followed by AFQ056 100 mg bid from Day 8 to Day 14, and then fixed-dose 200 mg bid for 84 days)
- Placebo arm: matching placebo

6.3 Treatment assignment and randomization

Randomized treatment will be assigned to individual subjects by way of a randomization number, which will be in the range of 5101-5300. Randomization numbers will be assigned to the different centers in multiples of the block size, depending on the recruitment of each site.

The Subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see 'Subject numbering' section in the SOM.

Replacement randomization numbers will be in the range of 6101-6300. If a subject requires a replacement (for reasons other than safety or/and if the drop-out rate is higher than anticipated (20%higher), the replacement subject will be assigned a randomization number corresponding to the original subject (e.g. Subject 6103 would replace Subject 5103). Any additional subjects enrolled will use sequential subject numbering.

The table below details the general details of the numbering of the subjects once randomized to treatment:

Table 6-2 Randomization assignment numbering

Randomization numbers	Replacement randomization numbers
5101 – 5300	6101 – 6300

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of subjects

6.4 Treatment blinding

This is a subject and investigator-blinded study. Subjects and investigators will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.7).

Drug product will be supplied as single blind patient specific kits, so an unblinded pharmacist who is independent of the study team will be required in order to maintain the blind. This unblinded pharmacist will receive treatment allocation cards from Drug Supply Management with the appropriate treatment allocation numbers. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

Sponsor staff or delegate

The following unblinded sponsor roles are required for this study:

- unblinded field monitor(s)
- unblinded sample analysts (PK, PD)

The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded monitors are not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist,

which details treatment allocation to individual subjects. The unblinded monitors will also be able to review the treatment allocation cards/randomization list provided to the unblinded pharmacist. The names of the unblinded monitor(s) are to be detailed in the Monitoring Plan.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-3. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis (e.g.) are allowed to access treatment assignment information for the purpose of conducting interim analyses. Commercially Confidential Information

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

Table 6-3 Blinding levels

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis
Subjects/Patients	B	B	UI	B
Site staff	B	B	UI	B
Unblinded site staff (see text for details)	B	UI	UI	UI
Drug Supply and Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff (see text for details)	B	B	UI	UI
Statistician/statistical programmer/data analysts	B	B	UI	UI
All other sponsor staff not identified above	B	B	UI	UI

B Remains blinded

UI Allowed to be unblinded on individual patient level

6.5 Treating the subject

AFQ056 or placebo will be administered to the subject via oral route of administration.

On the first day of each up-titration dosing and on days that PK samples are scheduled, the subject will be required to not take the medication before the visit, as it will be administered by the site personnel. Study medication (AFQ056/placebo) will be administered to subjects with solid food (i.e. breakfast /morning meal) in the morning and in the evening (i.e. dinner/evening meal).

On other days where no visits are scheduled at site, study treatment administration will occur at home/outpatient basis See the SOM for further details.

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

6.6 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments and/or interruptions are not permitted.

6.7 Emergency breaking of assigned treatment code

Emergency unblinding must only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. A complete set of emergency code break cards will be provided to the investigator site(s) and a complete set will be available at Novartis. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secure place but be accessible to the investigator 24 hours per day in case of emergency. The investigator will receive a blinded code break card for each subject, with the details of study treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason other than an emergency. When the investigator removes the scratch-off cover he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. The unblinded treatment code must not be recorded on the CRF. The investigator must also immediately inform the study monitor that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the code break cards at any time in case of emergency. The investigator will need to provide:

- protocol number
- study drug name (if available)
- subject number.

In addition, the investigator must provide oral and written information to inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given subject.

6.8 Treatment exposure and compliance

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

Compliance will be assessed by the Investigator and/or study personnel at each visit using pill counts and information provided by the subject. This information should be captured in the source document at each visit.

The subjects will also be instructed to bring back used packaging and unused medication at each visit for drug accountability checking. Subjects will be provided with individual Medication Diary (paper version) to record each administration of study. This record will be checked regularly (at least weekly) by site staff.

All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

For the titration of the study medication, the investigator should provide clear instruction along with the dispensed medication in order to comply with the dosing titration schedule. Actual study medication intake by the subject (recorded during site administration or Medication Diary) and all titrated dose (up-titration to 200 mg bid) during the study must be recorded on the Dosage Administration Record CRF.

6.9 Recommended treatment of adverse events

Patients in the study may develop symptoms that normally appear in CUD, however an increase in these symptoms is not expected. If during the study symptoms occur that are severe enough to interfere with the activities of daily living of the patients, they should be treated according to current clinical practice:

If patients develop adverse events such as hallucinations, agitation, delirium and/or confusion medical supervision should be implemented, and if severe enough to warrant pharmacological intervention then antipsychotic medication can be given, along with the discontinuation of study medication following the follow-up period, where possible.

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.10 Rescue medication

Rescue medication should be given according to clinical practice, and it should be documented

6.11 Concomitant treatment

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

All concomitant diseases and conditions will be treated in accordance with prevailing medical practice.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

Study completion is defined as when the last subject completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

All randomized and/or treated subjects will have a safety follow-up call conducted 14 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 9.2 and the Site Operations Manual. Documentation of attempts to contact the subject should be recorded in the source documentation.

Continuing care should be provided by investigator and/or referring physician based on subject availability for follow-up. This care may include:

- promote compliance for the visits schedule for urine samples collection
- promote compliance for data entry in TLFB cocaine , as well as TLFB alcohol

7.2 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration. Discontinuation of study treatment can be decided by either the subject or the investigator.

Discontinuation of study treatment and **patient withdrawal** will be **at the discretion of the Investigator,** under the following circumstances:

- Moderate and persistent (>24 hours) CNS related AEs, i.e.. behavioral effects and/or neurological adverse effects, in the opinion of the Investigator as suspected to be related to AFQ056 study medication
- Missed > 6 consecutive visits
- Missed > 7 consecutive doses of study medication during the fixed-dose treatment period or a total of more than 14 cumulative doses at any time during the study
- Use any of prohibited treatment

* If a liver or renal event occurs, follow guidelines outlined in Appendix 2 regarding discontinuation of study treatment.

Study treatment **must be** discontinued under the following circumstances:

- Subject/guardian decision - subjects may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the subject or the risk/benefit ratio of trial participation.
- Any protocol deviation that results in a significant risk to the subject's safety.
- Pregnancy (see Section 8.6 (Safety) and Section 9.6 (Pregnancy reporting).
- Severe withdrawal syndrome or need for detoxification

For all discontinued patients, the follow-up period is to be followed, where possible.

Patients, who discontinue study treatment must NOT automatically be considered withdrawn from the study. Patients who discontinue study treatment before completing the study, and those who prematurely withdraw from the study for any reason, must be scheduled for a visit approximately 1 week after the last dose of study medication, at which time all of the assessments listed for the final visits (End of Study visit) must be performed (see Assessment schedule).

After study treatment discontinuation, at a minimum, the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

If discontinuation of study treatment occurs, investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the Dosage Administration CRF

For patients who are lost to follow-up (e.g.. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

If a patient needs to be hospitalized either temporarily or permanently during the course of this study, the sponsor needs to be notified by the investigator and the sponsor will make a decision whether the patient can remain in the study or needs to be discontinued.

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

7.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent from the study is defined as when a subject:

- Does not want to participate in the study anymore and
- Does not want any further visits or assessments and
- Does not want any further study related contacts and
- Does not allow analysis of already obtained biologic material.

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

7.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.5 Study stopping rules

The study will be placed "on hold" if any of the following criteria are met, and no new patients will be randomized, pending a safety review, if:

- at least 1 or more patients exhibits a life threatening or persisting/significant disabling SAEs such as confusion, mood alteration, somnolence and/or psychosis, that are deemed related to the study medication by the investigator, and confirmed to be on active treatment when blind is broken for that patient
- at least 3 and more patients exhibit at least one severe AE such as confusion, delirium, mood alteration (euphoria or agitation) and/or psychosis (hallucinations or delusions) which interfere with their activities of daily living, require medical intervention and medical supervision, and are deemed related to the study medication by the investigator, and confirmed to be on active treatment when blind is broken for that patient
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold.

Following the safety review, the study may continue, if the Investigator and Sponsor agree it is safe to proceed.

7.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely discontinued subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

Subjects should be seen for all visits/assessments as outlined in the Assessment schedule or as close to the designated day/time as possible.

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Table 8-1 Assessment schedule

Epoch	Screening				Treatment														
Visit Name	Screening[14]		Baseline[15]		Up-Titration 50 mg bid (Days 1 to 7)		Up-Titration 100 mg bid (Days 8 to 14)		Treatment										
Visit Numbers[1]	1	2	3[16]	4	101	102	103	104	105		106	107	108	109		110	111	112	113	114
Days	-28 to -12	-14 to -11	-13 to -10	-3 to -1	1	4 ±1	8 ±1	11 ±1	15 ±1		18 ±1	22 ±1	25 ±1	29 ±1		32 ±1	36 ±1	39 ±1	43 ±1	46 ±1
Time (post-dose)	-	-	-	-	-	-	-	-	0h	2h ±1	-	-	-	0h	2h ±1	-	-	-	-	-
Informed consent	X																			
Commercially Confidential Information																				
Demography	X																			
Body Weight	X																			
Body Height	X																			
Body Temperature	X			X	X[3]															
Blood Pressure and Pulse Rate	X			X	X[3]															
Physical Examination	X			X																
Medical history/current medical conditions	X																			
reduce / cease cocaine use [17]				X																
Amount spent on cocaine				X											X					
TLFB cocaine	X																			
TLFB alcohol	X																			
Urine drug screen	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X
Commercially Confidential Information																				
Hepatitis screen	S																			
Hematology	X			X										X						

Epoch	Screening				Treatment														
Visit Name	Screening[14]		Baseline[15]		Up-Titration 50 mg bid (Days 1 to 7)		Up-Titration 100 mg bid (Days 8 to 14)		Treatment										
Visit Numbers[1]	1	2	3[16]	4	101	102	103	104	105		106	107	108	109		110	111	112	113	114
Days	-28 to -12	-14 to -11	-13 to -10	-3 to -1	1	4 ±1	8 ±1	11 ±1	15 ±1		18 ±1	22 ±1	25 ±1	29 ±1		32 ±1	36 ±1	39 ±1	43 ±1	46 ±1
Time (post-dose)	-	-	-	-	-	-	-	-	0h	2h ±1	-	-	-	0h	2h ±1	-	-	-	-	-
Blood chemistry	X			X										X						
Urinalysis	X			X										X						
Pregnancy test[4]	X[5]			X[6]					X[6]					X[6]					X[6]	
ECG evaluation[7]	X			X					X	X				X	X					
HIV screen	S																			
Concomitant therapies[8]	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X
Drug administration record					X	X	X	X	X		X	X	X	X		X	X	X	X	X
Medication patient diary [9]					X	X	X	X	X		X	X	X	X		X	X	X	X	X
Commercially Confidential Information																				
C-SSRS[10]	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X
PK blood collection[11]									X	X				X	X					
Commercially Confidential Information																				
Adverse Events[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study completion information																				

Epoch	Treatment																	Follow up		
Visit Name	Treatment																	Follow up		
Visit Numbers[1]	115	116	117		118	119	120	121	122	123	124	125	126	127	128	199		201	202	203
Days	50 ±1	53 ±1	57 ±1		60 ±1	64 ±1	67 ±1	71 ±1	74 ±1	78 ±1	81 ±1	85 ±1	88 ±1	92 ±1	95 ±1	98 ±1		99 ±1	102 ±1	106 ±1
Time (post-dose)	-	-	0h	2h ±1	-	-	-	-	-	-	-	-	-	-	-	0h	2h ±1	-	-	-
Informed consent																				
Commercially Confidential Information																				
Demography																				
Body Weight																				
Body Height																				
Body Temperature	X[3]																			
Blood Pressure and Pulse Rate	X[3]																			
Physical Examination																				
Medical history/current medical conditions																				
reduce / cease cocaine use [17]																				
Amount spent on cocaine				X													X			
TLFB cocaine	X																			
TLFB alcohol	X																			
Urine drug screen	X	X	X		X	X	X	X	X	X	X	X	X	X	X			X	X	X
Commercially Confidential Information																				
Hepatitis screen																				
Hematology			X													X				
Blood chemistry			X													X				
Urinalysis			X													X				
Pregnancy test[4]			X[6]					X[6]				X[6]				X[6]				
ECG evaluation[7]			X	X												X	X			

Epoch	Treatment																	Follow up		
Visit Name	Treatment																	Follow up		
Visit Numbers[1]	115	116	117		118	119	120	121	122	123	124	125	126	127	128	199		201	202	203
Days	50 ±1	53 ±1	57 ±1		60 ±1	64 ±1	67 ±1	71 ±1	74 ±1	78 ±1	81 ±1	85 ±1	88 ±1	92 ±1	95 ±1	98 ±1		99 ±1	102 ±1	106 ±1
Time (post-dose)	-	-	0h	2h ±1	-	-	-	-	-	-	-	-	-	-	-	0h	2h ±1	-	-	-
HIV screen																				
Concomitant therapies[8]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Drug administration record	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X				
Medication patient diary [9]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X				
Commercially Confidential Information																				
C-SSRS[10]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
PK blood collection[11]			X	X												X	X			
Commercially Confidential Information																				
Adverse Events[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study completion information																				

Epoch	Follow up	
Visit Name	Follow up	EOS
Visit Numbers[1]	204	299
Days	112 ±1	113 ±3
Time (post-dose)	-	-
Informed consent		
Commercially Confidential Information		
Demography		
Body Weight		X
Body Height		
Body Temperature	X[3]	X[3]
Blood Pressure and Pulse Rate	X[3]	X[3]
Physical Examination		X
Medical history/current medical conditions		
reduce / cease cocaine use [17]		
Amount spent on cocaine		X
TLFB cocaine	X	
TLFB alcohol	X	
Urine drug screen	X	
Commercially Confidential Information		X
Hepatitis screen		
Hematology		X
Blood chemistry		X
Urinalysis		
Pregnancy test[4]		X[6]
ECG evaluation[7]		X
HIV screen		

Epoch	Follow up	
Visit Name	Follow up	EOS
Visit Numbers[1]	204	299
Days	112 ±1	113 ±3
Time (post-dose)	-	-
Concomitant therapies[8]	X	X
Drug administration record		
Medication patient diary [9]		
Commercially Confidential Information		
C-SSRS[10]	X	X
PK blood collection[11]		
Commercially Confidential Information		
Adverse Events[12]	X	X
Serious Adverse Events[13]	X	X
Study completion information		X

[1] Visit structure given for internal programming purpose only.

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[3] Assessment to be done once per week, during one of the visits when urine sample is collected.
[4] Assessment for females patients only.
[5] Serum pregnancy test
[6] Urine pregnancy test
[7] On PK days , assessment to be done after post dose PK sample
[8] Record includes: Positive Reinforcement
[9] Medication compliance to be assessed at least once per week
[10] Assessment to be done at every visit
[11] Pk samples collected in the morning at predose and 2 ± 1 hours post-morning dose
[12] AEs to be collected from signed ICF up to study completion visit (EOS)
[13] SAEs to be collected from signed ICF up to 30 days following study completion visit (EOS)
[14] If considered appropriate by the investigator, screening assessments may be carried out on two separate days.
[15] If considered appropriate by the investigator, baseline assessments may be carried out on two separate days.
[16] Visit 3 should take place 1-3 days after visit 2.
[17] Subjects should be asked about their goals to cease/reduce cocaine use. Guidance is provided in the SOM.

8.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the subject's representative gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators a proposed informed consent form that complies with the ICH E6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the subject.

A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

Refer to the Site Operations Manual for a complete list of Informed Consent Forms included in this study.

8.3 Subject screening

It is permissible to re-screen a subject if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

Information on what data should be collected for screening failures is outlined in the Site Operations Manual.

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the Site Operations Manual.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.5 Efficacy / Pharmacodynamics

Pharmacodynamics assessments are detailed below. For all completed scales/questionnaire described below, the Investigator will be required to review and examine responses which may indicate potential AEs or SAEs. The investigator should review not only the responses to the scale but also for any unsolicited comments written by the patient. If the occurrence of AEs or SAEs is confirmed, the physician should record the events as per instructions given in Section 9. Investigators should not encourage the subjects to change the responses reported on the scale.

Pharmacodynamics samples will be collected at the timepoints defined in the Assessment schedule. Follow instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing and shipment. In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

8.5.1 Clinical Outcome Assessments (COAs)

Clinical Outcome Assessments such as Patient report Outcome and Observer reported Outcome are specific methods for assessment and recording are specified in the Site Operations Manual, with the Assessment schedule (Section 8.1) detailing when each assessment is to be performed. Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment schedule (Section 8.1) detailing when each assessment is to be performed.

Patient Reported Outcome includes:

- **The TLFB cocaine**: is a cocaine assessment method that obtains estimates of daily cocaine intake and has been evaluated with clinical and nonclinical populations. Using a calendar, people provide retrospective estimates of their daily cocaine use over a specified time period that can vary up to 12 months from the interview date. Several memory aids can be used to enhance recall (e.g., calendar; key dates serve as anchors for reporting cocaine use). The Cocaine TLFB has been shown to have good psychometric characteristics with a variety of cocaine use groups, and can generate variables that provide a wide range of information about an individual's cocaine use (e.g., pattern, variability, and magnitude of cocaine use). The method is recommended for use when relatively precise estimates of cocaine use are necessary, especially when a complete

picture of cocaine use days (i.e., high- and low-risk days) is needed (evaluating cocaine use pre-posttreatment). Clinically, the TLFB can be used to provide feedback about one's cocaine consumption in an effort to increase a client's motivation to change.

- **The TLFB alcohol**: is a drinking assessment method that obtains estimates of daily drinking and has been evaluated with clinical and nonclinical populations. Using a calendar, people provide retrospective estimates of their daily drinking over a specified time period that can vary up to 12 months from the interview date. Several memory aids can be used to enhance recall (e.g., calendar; key dates serve as anchors for reporting drinking; standard drink conversion). The Alcohol TLFB has been shown to have good psychometric characteristics with a variety of drinker groups, and can generate variables that provide a wide range of information about an individual's drinking (e.g., pattern, variability, and magnitude of drinking). The method is recommended for use when relatively precise estimates of drinking are necessary, especially when a complete picture of drinking days (i.e., high- and low-risk days) is needed (evaluating drinking pre-posttreatment). Clinically, the TLFB can be used to provide feedback about one's drinking in an effort to increase a client's motivation to change. Overall, the Alcohol TLFB method provides a relatively accurate portrayal of drinking, and has both clinical and research utility.

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- **The C-SSRS**: refer to Section 9.7

Observer Reported Outcome includes:

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8.5.1.1 Urine drug screen

Urine sample will be analyzed with primary objective for the presence of cocaine metabolite's Benzoylecgonine (BE) the main metabolite of cocaine present in urine. Urine specimen collection will take place in conjunction with regular clinic visits (see Assessment schedule for the visits).

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment schedule (Section 8.1) detailing when each assessment is to be performed.

8.6.1 Physical examination

See Site Operations Manual for details.

8.6.1.1 Vital signs

- Body temperature
- Blood pressure (BP)
- Pulse

8.6.2 Height and weight

- Height
- Body weight
- Body mass index (BMI) will be calculated as (Body weight (kg) / [Height (m)]^2)

8.6.3 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should be contacted.

8.6.4 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differentials (e.g. neutrophils, basophils, eosinophils, monocytes, lymphocytes presented as % of total white blood cell count and as absolute concentrations), and platelet count will be measured. Coagulation testing including prothrombin time (PT) also reported as INR and activated partial thromboplastin time (aPTT) will be measured.

8.6.5 Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO2, calcium, total cholesterol, chloride, creatinine, CK, γ-GT, glucose, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, urea and uric acid.If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

8.6.6 Urinalysis

Dipstick measurements for protein, nitrite, specific gravity, pH, blood, and WBC/leukocytes will be performed. If the dipstick result is positive for protein, nitrite, leucocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts, furthermore the protein-creatinine ratio (PCR) and the albumin-creatinine ratio (ACR) will also be measured.

8.6.7 ECG evaluation

Full details of all procedures relating to the ECG collection and reporting are contained in the Site Operations Manual.

- PR interval, QRS duration, QT interval and heart rate,

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

As applicable, QTcF and QTcB may be calculated in-house. Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the Screening and/or Baseline visit(s) (as applicable) to assess eligibility. See the Site Operations Manual for additional details.

Clinically significant abnormalities must be reported in the AE CRF.

8.6.8 Pregnancy and assessment of fertility

Pregnancy Testing

Pregnancy tests are required of all female subjects regardless of age or reported sterilization. The result of this test must be received before any female subject may be dosed. See the Assessment schedule (Section 8.1), for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative.

Refer to Section 9.6 for details on Reporting Pregnancy.

Assessments of Fertility

Refer to Section 4.2 for criteria to determine women that are not of child bearing potential.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

- surgical bilateral oophorectomy without a hysterectomy
- reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female subject, regardless of reported reproductive/menopausal status at Screening/Baseline

8.7 Pharmacokinetics

PK samples will be collected at the time points defined in the Assessment schedule (Section 8.1). Follow instructions outlined in the Bioanalytics Study Specifications (BSS) and Central Laboratory Manual regarding sample collection, numbering, processing and shipment. See Section 8.9 regarding the potential use of residual samples.

PK samples post morning dose will be obtained and evaluated in all subjects, except the samples collected during treatment with placebo.

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The PK blood collection log is provided in the Site Operations Manual.

Conventional PK parameters will not be calculated due to the limited sampling schedule. However, plasma concentrations will be listed and summary statistics for concentrations will be provided for plasma. The data will be part of the over-all Population PK model

8.8 Other assessments

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8.8.3 Positive Reinforcement (PR)

For each study visit patients will receive money compensation for travel expenses. In order to stimulate clinic attendance and to enable optimal monitoring of patients' medication adherence and health (including adverse events), patients will be remunerated for complying with study visits and standard requirements (urine submission, TLFB, medication diary, adverse events, and basic physical examination). In order to reinforce regular participation with study assessments a bonus will be provided each time patients attend two consecutive study visits. Finally, patients will receive additional remuneration for their time investment in case of ECG-evaluations and for extended study visits with additional questionnaires and/or PK-blood sampling. The maximum remuneration for patients complying with all study assessments. Given our experience with pharmacotherapy studies with cocaine dependent patients, we expect that patients, on average, will attend a maximum of 70-80% of all planned study visits.

In addition to positive reinforcement, participants will be stimulated at every planned visit and encouraged for attending appointments, as well as adherence to the protocol.

Positive Reinforcement will be made available for the sites as a separate document.

8.9 Use of residual biological samples

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9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 9.5 for an overview of the reporting requirements.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination finding, laboratory test finding, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively.

For all completed scales/questionnaire described below, the Investigator will be required to review and examine responses which may indicate potential AEs or SAEs. The investigator should review not only the responses to the scale but also for any unsolicited comments written by the subject. If the occurrence of AEs or SAEs is confirmed, the physician should record the events as per instructions given in Section 7. Investigators should not encourage the subjects to change the responses reported on the scale.

Adverse events should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

- AE severity grade (mild/moderate/severe):
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment
  - Yes or
  - No
  - No Relationship to study treatment or other investigational treatment or
  - Relationship to study treatment or
  - Relationship to other investigational treatment or
  - Relationship to both study treatment and other investigational treatment or indistinguishable
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a SAE (see Section 9.2 for definition of SAE) and which seriousness criteria have been met
- action taken regarding investigational treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- investigational treatment dosage increased/reduced
- investigational treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

*Refer to the Site Operations Manual for data capture methodology regarding AE collection for subjects that fail screening.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- elective or pre-planned treatment for a pre-existing condition (that is unrelated to the indication under study and has not worsened since the start of study drug
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to European Medicines Agency (EMA) (2003) ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to European Medicines Agency (EMA) (2003) ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Chief Medical Office and Patient Safety (CMO & PS) as per Section 9.2.2.

9.2.2 SAE reporting

Screen Failures

Note the following requirement for Screen Failures: SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

Randomized / Treated Subjects

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last administration of study treatment must be reported to Novartis within 24 hours of learning of its occurrence as described below.

Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Chief Medical Office and Patient Safety (CMO& PS) Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the

same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis. Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

9.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 15-1-Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Table 15-1-Appendix 1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 15-2 - Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation within 48-72 hours.

These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.

- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 7.2 (Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event

Thorough follow-up of the liver event should include

- Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and GGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.

- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Exclusion of underlying liver disease, as specified in Table 15-3.
- Imaging such as abdominal US, CT or MRI, as appropriate
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the Site Operations Manual for additional details.

9.4 Renal safety monitoring

Every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Appendix 2.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the Site Operations Manual for additional details.

9.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient/subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Chief Medical Office and Patient Safety (CMO& PS) department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Chief Medical Office and Patient Safety (CMO& PS). As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

Table 9-1 Guidance for capturing study treatment errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 9.1 and Section 9.2, respectively.

9.6 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be **reported to Novartis within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO& PS) Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued*, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

9.7 Prospective suicidality assessment

The Columbia-Suicide Severity Rating Scale (C-SSRS), is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior. The C-SSRS must be administered at each visit, including unscheduled visits.

The C-SSRS, which uses a semi-structured interview to probe subject responses, will be administered by an individual who has received training and certification in its administration. At the first study visit, the “baseline/screening” version of the C-SSRS, will be administered. This version assesses Suicidal Ideation and Suicidal Behavior during the subject’s lifetime and during a predefined period. At subsequent visits, the “since last visit” version will be administered.

If, at any time after screening and/or baseline, the score is “yes” on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS or “yes” on any item of the Suicidal Behavior section, the subject must be referred to a mental health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the investigator in consultation with the mental health professional to whom the subject is referred.

In addition, all life-threatening events must be reported as SAEs. For example, if a subject answers “yes” to one of the questions in the Suicidal Behavior section, an SAE must be reported if the event was life-threatening. All events of “Non-Suicidal Self-Injurious Behavior” (question also included in the Suicidal Behavior section) should be reported as AEs and assigned the appropriate severity grade.

All SAEs relating to suicidal behavior must be reviewed by the Safety Management Team or Early Project Teams.

9.8 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (eCRFs) with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

Continuous remote monitoring of each site's data may be performed by Novartis or CRO working on behalf of Novartis. Additionally, a central analytics organization may analyze data and identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

Certain data may be captured via other source documentation (such as safety laboratory data report) and then transcribed, uploaded or transferred into the EDC system. This, and any additional data treated in this manner, will be source data verified by the study monitor per the monitoring plan and the location of source data (i.e., Source, paper or a local electronic system) will be documented prior to study start in the Data Handling Plan.

Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the vendor working on behalf of Novartis.

Remote monitoring of the original electronic source records will take place, however on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess site operational capabilities, and to perform other monitoring activities that cannot be performed remotely.

The investigator must certify that the data entered into CRFs are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and Assessment schedule (Section 8.1) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

10.3 Database management and quality control

CRO working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to CRO working on behalf of Novartis who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis management.

10.4 Data Monitoring Committee

Not applicable.

10.5 Adjudication Committee

Not applicable.

11 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

11.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment received.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

11.3 Treatments

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject.

11.4 Analysis of the primary variable(s)

The primary objective is to evaluate the effect of AFQ056 in reducing cocaine use.

11.4.1 Primary Variable(s)

The primary variable is the proportion of cocaine use days during the treatment period (days 1-98).

For each patient, the proportion of cocaine use days will be calculated by dividing the number of days of cocaine use during the treatment period, i.e. 98 days for completers and number of days between Day 1 and day of last dose in case of premature discontinuation of study treatment. It is considered as a continuous variable with a normal distribution. The cocaine consumption will be recorded daily (Yes/No) using the TLFB during the entire study.

11.4.2 Statistical model, hypothesis, and method of analysis

A Bayesian analysis will be conducted on the proportion of cocaine use days

11.4.3 Handling of missing values/censoring/discontinuations

In case of premature discontinuation of study treatment, the calculation of the primary variable will be done on the period with both TLFB data available and study treatment was taken. No missing data is expected between visits per the TLFB completion guidelines an investigator's checks at the visits.

For sensitivity analysis, the incomplete profiles will be included in longitudinal analyses.

11.4.4 Sensitivity analyses

Sensitivity analyses will be performed using other models if the distribution of the data is not deemed normal.

Additionally, the profiles of consumption over time will be compared between treatment groups through analyses of longitudinal data (weekly use and monthly use) using linear mixed models for repeated measures or other models depending on th distribution.

Data visualization techniques will be used in order to detect potential patterns in the daily data obtained from the TLFB.

The missing data mechanism will be explored to check that the missing data due to dropouts are at least missing at random.

11.5 Analysis of secondary variable(s)

The secondary objectives are to assess the effect of AFQ056 on other measures of cocaine use and on measures of alcohol use, to assess the safety and tolerability and to evaluate the PK of AFQ056.

11.5.1 Efficacy / Pharmacodynamics

11.5.1.1 Measure of cocaine in (BE) in urine

Two urine samples per week will provide a quantitative measure of cocaine's metabolite BE. The proportions of positive urine samples over the treatment period will be compared between groups using a t-test.

The quantitative BE profiles over time will be explored using visualization techniques and compared between groups using models appropraite to the distribution of the data.

11.5.1.2 Measures of alcohol use

Alcohol consumption will be recorded by the patients using TLFB. The number of standard drinks will be recorded daily.

The proportion of days of alcohol consumption during the study treatment period will be compared between groups using an ANCOVA model with treatment as factor and past alcohol consumption as covariate.

The longitudinal profiles (daily number of drinks, weekly and monthly mean number of drinks) will be explored.

11.5.2 Safety

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment group, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment group and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

Other safety evaluations

Columbia Suicide Severity Rating Scale (C-SSRS). The C-SSRS data will be listed by treatment group, subject and visit.

11.5.3 Pharmacokinetics

Analysis will be performed under PK analysis set.

AFQ056 plasma concentration data will be listed by treatment, subject, and visit/sampling time point.

Commercially Confidential Information

Conventional PK parameters will not be calculated due to the limited sampling schedule. However, plasma concentrations will be listed at pre-dose and 2±I hour sampling window post morning dose and summary statistics for concentrations will be provided for plasma. The data will be part of the over-all Population PK model.

Commercially Confidential Information

11.5.4 Pharmacokinetic / pharmacodynamics interactions

Not applicable.

11.5.5 Other assessments

Not applicable.

11.6 Analysis of exploratory variables (if applicable)

Commercially Confidential Information

11.7 Sample size calculation

A sample size of approximately 60 patients (30 patients on AFQ056 and 30 patients on placebo) was determined, assuming a SD of 32% (Nuijten et al 2016) for the proportion of cocaine use days. Patients who are withdrawn from the study for reasons other than safety may be replaced, if the drop-out rate is higher than anticipated (20 % higher).

Commercially Confidential Information

Commercially Confidential Information

11.8 Power for analysis of key secondary variables

Not applicable.

11.9 Interim analyses

Commercially Confidential Information

12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis by the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed or overseen by Novartis Pharma Auditing and Compliance Quality Assurance (or CRO working on behalf of Novartis), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

13.1 Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

14 References

References are available upon request.

American Psychiatric Association (APA) (2006) Practice Guidelines Substance Use Disorder.

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Nakajima M, Yoshida R, Shimada N, et al (2001) Inhibition and inactivation of human cytochrome P450 isoforms by phenethyl isothiocyanate. 29:1110-3.

Nuijten M, Blanken P, van de Wetering B, et al (2016) Sustained-release dexamfetamine in the treatment of chronic cocaine-dependent patients on heroin-assisted treatment: a randomised, double-blind, placebo-controlled trial. www.thelancet.com Vol 387 May 28, 2016.

Pellinen P, Stenbäck F, Kojo A, et al (1996) Regenerative changes in hepatic morphology and enhanced expression of CYP2B10 and CYP3A during daily administration of cocaine. Hepatology. 23(3):515–523.

Robinson SM, Sobell LC, Sobell MB, et al (2012) Reliability of the Timeline Followback for Cocaine, Cannabis, and Cigarette Use. doi: 10.1037/a0030992.

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Stocchi F, Rascol O, Destee A, et al (2013) AFQ056 in Parkinson patients with levodopainduced dyskinesia: 13-week, randomized, dose-finding study. Mov Disord. 28: 1838-46.

The United Nations Office on Drugs and Crime (UNODC) (2016) UNODC-WHO International Standards for the Treatment of Drug Use Disorders.

15 Appendix 1: Liver Event Definitions and Follow-up Requirements

Table 15-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST ≤ 8 x ULN • 3 x ULN < ALT/AST ≤ 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) • Any adverse event potentially indicative of liver toxicity

Table 15-2 Actions required for Liver Events

Criteria	Actions required
Potential Hy's Law case ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 × ULN Jaundice	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	• If confirmed, consider interruption or discontinuation of study drug • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly • Repeat liver chemistry tests within 48-72 hours
Isolated ALP elevation	• If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance*
Any AE potentially indicative of liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Complete CRFs per liver event guidance*

*Liver event guidance for CRF completion is available in the Site Operations Manual

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

16 Appendix 2: Specific Renal Alert Criteria and Actions

Table 16-1 Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase > 50%	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold or new onset dipstick proteinuria ≥ 1+ or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; or Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin & serum protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	Assess & document: • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	Assess & document: • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema

- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 16-2 Follow-up of renal events

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output • Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline)
Monitor subject regularly (frequency at investigator's discretion) until:	or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

* Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.

17 Appendix 3: Drugs affecting CYP3A4

Drugs affecting CYP3A4

This appendix provides a specific list of drugs that should not be co-administered with AFQ056 because of their CYP3A4 inhibiting potency or CYP3A4 inducing potency.

Drugs inhibiting CYP3A4

This list is by no means exhaustive and medical judgment should always prevail. The clinical investigators must refer to the product information of any concomitant medication to ascertain any potential drug interactions. This list is adapted to the patient population and the exclusion criteria.

List of CYP3A4 inhibitors not to be co-administered with AFQ056 in study CAFQ056A2201

- Amiodarone
- Amprenavir
- Aprepitant
- Atazanavir
- Cimetidine
- Clarithromycin
- Diltiazem
- Erythromycin
- Fluconazole
- Fluoroquinolones (e.g. ciprofloxacin)
- Fluvoxamine
- Fosamprenavir
- Gestodene
- Grapefruit juice
- Indinavir
- Itraconazole
- Ketoconazole
- Mibefradil
- Nefazodone
- Nelfinavir
- Ritonavir

- Saquinavir
- Telithromycin
- Verapamil
- Voriconazole

Drugs inducing CYP3A4:

- Barbiturates (e.g. primidone, phenobarbital)
- Carbamazepine
- Efavirenz
- Glucocorticoids (except for topical or inhalation use)
- Phenytoin
- Rifabutin
- Rifampin
- Rifapentin
- St. John's Wort