A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Single/Multiple Day Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of 18-Methoxycoronaridine Administered Orally to Normal Healthy Volunteers

Sponsor Protocol Number:	MMED003
Investigational Product:	18-Methoxycoronaridine hydrochloride
Sponsor:	Mind Medicine, Inc.
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Protocol Version / Date:	Version 2, 20 January 2020

SIGNATURES

Sponsor Signature

Study Title:	A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Single/Multiple Day Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of 18-Methoxycoronaridine Administered Orally to Normal Healthy Volunteers
Study Number:	MMED003
Version/Date:	Version 2, 20 January 2020

I agree to the content of this protocol.

Signed:_____ Date:_____

Scott M. Freeman, MD
Chief Medical Officer
Mind Medicine, Inc.

Signature of Principal Investigator

Study Title:	A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Single/Multiple Day Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of 18-Methoxycoronaridine Administered Orally to Normal Healthy Volunteers
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I, the undersigned, have read the protocol and agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), and all applicable local and federal regulatory requirements.

I will provide copies of the protocol and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the investigational product and the study. I understand that the study may be terminated or enrollment suspended at any time by sponsor with or without cause, or by me if it becomes necessary to protect the best interests of the study participants.

Signed:_____ Date:_____

Name and title: _____

Address:_____

Telephone number: _____

PROTOCOL SYNOPSIS

SPONSOR

Mind Medicine, Inc.

INVESTIGATIONAL PRODUCT

18-Methoxycoronaridine hydrochloride (18-MC HCl)

STUDY TITLE

A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Single/Multiple Day Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of 18-Methoxycoronaridine Administered Orally to Normal Healthy Volunteers

PHASE OF DEVELOPMENT

Clinical pharmacology (Phase 1)

OBJECTIVES

Primary Objective

To assess the safety and tolerability of a single day dosing and a separate multiple day dosing of 18-MC HCl administered orally, each part of the study having a different set of healthy male and female volunteers (of non childbearing potential).

Secondary Objectives

1) To characterize the PK of 18-MC in plasma following oral administration of a single day dosing and multiple day dosing

2) To detect and quantify metabolites of 18-MC in plasma

3) To characterize the PD effects and duration of PD effects of 18-MC following oral administration of a single dose

4) As an exploratory objective, the concentration of 18-MC and metabolites in the urine may be determined

STUDY DESIGN

This is a Phase 1, double-blind, randomized, placebo-controlled, single day and multiple day dosing, in healthy, non-smoking, male and female volunteers.

Part 1: Single day dosing

Seven (7) healthy male and female volunteers (of non childbearing potential) will be randomly assigned to receive in a single day either 18-MC HCl (n=5) or placebo (n=2) in each cohort. There will be 4 cohorts: 1) 4 mg bid, 2) 8 mg bid, 3) 12 mg bid, and 4) 16 mg bid.

All participants will be assessed for PK and safety for 14 days. There will be two sentinel participants in each cohort, who will receive their first dose at least 48 hours prior to the rest of the cohort. Participants will report to the clinical unit (CU) for a screening visit within 28 days prior to Day -1 and all screening procedures and evaluations will be completed. Participants who meet the eligibility criteria will be admitted to the CU on Day -1 and will undergo safety and compliance assessments on this day. The results will be evaluated prior to study drug dosing on Day 1. After treatment administration on Day 1, participants will remain at the CU and undergo serial safety and PK assessments until Day 3. On Day 3, participants will be discharged from the CU. Participants will return to the study site for a follow-up assessment on study Day 7 and Day 14.

A Safety Review Committee (SRC) will review the safety data and exposure of 18-MC, derived from available PK analysis of each cohort. The SRC will confirm the next dose in a subsequent cohort (Cohort 2, 3 and 4) as well as progression to the MAD component of the study.

Part 2: Multiple day dosing

After completion of Cohort 2 (8mg bid) in Part 1, based on PK and subject to SRC review, Part 2 will begin as follows:

Seven (7) healthy male and female volunteers (of non childbearing potential) will be randomly assigned to receive either 18-MC HCl (n=5) or placebo (n=2) in each cohort. There will be 4 cohorts: 5) 2 mg bid x 7 days, 6) 4 mg bid x 7 days, 7) 8 mg bid x 7 days, and 8) 12 mg bid x 7 days

All participants will be assessed for PK and safety for 21 days. Participants will report to the clinical unit (CU) for a screening visit within 28 days prior to Day -1 and all screening procedures and evaluations will be completed. Participants who meet the eligibility criteria will be admitted to the CU on Day -1 and will undergo safety and compliance assessments on this day. The results will be evaluated prior to study drug dosing on Day 1. After treatment administration on Day 1, participants will remain at the CU and undergo serial safety and PK assessments. Participants will be confined for the entire dose administration period for safety

and PK collection and will be discharged on Day 9. On Days 14 and 21, participants will return to the CU for further follow-up assessment.

STUDY POPULATION

Healthy, non-smoking male and female volunteers aged 18 to 55 years.

For details on exclusion and inclusion criteria, please see section 4.1.

NUMBER OF PARTICIPANTS PLANNED

In Part 1, twenty-eight (28) healthy participants will be randomized in 4 cohorts to receive dosage of 18-MC HCl (n=20) or placebo (n=8) in a single day.

In Part 2, twenty-eight (28) healthy participants will be randomized to receive a bid dose of 18-MC HCl (n=20) or placebo (n=8) for 7 consecutive days.

INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION

Participants will receive either 18-MC HCl or matching placebo in a liquid formation.

Dosage: After a safety and pharmacokinetic review of data from Part 1 Cohort 1, the next cohort will be enrolled, Cohort 2, Cohort 3, and then Cohort 4.

After completion of Part 1 Cohort 2 (8 mg bid), based on PK and subject to SRC review, Part 2 will begin, starting with Cohort 5, Cohort 6, Cohort 7, and Cohort 8.

OUTCOME VARIABLES

Safety

Safety and tolerability will be assessed by the incidence and severity of adverse events (AEs), vital sign assessments, electrocardiograms (ECGs), clinical laboratory assessments, DSST, physical and neurologic examinations.

Pharmacokinetics

As the data allow, the following PK parameters will be calculated for 18-MC: C_{max}, time to maximum plasma concentration (T_{max}), terminal rate constant (λ_z), area under the plasma concentration-time curve from zero to 24 hours after dosing [$AUC_{(0-24)}$], area under the plasma concentration-time curve from zero to time of the last measurable concentration [$AUC_{(0-t)}$], $t_{½\lambda z}$, apparent volume of distribution of the terminal phase (V_z/F), apparent plasma clearance

(CL/F), renal clearance (CL_R), cumulative amount of unchanged drug excreted in urine [$Ae_{(0-t)}$], and fraction of dose excreted into urine [$fe_{(0-t)}$].

All participants will be required to provide plasma and urine samples for possible detection and identification of 18-MC metabolites.

Pharmacodynamic Effects

The PD effects will be evaluated using an abbreviated neurologic examination and, the number of attempts and number of correct substitutions on the 90-second digit symbol substitution test (DSST). For the DSST, the sections of the test where the number of attempted or correct substitutions versus time, time of maximum change in attempt and correct, and the percentage of correct substitution will be determined.

SAMPLE SIZE

No formal power calculations have been performed. The sample size is based on the desire to obtain adequate safety, tolerability, PK, and PD data to achieve the objectives of the study while exposing as few participants as possible to the investigational product and study procedures.

STATISTICAL METHODS

Adverse events will be summarized for each treatment group and cohort by system organ class and preferred term. Tabulations and listings of data for vital signs, clinical laboratory tests, ECGs, DSST, neurological examination and physical examination will be presented as appropriate.

18-MC concentrations and PK parameters will be summarized using descriptive statistics and graphic displays as appropriate. PK parameters such as AUC and C_{max} may be illustrated graphically, as appropriate, for preliminary dose proportionality analyses.

Pharmacodynamic effects will be summarized for each treatment group and cohort using descriptive statistics and graphic display as appropriate. The parameters may be displayed for preliminary assessment of dose proportionality or duration of effects. For the DSST, the following variables will be determined: area under the effect-versus-time curves for the number substitutions attempted and correct, time to maximum decrease or increase in the number of attempted or correct substitution (T_{max}, h), and maximum percentage decrease or increase in number of attempted or correct substitution ($E\%_{max}$).

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
18-MC	18-methoxycoronaridine freebase (parent and circulating molecule)
18-MC HCl	18-methoxycoronaridine hydrochloride
Ach	Acetylcholine
AE	adverse event
$A_{e(0-t)}$	amount of unchanged drug excreted into urine from zero to time t
APD	action potential duration
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under plasma concentration-time curve from zero to infinity
$AUC_{(0-t)}$	area under the plasma concentration time curve from zero to the time of the last quantifiable plasma concentration
BQL	below quantifiable limit
BMI	body mass index
BP	blood pressure
CI	confidence interval
CL/F	apparent plasma clearance
CL_R	renal clearance
C_{max}	maximum plasma concentration
CU	clinical unit
CRF	case report form
CV	coefficient of variation
CYP	cytochrome P450
DSST	digit symbol substitution test
ECG	Electrocardiogram
EDC	electronic data capture
FDA	Food and Drug Administration
$f_{e(0-t)}$	fraction of dose into urine
FSH	follicle-stimulating hormone
FTIH	first time in human
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HED	human equivalent dose
hERG	human Ether-à-go-go-Related Gene
HIV	human immunodeficiency virus
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ICF	informed consent form
IRB	Institutional Review Board

λ_z	terminal elimination rate constant
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MFD	maximum feasible dose
NOAEL	no observed adverse effect level
OAE	other significant adverse event
PD	Pharmacodynamics
PK	Pharmacokinetics
PR(PQ)	ECG interval measured from the onset of the P wave to the onset of the QRS complex.
%AUCex	percentage of AUC obtained by extrapolation
PI	principal investigator
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QT_c	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTcV	QT interval corrected according to the Van de Water formula
RR	time between corresponding points on 2 consecutive R waves on ECG
Rsq	goodness-of-fit statistic
SAD	single ascending dose
SAE	serious adverse event
SD	standard deviation
SRC	Safety Review Committee
SUD	substance use disorder
T_{max}	time to maximum plasma concentration
$t_{½\lambda z}$	half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve [time]
ULN	upper limit of normal
US	United States
V_d/F	apparent volume of distribution

1. INTRODUCTION

1.1 Disease Background

Substance use disorders (SUD) represent a major public health and social issue worldwide. In the United States (US), drug and alcohol misuse and abuse are currently leading causes of death, disability, and disease. In addition, current misuse and abuse of prescription medications (including opioids and benzodiazepines) is an epidemic, doubling in the last decade and now responsible for more deaths than motor vehicle accidents (Centers for Disease Control and Prevention [CDC], 2011). The financial cost of SUDs to society, including the cost of treating drug and alcohol abuse, the cost of secondary illnesses and injuries, and lost earnings and years of life due to abusers' illness, incarcerations, and premature death, is staggering. It has been estimated that the cost of drug and alcohol abuse to US society is nearly a half trillion dollars each year (National Institute on Drug Abuse [NIDA], 2010).

Currently, there are limited effective pharmacotherapies for the treatment of SUDs. The only medications approved for SUDs by the US Food and Drug Administration (FDA) are for nicotine, alcohol, and opiate use disorders, and their efficacy is considered to be modest (Marsch, 1998). Therefore, a need exists for safe, effective, orally-available, and low-cost pharmacologic approaches to treat SUDs, particularly cocaine disorders for which there are currently no approved therapies. 18Methoxycoronaridine hydrochloride (18-MC HCl) has demonstrated activity in several animal models of addiction, including those involving nicotine, cocaine, alcohol, morphine, and methamphetamine. 18-MC HCl is being developed as a potential treatment for multiple types of addictions as it has effects on the brain's pleasure center and may prevent craving.

1.2 18-MC HCl Background

1.2.1 Summary of 18-MC Addiction Pharmacology

18-MC reduces the reinforcing effects of addictive drugs, decreasing self-administration of cocaine and other addictive drugs in rats. Mechanistic studies have shown that 18-MC acts as an allosteric, noncompetitive antagonist of the nicotinic acetylcholine (nACh) α3β4 receptor. The α3β4 nACh receptor is predominantly localized in two brain nuclei: the medial habenula and the interpeduncular nucleus. 18-MC has greater than 20-fold lower affinity for the α4β2 nACh receptor, which is expressed ubiquitously in the brain. Local administration of 18-MC into the interpeduncular nuclei or medial habenula can reduce drug self-administration, whereas local administration of 18-MC into the ventral tegmental area has no such effect. Lastly, in a well characterized animal model for "craving" behaviours, 18-MC attenuated the effects of the environmental cues responsible for stimulating cocaine-seeking behaviour.

1.2.2 Role of Dorsal Diencephalic Conduction System in Drug Addiction

There are two major circuits in the diencephalon that connect the flow of information between the forebrain regions and the mid- and hind-brain. The dopaminergic mesolimbic system -- specifically, dopamine neurons projecting from the ventral tegmental area of the mid-brain releasing dopamine in the nucleus accumbens -- has been implicated in the reinforcing and craving effects of drugs of abuse (Wise et al., 1987). The second circuit is the dorsal diencephalic conduction system, which is separate from the mesolimbic pathway in the medial forebrain bundle, and functions as a reward system (Sutherland, 1982). The dorsal diencephalic conduction system

consists of the medial habenula, its afferents in the stria medullaris, and its projections via the habenulo-interpeduncular pathway to the interpeduncular nucleus (Groenewegen et.al., 1986; Ellison 1994).

In summary, the dorsal diencephalic conduction system functions as a reward pathway that is independent from the mesolimbic system that has been implicated in the "craving" phenomenon. A mutual inhibitory relationship seems to exist between the two systems. The dorsal diencephalic conduction system has many interconnections with the dopaminergic mesolimbic system, and drugs of abuse activate both systems (Nishikawa et al., 1986). The α3ß4 nicotinic receptors control cholinergic transmission through the medial habenula, which gates information flowing via the dorsal diencephalic conduction system. The α3ß4 nicotinic receptor is the target of 18-MC.

1.2.3 Selection of 18-MC HCl for Candidate Drug

The naturally-occurring substance ibogaine (a coronaridine backbone structure) had long been claimed to have anti-addiction effects. Glick and colleagues initiated studies of ibogaine in rats. Despite positive and encouraging efficacy in animals with ibogaine, there are serious side effects, such as irreversible neurotoxicity and cardiovascular toxicities. After testing many synthetic coronaridine congeners, 18-MC HCl was found in animal models to reduce morphine (Glick et al., 1996), cocaine (Glick et al., 1996), methamphetamine, and nicotine self-administration (Glick et al., 2000a); oral alcohol (Rezvani et al., 1997) and nicotine intake (Glick et al., 1998); and attenuated signs of opioid withdrawal (Rho and Glick, 1998). 18-MC HCl had no effect on the response to a non-drug reinforcer (water; Glick et al., 1996, 1998) and produced no apparent toxicities that were inherent to ibogaine (Glick et al., 1996, 1999).

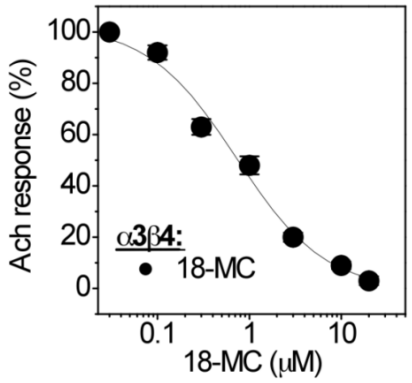
1.2.4 *In Vitro* Pharmacology on Receptor Binding

In a functional assay (86Rb+ efflux from KXα3β4R2 cells), 18-MC was found to be an antagonist at α3β4 nicotinic receptors (KJ Kellar, Georgetown University; personal communication). However, this work did not establish whether 18-MC's nicotinic antagonist action was specific to the α3β4 subtype or whether other nicotinic subtypes were also affected, (Flores et al., 1992). Hence, the actions of 18-MC at both α3β4 and α4β2 receptors were studied as described below.

1.2.4.1 18-MC Antagonism at the α3β4 Nicotinic Acetylcholine Receptor

Transfected HEK293 cells expressing various nACh receptor subunit cDNAs were examined by whole-cell patch-clamp recording with fast perfusion of agonist and drug solutions (Glick *et al.*, 2002). Application of 20 μM 18-MC in the absence of the agonist ACh did not produce any response, indicating that 18-MC activity is dependent on the presence of ACh. In addition, 18-MC dose-dependently decreased ACh-evoked responses (Figure 1) with an IC_{50} of 0.75 μM. The concentration–response relationship had a Hill slope of 1, which is consistent with a single site of action. At 20 μM, 18-MC nearly abolished the ACh-evoked responses in all cells tested. The inhibition developed rapidly in the presence of ACh and reversed more slowly following the removal of 18-MC (Glick et al., 2002).

Figure 1: Effect of 18-MC on α3β4 nicotinic acetylcholine receptor

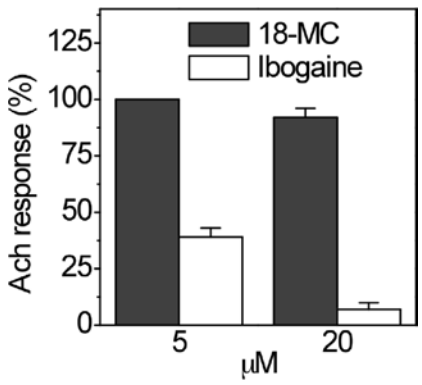


Transfected HEK293 cells expressing α3β4 nAChreceptors were voltage-clamped to –70 mV and stimulated with ACh (1 mM) at 30s intervals. ACh evoked a largeinward current not seen in untransfected cells. 18-MC, by itself, had no effect at the highest concentration tested (20μM). In all α3β4 transfected cells (N=15), co-application of 18-MC dose-dependently inhibited the ACh-evoked responses.

1.2.4.2 Lack of 18-MC Antagonism at the α4β2 Nicotinic Acetylcholine Receptor

18-MC is inactive at the α4ß2 nACh receptor (IC_{50} >20 μM). In contrast, ibogaine blocks both α3β4 and α4β2 receptors (Glick et al., 2002) (Figure 2). These data demonstrate that 18-MC does not interact with the most prevalent type of nicotinic receptors in brain, α4β2.

Figure 2: 18-MC effect on α4β2 nicotinic acetylcholine receptor



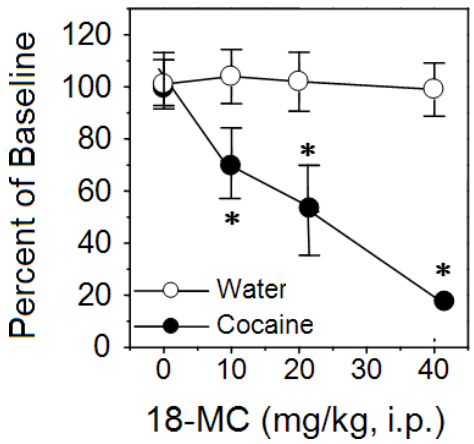
Transfected HEK293 cells expressing α4β2 nACh receptors were voltage-clamped to –70 mV and stimulated with ACh (300 μM) at 30 s intervals. ACh evoked a large inward current not seen in untransfected cells. 18-MC and ibogaine, by themselves, had no effects at the highest concentrations tested (20μM). N=6 for 18-MC, N=5-7 for ibogaine.

1.2.5 *In Vivo* Cocaine Addiction Pharmacology

1.2.5.1 Inhibition of Drug Self-Administration by 18-MC

18-MC HCl was assessed in an addiction model in rats (Glick et al., 1996). 18-MC HCl dose-dependently decreases cocaine self-administration in rats (Figure 3). Note that these effects are selective in that the same doses of 18-MC HCl do not affect responding for water, a non-drug reinforcer. Additional studies have also demonstrated 18-MC's effect on cocaine self-administration when 18-MC HCl is administered orally.

Figure 3: 18-MC effect on self-administration



Female Sprague-Dawley rats were trained to self-administer cocaine hydrochloride (0.4 mg/kg per infusion) or water (0.01ml per barpress) during daily one hour test sessions. 18-MC HCl (10-40 mg/kg, i.p.), administered 15 minutes prior to the session, significantly decreased responding for cocaine while having no effect on responding for water. Each data point is the mean (±S.E.M) from 4-8 rats. All doses of 18-MC HCl had significant effects (ANOVA and t-tests, *= $p<0.05$-0.001).

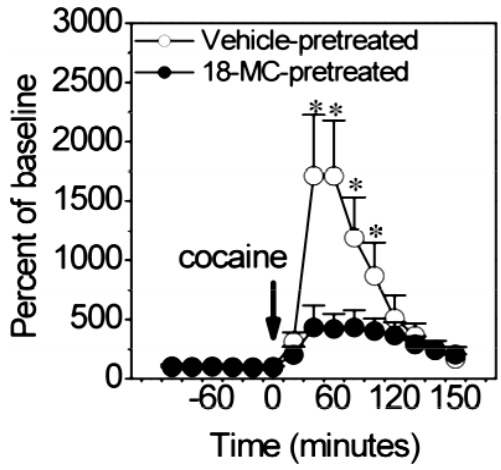
Other studies demonstrated that 18-MC HCl also decreases morphine (Glick et al., 1996), methamphetamine and nicotine (Glick et al., 2000a, 2000b) self-administration in rats. It is important to note that 18-MC HCl has no motor effects that would interfere with self-administration behaviors (Glick et al., 1999).

1.2.5.2 18-MC Blocks Sensitized Dopamine Response to Cocaine in Nucleus Accumbens

Dopamine release in the nucleus accumbens (NAC) has been implicated in the reinforcing actions of drugs of abuse. The effects of systemic 18-MC HCl (40 mg/kg) pretreatment (19 hours beforehand) on the acute and sensitized dopamine responses to cocaine in the nucleus accumbens shell were determined; 18-MC had little effect on the acute response to cocaine but abolished the sensitized dopamine response to cocaine (Szumlinski et al., 2000) (Figure 4).

The results indicate that 18-MC can reverse the sensitized dopaminergic responses to drugs, which is believed to be the neurochemical substrate for drug craving. These results are consistent with evidence that 18-MC decreases the rewarding effects of drugs.

Figure 4: 18-MC effect on sensitized dopamine response

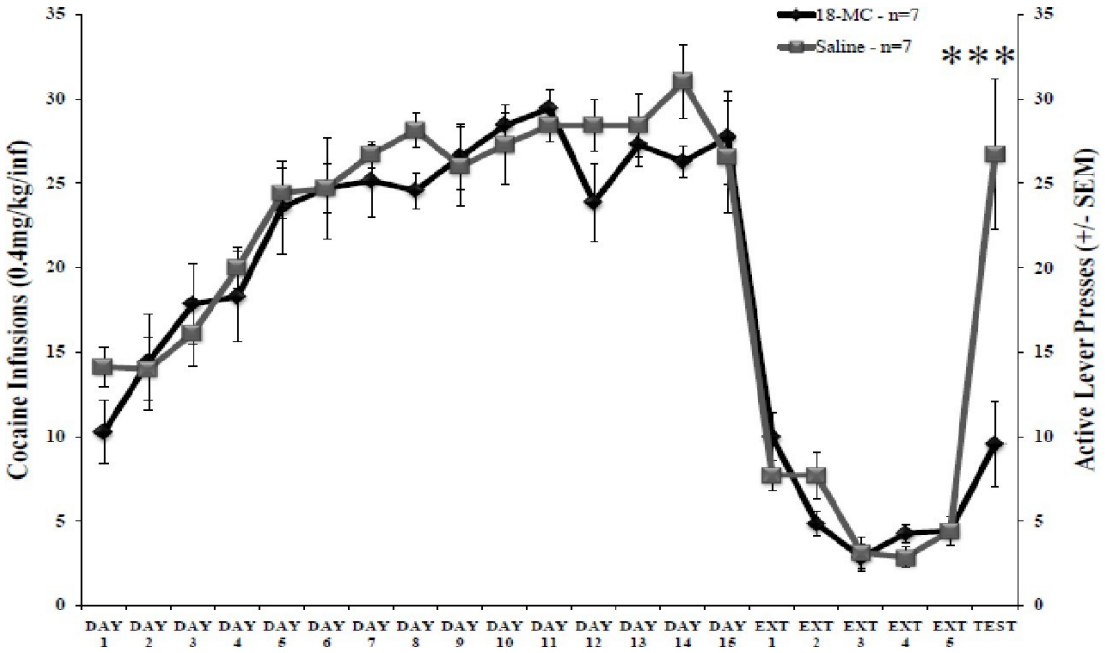


Rats were implanted with microdialysis guide cannula over the shell of NAC. Rats received daily injections of cocaine (15 mg/kg, i.p.) or saline for 5 days. Following 2 weeks of withdrawal, rats were pretreated with either 18-MC HCl (40 mg/kg, i.p.) or vehicle. The next day the effects of cocaine (20 mg/kg, i.p.) were assessed. 18-MC significantly decreased the dopamine response to the administered cocaine. The samples were analyzed by HPLC-EC. N=5-7/group. (Vehicle vs. 18-MC pretreated groups, * = $p<0.05$)

1.2.5.3 18-MC HCl Blocks Context-Induced Reinstatement of Cocaine Seeking(a "craving" model)

The ability to diminish drug craving is considered critical for any treatment of addiction. Several models of craving have been proposed to measure the tendency of rats to respond to stimuli associated with the self-administration of a drug. Polston et al., (2012) used prolonged music cues to alter the context of drug self-administration (Figure 5). Animals were trained to self-administer cocaine in the presence of music. Self-administration behavior was then extinguished over several days in the absence of music. Subsequently, under extinction conditions, when music was re-introduced, it reinstated cocaine seeking behavior (ie, responding on the cocaine paired lever). 18-MC HCl (40 mg/kg, i.p.) blocked the reinstatement effect of cues associated with cocaine self-administration.

Figure 5: 18-MC effect on context-induced craving



Effects of 18-MC HCl on musical cue-induced reinstatement. Data depicted as mean cocaine infusions (±SEM) during self-administration trials, extinction, and active lever presses during the reinstatement test session. Administration of 18-MC HCl (40 mg/kg) prior to the reinstatement test session (Test) significantly attenuated active lever responses previously associated with the music. *** $p < 0.001$.

1.2.6 Nonclinical Safety Pharmacology and Toxicology Studies

1.2.6.1 Summary of Key Findings

Below briefly summarizes pre-clinical studies and the FTIH study that have clinical implications that need to be considered in the next human studies. These studies are described in greater detail in the Investigator Brochure and a summary report of the FTIH.

In vivo safety studies have been performed in the mouse, the rat, and the monkey with observations of behaviour, cardiovascular system, respiratory rate, and body temperature. In addition, toxicology studies have included single-dose and 5-day dose-finding studies followed by 14-day GLP studies in the mouse and the monkey.

The effects of 18-MC HCl on behaviour and physiological state were studied in female rats using the modified Irwin observations. Effects on behaviour and activity of minimal intensity were observed after the administration of higher doses of 400 and 600 mg/kg (human equivalent of 5 to 7 g) including tremors, twitches, decreased motor activity and abnormal gait, increased response to touch and startle, slow respirations and decreased body temperature. The peak effects occurred between 90 and 150 minutes after the administration of 18-MC HCl.

In the study on the self-administration of cocaine in the rat, a 600 mg/kg dose resulted in the death of one of the animals. Before the animal died, there was hypoactivity, cool limbs, and decreased

respiration. After 800 mg/kg, there was hypoactivity, decreased respirations, wet material around the mouth and cool limbs.

The effects of 18-MC on the electrocardiogram, blood pressure, heart rate, respiratory rate and body temperature were studied in instrumented male cynomolgus monkeys. Doses administered were 30, 90 and 270 mg/kg. Emesis was observed after the administration of the 270 mg/kg dose. There was no consistent effect on vital signs during the initial 6 hours. Thereafter there was some statistically significant changes in diastolic blood pressure (decreases less than 10%) 18 hours after dosing with no effects on systolic pressure or heart rate. There were no effects on cardiac ECG intervals including the QT and QTcB throughout the study. Slight increases (<0.5°C) in temperature and decreases in respiratory parameters were noticed 6 hours after the dose. The minimal changes occurring greater than 6 hours after the administration of 18-MC HCl were not considered related to the treatment and the cardiac and respiratory no effect level was the highest dose administered (270 mg/kg). The changes observed, if they were to occur in human participants, would not be clinically meaningful.

A study was performed in mice to observe the physiological changes that occurred before death after the administration of a lethal dose of oral 18-MC HCl. Catheters were inserted to record vital signs and rectal temperatures were also obtained. The animals received 100 mg/kg and 8 hours later 200 mg/kg of 18-MC HCl. Two of the 6 animals died after receiving the 100 mg/kg and all of the other animals died after the 200 mg/kg dose of 18-MC HCl. Within one hour of dosing there was a decrease on average of about 50% in heart rate, with significant decreases in systolic and diastolic blood pressure, and rectal temperature. Terminally, there was further decrease in all of the parameters, with the rectal temperatures decreasing to as low as 22 °C before the mice died.

Non-GLP, 5-day dose-finding studies were performed in the monkey, rat, and mouse.

In the monkey, 18-MC HCl was administered at doses of 130 and 400 mg/kg orally for 5 days. The major observations were dose related and included weight loss associated with reduced appetite and emesis, increased liver weights with hypertrophy, slight bone marrow depletion, and signs of stress. In the 14-day GLP study, monkeys received 50, 150 and 400 mg/kg/day on the first day. One of the monkeys that received 400 mg/kg/day died on the first day of dosing and the dose was decreased to 300 mg/kg/day for all other monkeys. No other drug related mortality was observed, and the pathological findings were consistent with those observed in the 5-day dose finding study.

In the mouse, animals received a single dose or a daily dose for 5 days. In the single dose phase, 100, 150, 200 and 400 mg/kg were administered. Lethality occurred in 2 of 10 animals at doses of 150 mg/kg, and half of the animals after 200 mg/kg. In the pharmacokinetic satellite group, lethality was observed in 1 of 24 animals after 100 mg/kg. In the multiple dose phase, 1 animal died on the second day in the 60 mg/kg daily dose group. Animals showed lethargy and were cold to the touch after treatment with 18-MC HCl.

In the 14-day GLP study, mice received 25, 50 and 100 mg/kg/day. Two mice from the 100 mg/kg/day group died and on macroscopic examination they were noted to have dilated hearts without any microscopic observations. Lymphocyte counts were decreased but still within the historical range and without an effect on the bone marrow.

A 5-day dose-finding study was also performed in rats with male and female animals receiving 60, 180, 360 or 800 mg/kg/day. Clinical signs were observed mostly in the animals that received 800

mg/kg/day and included hypoactivity, dilated pupils, and shallow breathing. Some of the animals also had material around their mouths or nose or hair loss with the occurrence mostly in the 800 mg/kg/day group but also observed in animals that received lower doses. A laboratory change considered to be related to 18-MC HCl was an increase in alkaline phosphatase. Liver weights were increased with signs of hypertrophy. In the 800 mg/kg/day males there were lower heart weights with signs of atrophy. Additionally, signs of stress were noted.

Based on the pharmacology and toxicology studies, the following possible safety issues should be considered in the clinical studies.

When administered to rodents, the first signs that are observed are changes in behaviour and activity, including both increased excitation (tremors) and depression (lethargy and hypoactivity). With higher doses, there are more severe signs, infrequently including seizures, cold limbs reflecting a decrease in body temperature and significant changes in vital signs including decreases in heart rate, and blood pressure. The changes suggest that periodic neurological examinations should be performed along with close monitoring of vital signs and body temperature. Stopping of dose escalation based on early neurological signs, decreases in body temperature, or changes in blood pressure and/or pulse have been incorporated into the early studies as stopping criteria.

In the pharmacology studies, the effect on cardiac repolarization was inconsistent with high concentrations blocking the hERG channel, which is associated with prolongation of the QT interval while the action potential duration in Purkinje cells was shortened. In the monkey, 18-MC had no effect on the electrocardiogram, blood pressure, heart rate, or respiratory rate during the first 6 hours. In the rat 5-day dose-finding study, decreased heart weights and mild cardiac atrophy were observed only in male animals. In the 14-day toxicology studies in the mouse, 2 animals died with dilated heart, but no pathological effects were noted on the cardiac microscopy. While it is unlikely that 18-MC will affect the cardiovascular or respiratory system in humans, because of the *in vitro* data and toxicology observations in rat in the early studies, the effects of 18-MC on cardiac repolarization and cardiac function will be monitored in this clinical study.

In the toxicology studies, changes included the development of mild anemia with bone marrow suppression. Therefore, blood counts will be evaluated regularly.

In addition, increase in liver weights with hypertrophy was observed, which indicates that 18-MC may be a metabolic enzyme inducer, inducing its own metabolism or that of other drugs.

1.2.6.2 Benefit and Risk Based on Nonclinical Studies

In rats, 18-MC HCl significantly decreases the self-administration of cocaine and other drugs of abuse. There is no effective therapy for patients who abuse cocaine and medical therapy would be a significant advancement for these patients. In addition, treatments for other substances of abuse, such as smoking and alcohol abuse, have limited efficacy or side effects. Based on the preclinical data 18-MC HCl may provide a therapeutic advance by decreasing the craving for drugs of abuse.

Treatment with 18-MC HCl initially causes behaviour and neurological changes in animals at doses above the anticipated therapeutic dose. With higher doses seizures and/or significant decreases in body temperature, blood pressure, and heart rate may occur. Higher doses are lethal. Animals that survive the initial adverse events may have had gastrointestinal adverse events as decreased body weight was observed in monkeys. Toxicological changes include bone marrow

depletion and anemia along with hepatic hypertrophy (probably an indication of metabolic induction and not toxicology).

The effectiveness of 18-MC HCl has only been studied in rats. The lowest effective oral dose is 40 mg/kg while 600 to 800 mg/kg is over 80% effective in decreasing the self-administration of cocaine. The lowest lethal dose in rats was observed with the administration of 600 mg/kg, suggesting a therapeutic ratio of up to 12 fold.

The prediction of the clinical therapeutic dose in humans is difficult. In all species, 18-MC HCl undergoes extensive first pass metabolism, so that the parent molecule is a minor circulating species of the total drug content. In the rat, the major metabolite is M5, both after the incubation of 18-MC with hepatocytes and after administration to animals. In human hepatocytes, the major metabolite is M4, with the minor formation of other metabolites. 18-MC is being developed as an inhibitor of the α3β4 nicotinic cholinergic receptor. *In vitro,* M4 binds to the α3β4 nicotinic cholinergic receptors at 3.5 times less potency than18-MC while M5 is 76 times less potent. Therefore, the effective dose in rats is probably overly predicting the clinical dose, even when converted to the human equivalent dose based on body surface area.

In conclusion, 18-MC HCl has the potential to offer a drug with a new mechanism of action that is effective in decreasing the craving for substances of abuse. The initial adverse events are predicted to be behaviour and neurological changes occurring at higher doses than thetherapeutic dose. Dose escalation stopping rules based on significant behaviour and neurological endpoints and vital sign changes should provide a safe way of exploring the effective dose-response relationship.

1.3 Rationale for Study Conduct

A first-time-in-human (FTIH) study was conducted with 18-MC HCL in Brazil. 14 participants were given a single day of dosing in 2 cohorts; 4 mg bid and 20 mg single dose and placebo. There were 9 participants treated with 18-MC, and 5 participants with placebo in both cohorts. 18-MC was well tolerated at both 4 mg bid and 20 mg single dose, and PK was linear.

The starting dose for the FTIH was 20 mg based on $1/10^{th}$ the NOAEL in the most sensitive species, the mouse. However, the 20mg dose demonstrated that 18-MC is absorbed 30 times better than any other animal species, the dog, rat, mouse, or monkey. The plasma levels were at the highest dose levels observed in toxicology studies and 18-MC had a short distribution half-life and a longer terminal half-life. In addition, the toxicity of 18-MC in animal toxicology studies appears to be more associated with Cmax rather than AUC. Therefore, based on this data, the second cohort in the FTIH study was dosed at 4 mg bid in a single day. 18-MC was well tolerated in both cohorts (4 mg bid and 20 mg single dose) and the PK was linear.

The main objectives of this study is to repeat the first-time-in-human (FTIH) study to further assess the safety and tolerability, pharmacokinetics (PK), and pharmacodynamics of single ascending doses of 18MC HCl administered orally to healthy volunteers and evaluate multiple day dosing. Data from this study will form the basis for decisions concerning future studies to treataddiction.

1.3.1 Rationale for Exploratory Analysis

In this study, plasma samples collected for identification of 18-MC metabolites will be used to explore whether the metabolism in humans is similar to the FTIH data.

The extent and duration of PD effects of 18-MC will be evaluated using vital signs, and an abbreviated neurologic examination and a 90-second digit symbol substitution test (DSST), which measures cognitive function changes since these were the first changes in animal toxicology studies as 18-MC was dosed above the anticipated therapeutic dose. Additional testing will include ECG to demonstrate no QTc affect, as well as chemistry and hematology tests since 18-MC showed bone marrow and hematological affects at high doses. The neurological testing and ECG will be done at several time points but in particular at times when 18-MC plasma concentrations are high.

1.3.2 Rationale for Dose Selection

The starting dose for the SAD study is 4 mg bid (Cohort 1), which has been shown to be safe in the FTIH study, and in addition, the highest dose was a 20 mg single dose. Therefore, this dose is 2.5 fold below exposure and 5 fold below Cmax of the 20 mg dose. The first dose in Part 2, the MAD study, is 2 mg bid x 7 days (Cohort 5), because 18-MC has a short distribution half life (about 2-4 hours when considering 18-MC and major metabolites) and a longer terminal half life (about 17 hours). Therefore, Cohort 5 will be less than double the exposure (28 mg total) and 25% Cmax over the Cohort 2 in the SAD, 8 mg bid (16 mg total), and safely allow for assessment of 18-MC potential accumulation to inform further dose escalation. It is reasonable to begin Part 2, Cohort 5 of the MAD study after completion of Cohort 2 (8 mg bid) of SAD because SAD is a repeat of FTIH which assessed a 20 mg single dose, provided that Cohort 1 and Cohort 2 demonstrate safety and PK similar to FTIH.

1.3.3 Benefit/Risk and Ethical Assessment

There will be no benefit for participants participating in this study. Eligibility criteria and study restrictions are chosen to minimize the risk to the selected healthy male and female (of non-childbearing potential) volunteers.

It is concluded that doses of 18-MC HCl, together with the safety monitoring procedures, are not expected to pose any foreseeable risk.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to assess the safety and tolerability of a single day dosing and a separate multiple day dosing of 18-MC HCl administered orally to healthy male and female volunteers.

2.2 Secondary Objectives

The secondary objectives are:

1) To characterize the PK of 18-MC in plasma following oral administration of single day bid ascending doses and multiple day ascending doses
2) To detect and quantify metabolites of 18-MC in plasma

3) To characterize the PD effects and duration of PD effects of 18-MC following oral administration of single ascending doses

4) As an exploratory objective, the concentration of 18-MC and metabolites in the urine will be determined

3. STUDY PLAN ANDPROCEDURES

3.1 Overall Study Design

STUDY DESIGN

This is a Phase 1, double-blind, randomized, placebo-controlled, single day/multiple day dosing, in healthy, non-smoking, male and female volunteers of non childbearing potential.

Part 1: Single day dosing

Seven (7) healthy male and female volunteers (of non childbearing potential) will be randomly assigned to receive in a single day either 18-MC HCl (n=5) or placebo (n=2) in each cohort. There will be 4 cohorts; 1) 4 mg bid, 2) 8 mg bid, 3) 12 mg bid, and 4) 16 mg bid.

All participants will be assessed for PK and safety for 14 days. There will be two sentinel participants in each cohort, who will receive their first dose at least 48 hours prior to the rest of the cohort. Participants will report to the clinical unit (CU) for a screening visit within 28 days prior to Day -1 and all screening procedures and evaluations will be completed. Participants who meet the eligibility criteria will be admitted to the CU on Day -1 and will undergo safety and compliance assessments on this day. The results will be evaluated prior to study drug dosing on Day 1. After treatment administration on Day 1, participants will remain at the CU and undergo serial safety and PK assessments up to the third day. On Day 3, participants will be discharged from the CU. Participants will return to the study site for a follow-up assessment on study day 7 and day14.

Part 2: Multiple day dosing

After completion of Cohort 2 (8 mg bid) in Part 1, based on PK, Part 2 will begin. Cohort 5 (2 mg bid x 7 days) will be less than double the exposure (28 mg total) and 25% Cmax over the Cohort 2 in the SAD, 8 mg bid (16 mg total), and safely allow for assessment of 18-MC potential accumulation to inform further dose escalation. It is reasonable to begin Part 2, Cohort 5 of the MAD study after completion of Cohort 2 (8 mg bid) of SAD because SAD is a repeat of FTIH which assessed a 20 mg single dose, provided that Cohort 1 and Cohort 2 demonstrate safety and PK similar to FTIH.

Seven (7) healthy male and female (of non-childbearing potential) volunteers will be randomly assigned to receive either 18-MC HCl (n=5) or placebo (n=2) in each cohort. There will be 4 cohorts: 5) 2 mg bid x 7 days, 6) 4 mg bid x 7 days, 7) 8 mg bid x 7 days, and 8) 12 mg bid x 7 days

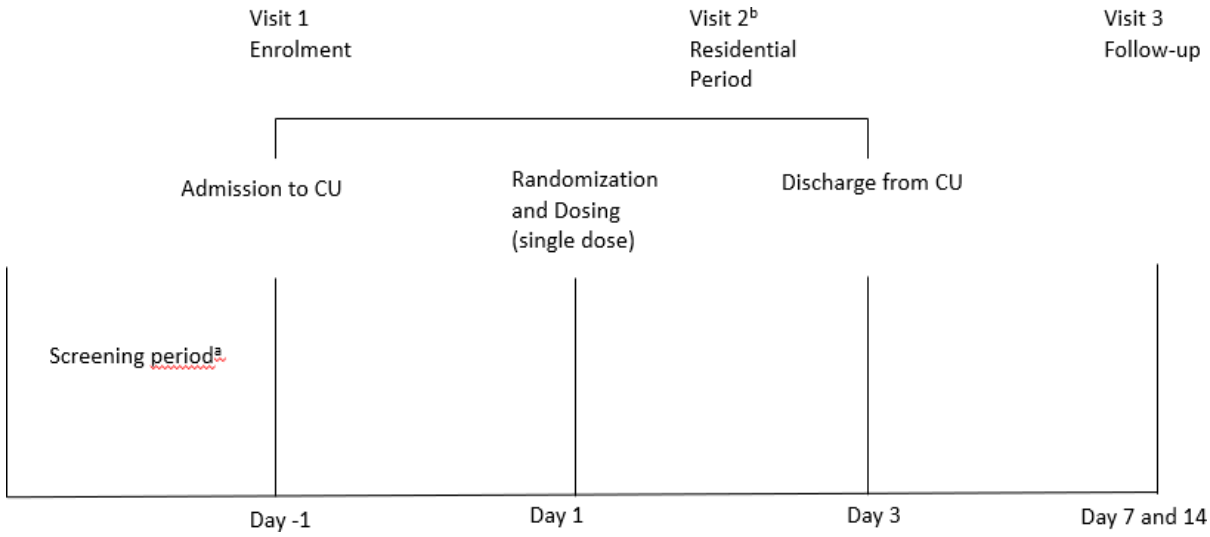
All participants will be assessed for PK and safety for 21 days. Participants will report to the clinical unit (CU) for a screening visit within 16 days prior to Day -1 and all screening procedures and evaluations will be completed. Participants who meet the eligibility criteria will be admitted to the CU on Day -1 and will undergo safety and compliance assessments on this day. The results will be evaluated prior to study drug dosing on Day 1. After treatment administration on Day 1, participants will remain at the CU and undergo serial safety and PK assessments. Participants will be confined for the entire 7 day dose administration period for safety and PK collection, and will be discharged on Day 9. On Days 14 and 21, participants will return to the CU for further follow-up assessment.

A Safety Review Committee (SRC) will review the safety data and exposure of 18-MC derived from available PK analysis (real-time pharmacokinetic analysis), from the participants in all cohorts. The SRC will confirm the next dose in a subsequent cohort (Part 1: Cohorts 2, 3, 4 and Part 2: Cohort 5, 7, and 8).

The study design schema is illustrated in Figure 6.

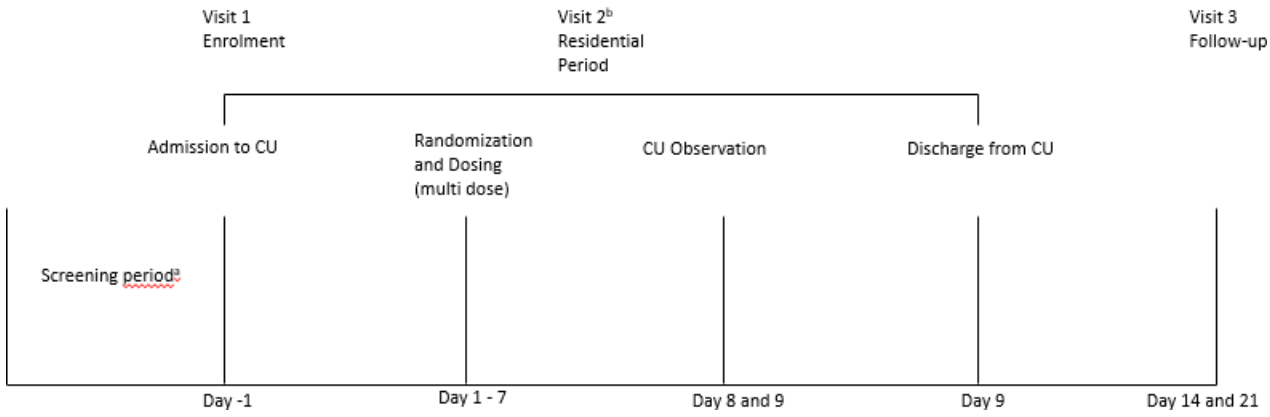
Figure 6: Study Design Schema

PART I: SAD STUDY



Abbreviations: CU = clinical unit.
[a] Screening period may be conducted over 1 or more days during the screening period.
[b] Visit 2 duration may be modified based on the pharmacokinetic parameters determined in earlier cohorts.

Part 2: MAD STUDY



Abbreviations: CU = clinical unit.
[a] Screening period may be conducted over 1 or more days during the screening period.
[b] Visit 2 duration may be modified based on the pharmacokinetic parameters determined in earlier cohorts.

3.1.1 Safety Review Committee

The SRC will consist of the following core individuals:

- Principal investigator or delegate physician (Chair)
- An independent physician
- The sponsor's medical director or delegate

The SRC will be responsible for reviewing the safety and PK analysis results after each cohort. Further dose escalation in Part 1 (SAD) and Part 2 (MAD) will be determined by the SRC, and they will determine whether Cohort 2, 3, and 4 and Cohort 6, 7, and 8 will proceed with enrolment and the dose(s) for each cohort, based on a review of available safety, tolerability, PD, and PK data from the previous dose cohorts.

The data will be reviewed blinded, unless the SRC considers it necessary to unblind the data for safety concerns. Before breaking the code per standard procedures, the potential decisions and actions will be determined.

SRC decisions on dose escalation will be taken in consensus between the physicians. If consensus cannot be reached, the investigator, who has the ultimate responsibility for the safety of participants, will make the final decision on whether to continue or stop the study. The SRC's decisions and their rationale will be documented.

3.1.2 Dose Escalation Criteria Based on PK

The proposed doses for Cohort 1, 2, 3, and 4 of Part 1 (single day) are: 4 mg bid, 8 mg bid, 12 mg bid, and 16 mg bid, and for Cohorts 5, 6, 7, and 8 of Part 2 (multiple day) are: 2 mg bid x 7 days, 4 mg bid x 7 days, 8 mg bid x 7 days and 12 mg bid x 7 days respectively. The dose for each cohort may be revised based on exposure results obtained from the previous dose cohort, however, will not exceed the highest dose stated. Dose escalation from Cohort 1 to 4 and Cohort 5 to 8 will be determined using the stopping guidelines described below.

3.1.3 Stopping Criteria for Safety

After each cohort, the SRC will review all available safety data from all previous cohort(s).

The SRC will stop further dose escalation if any of the following scenarios occur with a reasonable possibility of having been caused by the study drug based onunblinding.

- Two or more participants receiving 18-MC.HCl with reported serious adverse events (SAE) or experience non-tolerable adverse events (AEs).
- Two or more participants receiving 18-MC.HCl observe a significant decrease (greater than 30%) in the number of symbol substitutions tried or number of correct substitutions in the DSST.
- Two or more participants receiving 18-MC.HCl have a clinically significant change in their neurological examination that may include an onset of ataxia, decrease or increase in reflex, loss of proprioception, or change in the ability to do tasks such as finger-nose pointing or heel, knee, foot exam.
- Two or more participants receiving 18-MC.HCl, have QTc prolongation defined as QTcF greater than 500 ms and confirmed persistent on a repeat 12-lead electrocardiogram (ECG).
- Two or more participants receiving 18-MC.HCl, have hepatic toxicity, defined as 1 or more of:
    - Confirmed alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase to greater than 3 times the upper limit of normal (ULN);
    - Confirmed isolated total bilirubin increase to greater than 2 times the ULN; or
    - Confirmed ALT or AST increase to greater than 2 times the ULN concurrent with an increase in total bilirubin to greater than 1.5 times the ULN.
- Two or more participants receiving 18-MC.HCl, have clinically significant changes in laboratory values or other safety parameters, as judged by the investigator along with the SRC.
- Two or more participants receiving 18-MC.HCl have a documented tachyarrhythmia of concern.
- Two or more participants receiving 18-MC.HCl have tachycardia, defined as resting supine heart rate greater than 125 bpm persisting for at least 5 minutes.
- Two or more participants receiving 18-MC.HCl have symptomatic bradycardia with resting supine heart rate less than 30 bpm while awake, persisting for at least 5 minutes.

- Two or more participants receiving 18-MC.HCl develop hypotension, defined as an asymptomatic fall in systolic blood pressure greater than 20 mmHg to below 70 mmHg, persisting for at least 5 minutes.
- Two or more participants receiving 18-MC.HCl develop Hypertension defined as an increase in resting supine systolic blood pressure greater than 40 mmHg to above 180 mmHg, persisting for at least 5 minutes.
- Two or more participants receiving 18-MC.HCl have an increased respiratory rate (30 breaths per minute or more that persisted for 5 minutes) or had respiratory distress defined as symptoms of moderately severe dyspnea.
- Two or more participants receiving 18-MC.HCl have renal toxicity defined as a confirmed serum creatinine increase to greater than 1.5 times the ULN.
- Two or more participants with hematologic toxicity, defined as 2 or more of:
    - Confirmed leukocyte count less than 2.0×10^3/L;
    - Confirmed neutrophil count less than 1.0×10^3/L; or
    - Confirmed platelet count less than 75×10^3/L.
- One or more participants receiving 18-MC.HCl develop hallucinations, paranoia, or other clinically significant psychological effects as determined by the investigator.
- A significant other concern is raised by the investigator in discussion with the SRC.

The SRC will determine whether to dose escalate, stop dosing, repeat the current dose level, or test a lower dose.

3.2 Rationale for Study Design, Doses, and Control Groups

The main objectives of this study is to repeat the first-time-in-human (FTIH) study in Brazil to further assess the safety and tolerability, pharmacokinetics (PK), and pharmacodynamics of single day ascending doses of 18-MC HCl administered orally to healthy volunteers. Further investigations will continue with a multiple day dosing. Data from this study will form the basis for decisions concerning future studies.

The study is randomized and double blinded to minimize bias, and it includes placebo to facilitate identification of effects related to administration of investigational product rather than the study procedures or situation. The study will be conducted in healthy male and female (of non-childbearing potential) volunteers to avoid interference from disease processes or other drugs, and to avoid any potential for teratogenicity in females. The eligibility criteria are defined such that participants selected for participation in the study are known to be free from any significant illness.

The rationale of the starting dose for this study is outlined in Section 1.3.

4. SUBJECT SELECTION CRITERIA

The investigator should keep a record (ie, screening log) of participants who were screened.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study at the time of randomization. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion Criteria

All inclusion criteria will be based on the medical judgment of the investigator. For inclusion in the study, participants must meet all of the following criteria:

1) Written informed consent prior to any study-specific procedures
2) Healthy male and female volunteers aged 18 to 55 years (inclusive) with suitable veins for cannulation and repeated venipuncture.
3) Females must be of non-childbearing potential and must not be pregnant or lactating, confirmed at screening by fulfilling 1 of the following criteria:
    a) Postmenopausal, defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone (FSH) levels within the laboratory-defined postmenopausal range.
    b) Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or tubal ligation. If only verbal confirmation is available, then a pregnancy test must be part of inclusion criteria review at screening (serum test) and Day -1 (urine test).
4) Body mass index (BMI) between 18.0 and 32.0 kg/m^2 and weight of at least 50 kg and no more than 100 kg, inclusive at screening.
5) As judged by the investigator, able to understand and willing to comply with study procedures, restrictions, and requirements
6) Have not smoked or used any tobacco or nicotine containing products in the 3 months prior to screening, and agree not to smoke during the entire study.
7) Male participants must agree to practice abstinence; be surgically sterilised; or agree to use of a condom, plus effective contraception (i.e. established use of oral, injected, orimplanted hormonal contraception; or placement or an intrauterine device (IUD) or intrauterine system (IUS)) for their female partner, if of child bearing potential, throughout the study and for 3 months after the final dose.

4.2 Exclusion Criteria

Participants should not be randomized in the study if any of the following exclusion criteria are met:

1) History of any clinically important disease or disorder that, in the opinion of the investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.
2) History or presence of gastrointestinal, hepatic, cardiac, or renal disease or any other condition known to interfere with absorption, distribution, metabolism, or excretion of study drug.

3) Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of investigational product.

4) History of gastrointestinal ulcer disease, inflammatory bowel disease, indigestion symptoms > 3 times a week, or blood in stool in previous 6 months not related to anal trauma.

5) Any clinically significant abnormalities in clinical chemistry, hematology, or urinalysis results as judged by the investigator at screening or Day -1. Two repeats may be performed at the discretion of the investigator.

6) History of seizures or epilepsy.

7) Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus (HIV).

8) Abnormal vital signs at screening or Day -1, after 5 minutes supine rest, defined as any of the following. Two repeats may be performed at the discretion of the investigator.

   a) Systolic blood pressure > 140 mm Hg;

   b) Diastolic blood pressure > 90 mm Hg;

   c) Pulse rate < 40 or > 90 beats per minute; or

   d) An orthostatic change in systolic blood pressure defined as a decrease in standing systolic blood pressure ≥ 20 mm Hg or diastolic reduction of 10 mm Hg within 1- 3 minutes after assuming an upright position as compared with the supine systolic blood pressure.

9) Any clinically significant abnormalities in rhythm, conduction or morphology of resting ECG that may interfere with the interpretation of QTc interval changes. Two repeats may be performed at the discretion of the investigator. This includes participants with any of the following:

   a) Clinically significant PR (PQ) interval prolongation

   b) Intermittent second- or third-degree atrioventricular (AV) block (Mobitz type I/Wenckebach during sleep is not disqualifying)

   c) Incomplete, full or intermittent bundle branch block (QRS < 110 ms with normal QRS and T-wave morphology is acceptable if there is no evidence of left ventricular hypertrophy)

   d) Significant Abnormal T wave morphology

10) Prolonged QTcF > 450 ms for males and >470 ms for females, or shortened QTcF < 340 ms or family history of long QT syndrome

11) Known or suspected history of substance abuse disorder (as per DSM 5) as assessed by the investigator

12) History of alcohol abuse or excessive intake of alcohol as judged by the investigator, defined as an average weekly intake of > 21 drinks for men or > 14 drinks for women. One drink (12 g alcohol) is equivalent to 150 mL of wine or 285 mL of beer or 30 mL of 80 proof (40% alcohol content) distilled spirits.

13) Positive screen for drugs of abuse, cotinine (nicotine) or alcohol at screening or on admission to the CU. One repeat may be performed at the discretion of the investigator.

14) History of severe allergy/hypersensitivity to any medicine as judged by the investigator.

15) History of hypersensitivity to medicines with a similar chemical structure.

16) Excessive intake of caffeine-containing drinks within two weeks of the study, eg, coffee, tea, energy drinks, and cola (more than 5 caffeinated beverages or products per day). Participants to avoid the above 3 days before admission.

17) Use of any prescribed or over-the-counter medication, including antacids, analgesics (other than paracetamol/acetaminophen up to 3g/day), herbal remedies, or vitamins and minerals during the 7 days prior to the first administration of investigational product or longer if the medication has a long half-life (ie >24 hours). Occasional use of paracetamol/acetaminophen is allowed for minor pains and headache. For female participants, hormone replacement therapy is not allowed.

18) Individuals who have been vaccinated within 2 weeks before the first dose of investigational product or who plan to be vaccinated during the study and up to 2 weeks after the last dose, excluding the flu vaccine.

19) Any intake of grapefruit, grapefruit juice, Seville oranges, or other products containing grapefruit or Seville oranges within 7 days before admission to the CU.

20) Plasma donation within 1 month of screening or any blood donation/blood loss of more than 500 mL during the 3 months prior to screening.

21) Has received another new chemical entity (defined as a compound, which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within 30 days (on the condition that 5 half-lives of the compound is < 30 days) of the first administration of investigational product in this study. The period of exclusion begins at the time of the last follow-up visit of the prior study. Note: participants consented and screened, but not dosed in this study or a previous Phase 1 study, are not excluded.

22) Previous randomization to dosing in the present study.

23) Involvement in the planning and/or conduct of the study.

24) Judgment by the investigator that the subject is unlikely to comply with study procedures, restrictions, and requirements.

Procedures for handling incorrectly randomized participants are described in Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions During Study

The following restrictions apply for the specified times during the study period:

1) Participants must fast two hours before and two hours after each dose. Water is allowed up to 1 hour prior to dosing and may be resumed 1 hour after dosing. 180 mL of regular caffeinated Coca-Cola will be given 30 minutes before dosing to acidify the stomach and

should be consumed within 10 minutes. Eat and drink only the standardized meals and drinks provided (apart from water) during the residential period in the CU.

2) Abstain from consuming any of the following:
   a) Alcohol from 72 hours before admission, during the residential period, and until completion of the study follow-up visit.
   b) Energy drinks containing taurine or glucuronolactone (eg, Red Bull) from 72 hours before admission, during the residential period, and until completion of the final study follow-up visit.
   c) Caffeine-containing drinks (decaf tea and coffee and other beverages allowed), with the exception of Coca-Cola required prior to dosing, during the residential period.
   d) Poppy seeds from time of consent until after the final medical examination at the study follow-up visit.
   e) Grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days before admission to the CU until after the final medical examination at the study follow-up visit.
3) Abstain from the following medications:
   a) Any prescription or over-the-counter medications including antacids, analgesics, herbal remedies (eg, St. John's Wort), vitamins, and minerals (with the exception of up to 3 g per day of paracetamol/acetaminophen), from 7 days prior to administration of investigational product (longer if half-life >24 hours) until after the final medical examination at the study follow-up visit.
   b) However, this should not obviate necessary medical treatment. If any medication is necessary during the residential period, it should be prescribed by the investigator, and the sponsor's physician should be informed (Section 13.1)
4) Participants should refrain from strenuous physical activity, which is not within the subject's normal daily routine, from 48 hours prior to admission to the CU through the final medical examination at the study follow-up visit.
5) Abstain from blood or plasma donation for 3 months after the final medical examination at the study follow-up visit.

5.2 Subject Enrollment and Randomization

The investigator will ensure:

1) Signed informed consent is obtained from each potential subject before any study-specific procedures are performed
2) The eligibility of each subject is determined, as described in Sections 4.1 and 4.2, before administering any study drug

Each screened subject will be identifiable by a unique enrollment number.

Randomization will be performed on the morning of dosing.

This will be a double blind study with the random code generated by the study biostatician who will maintain the code. The subjects, investigator, and Safety Review Committee (SRC) will remain blinded to treatment assignment until the conclusion of the study, unless the SRC considers it necessary to unblind the data.

The following personnel will have access to the randomization list:

- The pharmacy personnel preparing investigational product at the site
- The personnel in the bioanalytical laboratory who are responsible for analyzing the PK samples

The randomization list will be kept in a secure location until the end of the study.

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the pharmacist at the study site. Code break envelopes will also be provided to the study site for emergency unblinding. The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomization. The investigator will document and report any unblinding action to the sponsor.

The SRC retains the right to break the randomization code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

In the event that a subject is replaced, an unblinded pharmacy delegate at the site will determine the appropriate randomization code (subject number) for the replacement subject so that each replacement subject will be assigned to the appropriate treatment and will receive the same investigational product or placebo as the subject being replaced.

Participants who withdraw from the study due to reasons other than an AE may be replaced at the discretion of the sponsor and/or investigator. If a subject withdraws his/her consent to participate in the study, then his/her enrollment/randomization code cannot be reused. In the event that a subject is replaced, an unblinded pharmacy delegate at the site will determine the appropriate randomization code (subject number) for the replacement subject so that each replacement subject will be assigned to the appropriate treatment and will receive the same investigational product or placebo as the subject being replaced.

Within each consecutive dose cohort, participants will be allocated to 18-MC HCl or placebo.

5.3 Procedures for Handling Incorrectly Randomized Participants

Participants who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be randomized into the study. There can be no exceptions to this rule.

A subject who does not meet the eligibility criteria, is randomized in error, and is identified before dosing, should be withdrawn from the study and another subject should be enrolled and receive the same treatment (see Section 5.2).

5.4 Blinding and Procedures for Unblinding of Study

5.4.1 Methods to Ensure Blinding

This study is double blind with regard to treatment at each dose level. The participants, investigator, and SRC will remain blinded to treatment assignment until the conclusion of the study, unless the SRC considers it necessary to unblind the data.

The following personnel will have access to the randomization list:

- The pharmacy personnel preparing investigational product
- The personnel in the bioanalytical laboratory who are responsible for analyzing the PK samples

The randomization list should be kept in a secure location until the end of the study.

5.4.2 Methods for Unblinding

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the pharmacist at the study site. The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomization, or when stopping criteria are being assessed in discussion with the SRC (2 members minimum). The investigator will document and report any unblinding action to the sponsor.

The SRC retains the right to break the randomization code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

After each dose cohort is completed, the SRC will determine the dose for the next cohort. This decision will generally be made without breaking the randomization code. If judged necessary by the SRC, an individual subject or the entire cohort may be unblinded during evaluation of the study data. Before unblinding, a decision should be made about the action to be taken based on the revealed treatment allocation.

5.5 Treatments

It is the investigator/institution's responsibility to establish a system for handling trial treatments, including investigational products, to ensure that:

- Deliveries of such products are correctly received by a responsible person (eg, the staff pharmacist)
- Deliveries are recorded and trial treatments are handled and stored safely and properly
- Investigational product provided for this study will be used only as directed in the study protocol
- The study personnel will account for all investigational product received at the site, dispensed to the subject, and returned to the pharmacy. Any discrepancies should be documented, investigated, and appropriately resolved
- A portion of prepared study drug liquid formations will be shipped to a testing facility for analysis to confirm the dose of drug/placebo given
- Any unused products are accounted for and returned to designated facility for destruction or destroyed by the research site with such standard operating procedures and facilities

At the end of the study, it must be possible to reconcile delivery records of usage, storage (2-8 °C) and returned stocks. Any discrepancies must be accounted for. The Certificates of Delivery and Return must be signed, preferably by the investigator or a pharmacist.

5.5.1 Identity of Investigational Product

The drug substance is 18-MC HCl. The identity of the investigational product is presented in Table 1.

Table 1: Identity of Investigational Product(s)

Investigational product	Dosage form and strength	Manufacturer
18-MC HCl	API	Sterling Pharma Solutions
Placebo	Dextrose	Oxford Compounding

5.5.2 Doses and Treatment Regimens

Each subject will receive liquid formations of 18-MC HCl or placebo with 240 mL of water according to their randomization sequence. The dose will be administered in the morning and afternoon (approximately 10 hours ± 30 minutes apart) with fasting two hours before and two hours after each dose. The study drug doses are outlined in Table 2. For the second dose, the conditions remain the same as for the first dose. The preparation of 18-MC HCl and placebo oral liquid formations will be described in the pharmacy manual.

Table 2A: Part 1 Dose-Escalation Schedule

Dose Cohort	Proposed Dose (mg)
1	4 mg bid
2	8 mg bid based on exposure (Section 3.1.2)
3	12 mg bid based on exposure (Section 3.1.2)
4	16 mg bid based on exposure (Section 3.1.2)

Table 2B: Part 2 Dose-Escalation Schedule

Dose Cohort	Proposed Dose (mg)
5	2 mg bid x 7 days
6	4 mg bid x 7 days based on exposure (Section 3.1.2)
7	8 mg bid x 7 days based on exposure (Section 3.1.2)
8	12 mg bid x 7 days based on exposure (Section 3.1.2)

Dosing will be twice per day (ie BID). The liquid formation will be administered orally with 240mL of water to each subject, for each dose per day by study staff. Coca-Cola (180 ml) will be given 30 minutes before dosing to acidify the gastric environment for each dose administered daily and should be consumed within 10 minutes. For each dose per day, subjects will fast from 2 hours prior to dosing until 2 hours after.

5.5.3 Labeling

All investigational products will be packaged and labeled. Labeling of the investigational products will be performed in accordance with Good Manufacturing Practice.

The label will include the following information.

The clinical trial material will be clearly marked according to national requirements regarding use for clinical trial investigation only and will be labeled with the drug name, study reference number, and storage conditions. It is the responsibility of the investigator to ensure that accurate accountability records are maintained throughout the study. The pharmacy will prepare and dispense the investigational product according to the randomization scheme. Individual dosing containers will be labeled by the investigational site with the following:

a) "For Clinical Trials Use Only"
b) Drug name and strength
c) Quantity of liquid formations in bottle
d) Protocol Number
e) Principal Investigator Name
f) Subject name and subject number/ Randomization No.
g) Dosing directions
h) Name of Sponsor and Contact Details
i) Batch Number
j) Expiry Date
k) Storage Conditions

5.5.4 Storage

All investigational products should be kept in a secure place under appropriate storage conditions. The CU will store the drug product protected from light at a temperature between 2°C and 8°C. The investigational product labels on the containers specify the appropriate storage conditions.

The storage location will be locked and accessible to authorized personnel only.

5.6 Concomitant and Post-Study Treatment(s)

Apart from paracetamol/acetaminophen (not more than 3 g per day) if needed, no concomitant medication or therapy will be allowed. The participants should be instructed that no other medication is allowed including herbal remedies, vitamin and mineral supplements, andover-the-counter products without the consent of the investigator.

Medication considered necessary for the subject's safety and well-being may be given at the discretion of the investigator during the residential period. When any medication is required, it should be prescribed by the investigator who should inform the sponsor as soon as possible. Following consultation with the sponsor's physician, the investigator should determine whether or not the subject should continue in the study.

5.7 Treatment Compliance

The administration of all medication (including the investigational product) should be recorded in the appropriate sections of the case report form (CRF).

Treatment compliance will be assured by supervised administration of the investigational product by the investigator or delegate. The dose, time, and date of administration of the investigational product will be recorded and checked by the monitor at monitoring visits.

5.8 Withdrawal from Study

Participants may be withdrawn at any time. Once dosing has occurred, every attempt should be made to continue assessments to ensure the safety of the subject. Specific reasons for withdrawing a subject should be documented on the CRF and include but are not limited to:

- Subject's decision. The subject is free to withdraw his/her consent to participate in the study at any time, without prejudice
- Adverse events
- Severe noncompliance to the study protocol as judged by the investigator and/or the sponsor

Participants who are withdrawn from the study by the investigator due to AEs after dosing will not be replaced. Participants who withdraw for any reason before dosing or for reasons other than AEs after dosing may be replaced.

5.8.1 Procedures for Withdrawal of a Subject from Study

Participants are free to withdraw their consent to participate in the study at any time, without prejudice. Such participants will always be asked about the reason(s) and the presence of any AEs. If possible, participants who withdraw from the study after dosing and before completion should be seen by an investigator and undergo the assessments and procedures scheduled for the follow-up visit. Adverse events should be followed up (see Sections 6.2.3 and 6.2.4).

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the sections below and the timing of these assessments are detailed in the Study Plans.

It is important that PK sampling occurs as close as possible to the scheduled times. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point. The sequence at a particular time point is digital ECG, vital signs, PK (PK sampling must be performed at the precise protocol-scheduled time), DSST, neurological exam followed by any other simultaneously scheduled laboratory samples as shown.

Table 3: SAD Schedule of Study Procedures

Visit Number	**1 Screening Period**	**2 CU Period**				**3 Follow-up**
Study Day	**Up to 28 days prior to Day -1**	**-1**	**1**	**2**	**3**	**Days 7 and 14 after treatment**
Informed consent	X					
Demography	X					
Medical/surgical history	X					
Admission		X				
Inclusion/exclusion criteria	X	X				
Pregnancy test (for women without documentation of sterilization)	X	X				
Physical examination [a]	X	X	X	X	X	X
Weight [b]	X	X				X
Height	X					
Vital signs [c,d]	X	X	X	X	X	X
Clinical Laboratory Tests [e]	X	X		X	X	X
HIV, Hepatitis B and C	X					
Urine Drug & Alcohol Breath Screen	X	X				
Urine Cotinine	X	X				
12-Lead ECG [f]	X	X	X	X	X	X
Neurologic examination [g]	X	X	X	X	X	X
DSST [g]		X	X	X	X	X
Randomization			X			
18-MC/placebo administration			X			
PK blood sampling [h]			X	X	X	X
PK urine collection [i]			X	X		
Adverse events	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X
Discharge from CU					X	

Abbreviations: BP = blood pressure; CU = clinical unit; DSST = digit symbol substitution test; ECG = electrocardiogram; HIV = human immunodeficiency virus; PK = pharmacokinetics.

[a] A complete physical examination will be performed at screening, admission, discharge, and Day 7, and a brief physical examination will be performed on all other days (up to 3 hours prior to the first dose on Day 1, and on Day 2 and Day 3 at 24 and 48 hours (± 1 hour) post the first dose on Day 1).

[b] Body mass index will be calculated using body weight at screening.

[c] Vital signs (pulse, supine BP, body temperature, respiratory rate) will be performed on Day 1 up to 3 hours pre- dose and 30 minutes pre-dose and then 0.25, 0.5, 1, 1.5, 2, 4 (± 10 minutes) and 10 hours (± 15 minutes) after the first dose and then 0.25, 0.5, 1, 1.5, 2 and 4 hours after the second dose (± 10 minutes). On Day 2 and Day 3, vital signs will be performed 24, 36 and 48 hours after the first dose (± 1 hour). Orthostatic BP should be recorded only at screening and Day -1.

[d] When oral temperatures are to be obtained, hot/cold beverage/food are not permitted 15 minutes before temperatures are obtained.

[e] Blood samples for clinical laboratory tests will be collected on Day 2 and Day 3 at 24 and 48 hours (± 1 hour) post the first dose.

[f] Triplicate ECG will be performed at screening and Day -1, and on Day 1 up to 3 hours pre-dose and then 1.5 and 6 hours after the first dose (± 20 minutes) and then 0.5 and 4 hours after the second dose (± 20 minutes). On Day 2 and Day 3, triplicate ECG will be performed 24, 36 and 48 hours after the first dose (± 1 hour). ECG timing may be adjusted based on PK and safety data from previous cohorts.

[g] Neurologic examination and DSST will be performed on Day 1 up to 3 hours pre-dose and then 0.5 and 4 hours after the first dose (± 30 minutes) and then 1.5 hours after the second dose (± 30 minutes). On Day 2 and Day 3, neurologic examination and DSST will be performed 24, 36 and 48 hours after the first dose (± 1 hour). Two practice DSST will be performed on Day -1.

[h] PK blood sampling will be performed on Day 1 up to 10 minutes pre-dose and then 0.25, 0.5, 1, 1.5, (± 3 minutes) 4 (± 5 minutes) and 10 hours (± 10 minutes) after the first dose and then 0.25, 0.5, 1, 1.5, (± 3 minutes) 4 (± 5 minutes) and 12 hours (± 10 minutes) after the second dose. On Day 2 and Day 3, sampling will be performed 36 and 48 hours after the first dose (± 15 minutes). PK samples will also be collected on Day 7 and Day 14 (± 1 day).

[i] Urine PK samples will be collected at pre-dose (1 sample to be collected during -12 to 0 hours) and at approximately 0-4, 4-8, 8-12 and 12-24 hours post the first dose Urine PK samples are pooled from collections within the intervals.

Table 4: MAD Schedule of Study Procedures

Visit Number	**Screening Period**	**CU Dosing Period**								**CU Observation Period**		**Follow -up**
Study Day	**Up to 28 days prior to Day -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**14, 21**
Informed consent	X											
Demography	X											
Medical/surgical history	X											
Admission		X										
Inclusion/exclusion criteria	X	X										
Pregnancy test (for women without documentation of sterilization)	X	X										
Physical examination [a]	X	X	X	X			X		X		X	X
Weight [b]	X	X	X		X				X		X	X
Height	X											
Vital signs [c,d]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests [e]	X	X		X			X		X		X	X
HIV, Hepatitis B and C	X											
Urine Drug & Alcohol Breath Screen	X	X										
Urine Cotinine	X	X										
12-Lead ECG [f]	X	X	X	X	X		X		X	X	X	X
Neurologic examination [g]	X	X	X	X	X		X		X	X	X	X
DSST [g]		X	X	X	X		X		X	X	X	X
Randomization			X									
18-MC/placebo administration			X	X	X	X	X	X	X			
PK blood sampling [h]			X	X	X		X		X	X	X	X
PK urine collection [i]			X	X					X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Discharge from CPU											X	

Abbreviations: BP = blood pressure; CU = clinical unit; DSST = digit symbol substitution test; ECG = electrocardiogram; HIV = human immunodeficiency virus; PK = pharmacokinetics.

[a] A complete physical examination will be performed at screening, admission, discharge, and Day 14, and a brief physical examination will be performed on all other days (up to 3 hours prior to the first dose of the day, and on Day 9 at 48 hours (± 1 hour) post the first dose on Day 7).

[b] Body mass index will be calculated using body weight at screening. Weight will be recorded up to 3 hours prior to the first dose of the day.

[c] Vital signs (pulse, supine BP, body temperature, respiratory rate) will be performed on Day 1 and Day 7 up to 3 hours pre-dose and 30 minutes pre-dose and then 0.25, 0.5, 1, 1.5, 2, 4 (± 10 minutes) and 10 hours (± 15 minutes) after the first dose and then 0.25, 0.5, 1, 1.5, 2 and 4 and 12 hours after the second dose (± 10 minutes). On Day 2 – Day 6, vital signs will be performed 30 minutes pre-dose and then 0.25, 0.5, 1, 1.5 and 2, 4 and 10 hours after the first dose (± 10 minutes) and then 0.25, 0.5, 1, 1.5, 2 and 4 and 12 hours after the second dose (± 10 minutes). Additional vital signs will be measured on Day 8 and Day 9 at 24, 36 and 48 hours after the first dose on Day 7 (± 2 hours). Orthostatic BP should be recorded only at screening and Day -1.

[d] When oral temperatures are to be obtained, hot/cold beverage/food are not permitted 15 minutes before temperatures are obtained.

[e] Blood samples for clinical laboratory tests will be collected pre-dose and on Day 9 at 48 hours (± 1 hour) post the first dose on Day 7).

[f] Triplicate ECG will be performed at screening and Day -1, and on Day 1 and Day 7 up to 3 hours pre-dose and then 1.5 and 6 hours after the first dose (± 20 minutes) and then 0.5 and 4 hours after the second dose (± 20 minutes). On Day 2, Day 3 and Day 5, triplicate ECG will be performed 1.5 hours after the first dose (± 20 minutes) and then 0.5 hours after the second dose (± 20 minutes). Additional ECG will be performed on Day 8 and Day 9 at 24, 36 and 48 hours after the first dose on Day 7 (± 2 hours). ECG timing may be adjusted based on PK and safety data from previous cohorts.

[g] Neurologic examination and DSST will be performed on Day 1 and Day 7 up to 3 hours pre-dose and then 0.5 and 4 hours after the first dose (± 30 minutes) and 1.5 hours after the second dose (± 30 minutes). On Day 2, Day 3 and Day 5, neurologic examination and DSST will be performed 0.5 hours after the first dose (± 30 minutes) and 1.5 hours after the second dose (± 30 minutes). Additional neurologic exam and DSST will be performed on Day 8 and Day 9 at 24, 36 and 48 hours after the first dose on Day 7 (± 2 hours). Two practice DSST will be performed on Day -1.

[h] PK blood sampling will be performed on Day 1 and Day 7 up to 10 minutes pre-dose and then 0.25, 0.5, 1, 1.5, (± 3 minutes) 4 (± 5 minutes) and 10 hours (± 2 minutes) after the first dose and then 0.25, 0.5, 1, 1.5, (± 3 minutes) 4 (± 5 minutes) and 12 hours (± 10 minutes) after the second dose. On Day 2, Day 3 and Day 5 PK samples will be collected up to 10 minutes prior to the first dose. Additional samples will be collected on Day 8 and Day 9, at 36 and 48 hours after the first dose on Day 7 (± 30 minutes) and on Day 14 and Day 21 (± 1 day). Time points may be adjusted based on available PK results. PK on days other than day 1 and day 7 are AM trough.

[i] Urine PK samples will be collected on Day 1 and Day 7 at pre-dose (1 sample to be collected during -12 to 0 hours) and at approximately 0-4, 4-8, 8-12 and 12-24 hours post the first dose. Urine PK samples are pooled from collections within the intervals. A PK analysis will be performed if a validated assay becomes available

6.1 Recording of Data

For this study, subject data will be collected on CRFs. The investigator will ensure the accuracy, completeness, and timeliness of the data recorded, data queries, and all required reports according to any instructions provided.

Data Collection Part 1

6.1.1 Visit 1: Screening and Enrollment Procedures

At enrollment (Visit 1), each potential subject will provide informed consent prior to starting any study-specific procedures.

Each subject will undergo screening during the 28 days prior to admission to confirm eligibility.

The following procedures will be performed:

1) Demographic data and other characteristics including date of birth, gender and race, alcohol consumption, and smoking history
2) A standard medical, medication, and surgical history with review of the inclusion and exclusion criteria with the subject
3) A complete physical examination
4) Height, weight, and calculation of BMI
5) Vital signs will be collected after subject has rested in a supine position for 5 min, and will consist of supine blood pressure (BP) and pulse, respiratory rate, and body temperature; and orthostatic BP and pulse (participants must sit for 1 minute, and stand for 1-2 minutes prior to collection)
6) Blood sample for clinical laboratory tests (chemistry, hematology, coagulation), pregnancy test (female without confirmation of sterilization only), and screening for hepatitis B surface antigen, antibodies to hepatitis C virus and antibodies to HIV
7) A midstream urine sample for routine urinalysis, screening for drugs of abuse, and cotinine and an alcohol breath test
8) Resting triplicate 12-lead ECG (the subject should be resting in a supine position for at least 5 minutes prior to the evaluation)
9) Neurological examination
10) Adverse events
11) Concomitant medication

6.1.2 Visit 2, Day -1

Participants will be admitted to the CU on Day -1. The following procedures will be performed:

1) Confirm inclusion/exclusion criteria
2) Pregnancy test for women without documentation of sterilization
3) A complete physical examination
4) Weight
5) Vital signs will be collected after subject has rested in a supine position for 5 min, and will consist of supine blood pressure (BP) and pulse, respiratory rate, and body temperature; and orthostatic BP and pulse (participants must sit for 1 minute, and stand for 1-2 minutes prior to collection)
6) Blood sample for clinical laboratory tests
7) Urine for routine urinalysis and screening for drugs of abuse and cotinine and an alcohol breath test
8) Triplicate ECG
9) Neurological examination
10) DSST practice tests (performed twice)
11) Adverse events
12) Concomitant medication

6.1.3 CU, Day 1

Participants will be randomized and undergo the following procedures:

1) Abbreviated physical examination
2) Vital signs
3) Triplicate ECG
4) Neurological exam
5) DSST
6) Randomization and study drug administration
7) 18-MC/placebo administration
8) PK plasma sampling
9) PK urine sample
10) Adverse events
11) Concomitant medications

The PK sample collection time points may be modified based on PK and safety findings in earlier cohort(s).

6.1.4 CU, Day 2

Participants will undergo the following procedures:

1) Abbreviated physical examination
2) Vital signs
3) Blood and urine sample for clinical laboratory tests
4) Triplicate ECG
5) Neurological Examination
6) DSST
7) PK plasma sample
8) PK urine sample
9) Adverse events
10) Concomitant medications

The PK sample collection time points may be modified based on PK and safety findings in earlier cohort(s).

6.1.5 CU, Day 3

Participants will undergo the following procedures:

1) Complete physical examination
2) Vital signs
3) Blood and urine sample for clinical laboratory tests
4) Triplicate ECG
5) Neurological Examination
6) DSST
7) PK plasma sample
8) Adverse events
9) Concomitant medications
10) Discharge from CU

6.1.6 Visit 3: Follow-up Procedures

A post-study medical examination will be performed on Day 7 and Day 14. The following procedures will be performed:

1) Physical examination (complete physical Day 7, brief physical Day 14)
2) Weight
3) Vital signs
4) Blood and urine sample for clinical laboratory tests
5) ECG
6) Neurological examination
7) DSST
8) PK plasma sample
9) Adverse events
10) Concomitant medications

Part 2

6.1.7 Visit 1: Screening and Enrollment Procedures

At enrollment (Visit 1), each potential subject will provide informed consent prior to starting any study-specific procedures.

Each subject will undergo screening during the 28 days prior to admission to confirm eligibility.

The following procedures will be performed:

1) Demographic data and other characteristics including date of birth, gender and race, alcohol consumption, and smoking history
2) A standard medical, medication, and surgical history with review of the inclusion and exclusion criteria with the subject
3) A complete physical examination
4) Height, weight, and calculation of BMI
5) Vital signs will be collected after subject has rested in a supine position for 5 min, and will consist of supine blood pressure (BP) and pulse, respiratory rate, and body temperature; and orthostatic BP and pulse (participants must sit for 1 minute, and stand for 1-2 minutes prior to collection) Blood sample for clinical laboratory tests (chemistry, hematology, coagulation), pregnancy test (female without confirmation of sterilization only), and screening for hepatitis B surface antigen, antibodies to hepatitis C virus and antibodies to HIV
6) A midstream urine sample for routine urinalysis, screening for drugs of abuse and cotinine and an alcohol breath test

7) Resting triplicate 12-lead ECG (the subject should be resting in a supine position for at least 5 minutes prior to the evaluation)
8) Neurological examination
9) Adverse events
10) Concomitant medication

6.1.8 Visit 2, Day -1

Participants will be admitted to the CU on Day -1. The following procedures will be performed:

1) Confirm inclusion/exclusion criteria
2) Pregnancy test for women without documentation of sterilization
3) A complete physical examination
4) Weight
5) Vital signs will be collected after subject has rested in a supine position for 5 min, and will consist of supine blood pressure (BP) and pulse, respiratory rate, and body temperature; and orthostatic BP and pulse (participants must sit for 1 minute, and stand for 1-2 minutes prior to collection
6) Blood sample for clinical laboratory tests
7) Urine for routine urinalysis and screening for drugs of abuse, and cotinine and an alcohol breath test
8) Triplicate ECG
9) Neurological examination
10) DSST practice tests
11) Adverse events
12) Concomitant medication

6.1.9 CU, Day 1

Participants will be randomized and undergo the following procedures:

1) Abbreviated physical examination
2) Weight
3) Vital signs
4) Triplicate ECG
5) Neurological exam
6) DSST
7) Randomization and study drug administration
8) 18-MC/placebo administration

9) PK plasma sampling
10) PK urine sample
11) Adverse events
12) Concomitant medication

The PK sample collection time points may be modified based on PK and safety findings in earlier cohort(s).

6.1.10 CU, Day 2

Participants will undergo the following procedures:

1) Abbreviated physical examination
2) Vital signs
3) Blood and urine sample for clinical laboratory tests
4) Triplicate ECG
5) Neurological Examination
6) DSST
7) 18-MC/placebo administration
8) PK plasma sample
9) PK urine sample
10) Adverse events
11) Concomitant medication

The PK sample collection time points may be modified based on PK and safety findings in earlier cohort(s).

6.1.11 CU, Day 3

Participants will undergo the following procedures:

1) Weight
2) Vital signs
3) Triplicate ECG
4) Neurological examination
5) DSST
6) 18-MC/placebo administration
7) Blood PK (AM trough)
8) Adverse events
9) Concomitant medication

6.1.12 CU, Day 4 and Day 6

Participants will undergo the following procedures:

1) Vital signs
2) 18-MC/placebo administration
3) Adverse events
4) Concomitant medication

6.1.13 CU, Day 5

Participants will undergo the following procedures:

1) Abbreviated physical examination
2) Vital signs
3) Blood and urine sample for clinical laboratory tests
4) Triplicate ECG
5) Neurologic examination
6) DSST
7) 18-MC/placebo administration
7) PK blood sampling (AM trough)
8) Adverse events
9) Concomitant medication

6.1.14 CU, Day 7

Participants will undergo the following procedures:

1) Abbreviated physical examination
2) Weight
3) Vital Signs
4) Blood and urine sample for clinical laboratory tests
5) Triplicate ECG
6) Neurologic examination
7) DSST
8) 18-MC/placebo administration
8) PK plasma sample
9) PK urine sample

10) Adverse events
11) Concomitant medication

6.1.15 CU, Day 8

Participants will undergo the following procedures:

1) Vital Signs
2) Triplicate ECG
3) Neurologic exam
4) DSST
5) PK plasma sample
7) Adverse events
8) Concomitant medication

6.1.16 CU, Day 9

Participants will undergo the following procedures:

1) Complete physical examination
2) Weight
3) Vital Signs
4) Blood and urine sample for clinical laboratory tests
5) Triplicate ECG
6) Neurologic exam
7) DSST
8) PK plasma sample
9) Adverse events
10) Concomitant medication
11) Discharge from CPU

6.1.17 Visit 4: Follow-up Procedures

A post-study medical examination will be performed on Day 14 and 21. The following procedures will be performed:

1) Physical examination (complete physical Day 14 and brief physical Day 21)
2) Weight
3) Vital signs
4) Blood and urine sample for clinical laboratory tests

5) Triplicate ECG
6) Neurological examination
7) DSST
8) PK Blood sampling
9) Adverse events
10) Concomitant medication

6.2 Safety Assessments

The investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.2.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product and that does not necessarily have a causal relationship with this administration. An AE can therefore be:

- Any unfavorable and unintended sign (eg, tachycardia, enlarged liver) or symptom (eg, nausea, chest pain), temporally associated with the use of the investigational product, whether or not considered related to the investigational product
- Abnormal laboratory values or other clinical tests (eg, electrocardiogram or x-ray) that result in symptoms, signs, a change in treatment, discontinuation from study drug, or are considered to be medically significant as determined by the investigator
- Any new disease or exacerbation of an existing disease
- Recurrence of a previously existing intermittent medical condition (eg, headache) not present at baseline

The term AE is used to include any AE, regardless of whether it is serious or nonserious, that has occurred at any time, including run-in or washout periods, even if no study treatment has been administered.

Treatment emergent AEs are any AEs that occur after the administration of the study drug.

6.2.2 Definition of Serious Adverse Event

A SAE is an AE that occurs during any study phase and meets 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization (does not include hospitalizations for elective procedures for pre-existing conditions that did not worsen from baseline);
- Results in persistent or significant disability or incapacity

- Is a congenital abnormality or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but from medical and scientific judgment, may jeopardize the subject or require intervention to prevent one or another of the outcomes listed above (e.g., convulsions that do not result in inpatient hospitalization).

For a definition of other significant adverse events (OAE) see Section 11.1.1.

6.2.3 Recording of Adverse Events

Time Period for Collection of Adverse Events

Adverse events and SAEs will be collected from first investigational product administration throughout the dosing period and including the follow-up visit.

Adverse events (serious and non-serious) will be collected by spontaneous reporting by the subject at any time from first investigational product administration until 30 days following the last administration of investigational product. Prior to dosing, the AE's will be listed in the medical history. Adverse events can also be identified from safety evaluations conducted throughout the trial and by the following methods:

- Asking the subject about their current welfare and if there has been any change in their wellbeing through non-leading questions such as "How are you feeling;"
- Reviewing subject cases histories;
- Reviewing any clinically significant changes in the findings of physical examinations or objective laboratory tests; or
- Signs observed by the study staff should also be considered to elicit AEs especially when the participants cannot be asked.

All observed or volunteered AEs (serious or non-serious) and abnormal test findings, regardless of treatment group or suspected causal relationship to the investigational product or study treatment, will be recorded in the participants' case histories. For all AEs, sufficient information will be pursued and/or obtained so as to permit:

- An adequate determination of the outcome of the event (ie, whether the event should be classified as a serious adverse event); and
- An assessment of the casual relationship between the AE and the investigational product or study treatment.

A cluster of signs and symptoms that results from a single cause should be reported as a single AE (eg, fever, elevated white blood cell count, cough, abnormal, and chest x-ray can all be reported as "pneumonia"). All efforts should be made to obtain a diagnosis for all signs and symptoms.

6.2.3.1 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated. The sponsor retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Results of abnormal liver function tests should be confirmed with a repeat test as soon as possible and within 48 hours, and the findings must be reported in the CRF.

6.2.3.2 Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study (yes or no)
- Outcome

Additional variables will be collected for all SAEs per standard SAE form, including treatment given for the event.

The following intensity ratings will be used:

1) Mild (awareness of sign or symptom but easily tolerated)
2) Moderate (discomfort sufficient to cause interference with normal activities)
3) Severe (incapacitating with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

6.2.3.3 Causality Collection

The investigator will assess causal relationship between the investigational product and each AE using the following classification

Not Related	In the investigator's opinion, there is not a causal relationship between the study product and the AE
Unlikely	The temporal association between the AE and study product is such that the study product is not likely to have any reasonable association with the AE
Possible	The AE follows a reasonable temporal sequence from the time of study product administration but could have been caused by the study subject's clinical state or other modes of therapy administered to the subject.

Probable	The AE follows a reasonable temporal sequence from the time of study product administration, abates upon discontinuation of the study product and cannot be reasonably explained by the known characteristics of the study subject's clinical state.
Highly Probable	The AE follows a reasonable temporal sequence from the time of study product administration, abates upon discontinuation of the study product and reappears when study product is reintroduced.

For SAEs causal relationship will also be assessed for other study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

6.2.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "Have you had any health problems since you were last asked?" or revealed by observation will be collected and recorded in the CRF. When collecting AEs, recording of diagnoses is preferred (when possible) to recording of a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.2.3.5 Adverse Events Based on Examinations and Tests

The results from protocol-mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarized in the Clinical Study Report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECGs, and other safety assessments should only be reported as AEs if: 1) they fulfill any of the SAE criteria; 2) the subject discontinues treatment with investigational product due to the results; or 3) the investigator insists that it should be reported as an AE.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical rather than the laboratory term (eg, anemia versus low hemoglobin value).

In the absence of clinical signs or symptoms, clinically relevant deteriorations in nonmandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.2.4 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

The minimum information to report includes:

- Name, title, and contact information of person reporting event
- Subject number
- Name of investigational product

- Date and time of most recent administration of investigational product
- Date and time of start of SAE
- Description of SAE (symptoms or disease/syndrome)
- Severity of SAE
- Assessment of causality

If any SAE occurs in the course of the study, the investigator or other site personnel will inform sponsor within 24 hours, ie, immediately but no later than the end of the next business day of when he or she becomes aware of it, by completing a SAE Report Form.

The designated sponsor's representative works with the Investigator to ensure that all the necessary information is provided regarding the subject's safety data within 1 calendar day of initial receipt for fatal and life threatening events, and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. The investigator or other site personnel must inform the sponsor's representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but no later than the end of the next business day of when he or she becomes aware of it.

Note: Study Manual will provide further details for all study procedures described below.

6.2.5 Clinical Laboratory Assessment

Participants need to fast 8 hours ahead of lab assessments. Blood and urine samples for determination of clinical chemistry, hematology, coagulation, and urinalysis will be taken at the times indicated in the Schedule of Study Procedures.

The laboratory parameters listed in Table 5 below will be measured.

Table 5: Scheduled Laboratory Tests

Clinical chemistry Albumin/globulin ratio Albumin ALP ALT Amylase AST Urea Calcium - total Chloride Bicarbonate Creatine phosphokinase Creatinine Calculated GFR (based on Cockcroft-Gault method) FSH (post-menopausal female only) GGT Glucose Total cholesterol Magnesium Phosphate Potassium Total protein Sodium Total bilirubin Triglycerides TSH (screening only) Lactate dehydrogenase Urate	**Urinalysis** [a] Occult blood Leukocyte esterase Protein Glucose Bilirubin Ketones Specific gravity pH Urobilinogen Nitrates Urine microanalysis (if indicated)
Coagulation Prothrombin time International normalized ratio Partial thromboplastin time	**Hematology** Leukocyte count Absolute leukocyte differential count Red blood cell count Hemoglobin Hematocrit Reticulocyte count Mean corpuscular volume Red blood cell distribution width Platelet count Differential count

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FSH = follicle-stimulating hormone; GFR = glomerular filtration rate; GGT = gamma glutamyl transferase; TSH = thyroid stimulating hormone.

[a] If a urine sample is positive for protein, blood, nitrites, or leukocyte esterase, a microscopic examination of the urine sediment will be performed.

Additionally, at screening, all participants will be tested for HIV, hepatitis B surface antigen, and antibodies to hepatitis C. Urine will be tested for the following drugs of abuse at screening and admission: amphetamines, barbiturates, cocaine, methadone, methamphetamine, benzodiazepines,

phencyclidine, tetrahydrocannabinol, tricyclic antidepressants and opiates. Urine will also be analyzed for cotinine at screening and admission. Alcohol breath test will be performed at screening and admission. Upon admission to the CU, the subject will be screened for alcohol and drugs. If a subject tests positive to any of these screening tests, he/she will be excluded from the study.

Laboratory values outside the reference limit suspected to be of any clinical significance will be repeated. Participants who have findings where suspected clinical significance is confirmed will either not be included or, if already randomized, will be followed until normalization or for as long as the investigator considers necessary. Additional laboratory variables may be performed for safety reasons if judged appropriate by the investigator.

The samples for clinical laboratory tests and urinalysis will be analyzed using routine methods at the local laboratory. See Section 7.1 for blood volume to be withdrawn. Alcohol breath test and urine drug and cotinine screen will be performed on site.

6.2.6 Physical Examination

A complete physical examination will include an assessment of the following: general appearance, skin, head and neck, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, respiratory, and neurological systems. An assessment for any signs or symptoms of skin irritation will be noted in source and CRF.

A brief physical exam will include at a minimum an assessment of the following: general appearance, skin, head and neck. An assessment for any signs or symptoms of skin irritation will be noted in source and CRF.

Height will be measured in centimeters and weight in kilograms. Measurements should be taken without shoes for all measurements. Body mass index will be calculated from the height and weight measurements at screening.

6.2.7 Neurologic Examination

A brief neurologic exam following a standard methodology will be performed before dosing and at the intervals listed in the footnotes of the Schedule of Study Procedures Table. The neurologic exam includes the assessment of eye movement, with observations for increase or decrease in the presence of nystagmus on limits of looking to the side, finger-nose pointing, heel-knee-toe movement, reflexes of the elbow, knee and ankle, fine touch on the foot, proprioception of the position of the large toe, gait assessment and flexion and extension of the leg at the knee and the foot (gait assessment).

6.2.8 ECG

6.2.8.1 Resting 12-Lead ECG

A 12-lead ECG will be obtained digitally after the subject has been resting in the supine position for at least 5 minutes at time points outlined in the Schedule of Study Procedures Table. All ECGs will be documented by recording date, time of collection, heart rate, PR, RR, QRS, QT, and QTcF intervals from the 12-lead ECG.

All ECGs should be done in triplicate at least 1-5 minutes apart.

If indicated, additional ECG assessments can be made at the discretion of the investigator. These assessments should be entered as an unscheduled assessment.

The investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided whether or not the abnormality is clinically significant or not clinically significant, and

the reason for the abnormality will be recorded. The date/time and the physician interpretation

(normal, abnormal clinically significant, abnormal not clinically significant) for the paper ECGs will be stored as source documents both digitally and as a paper printout.

Skin preparation must be thorough and electrode positions must be according to standard 12 lead ECG placement. Electrode positions will be marked with an indelible pen at the start of the study days to ensure exact reposition. Permanent electrodes will be applied at least 30 minutes before first study recording and left in place for the duration where possible. Electrodes may be replaced at the discretion of the investigator (or delegate) if required.

6.2.9 Vital Signs

Vital signs will be measured according to the Schedule of Study Procedures Table. Vital signs should be obtained after the subject has been resting in a supine position for at least 5 minutes.

6.2.9.1 Supine Pulse, Respiratory Rate, and Blood Pressure

Supine blood pressure will be measured using a semiautomatic blood pressure recording device with an appropriate cuff size. Participants will be required to rest in a supine position for at least 5 minutes prior to taking blood pressure, respiratory rate, and pulse rate measurements.

6.2.9.2 Orthostatic Pulse and Blood Pressure

Orthostatic (supine followed by sitting then standing) blood pressure and pulse will be measured using a semiautomatic blood pressure recording device with an appropriate cuff size. The participants will be required to rest in a supine position for at least 5minutes prior to blood pressure and pulse rate measurements. For the standing blood pressure evaluation, participants will be required to stand for 1-3 minutes prior to the evaluation.

6.2.9.3 Body Temperature

Oral body temperature will be measured in degrees of Celsius using an automated thermometer. No hot/cold beverage/food 15 minutes is allowed before the temperature is measured.

6.2.9.4 Seizure/Emergency Treatment

During and following a subject's participation in the trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any AEs, including clinically significant laboratory values, related to the trial. Should a subject develop a seizure during the clinical trial, standard medical care will be initiated by medical staff and may include (but is not limited to) securing the airway, administering oxygen, assisting with ventilation and suctioning and initiating emergency medical support where appropriate. If seizure lasts longer than 1 minute, then medical staff will administer appropriate anti-seizure medication and other relevant care at the discretion of the investigator.

6.3 Pharmacokinetics

6.3.1 Collection of Pharmacokinetic Samples

The timing and number of PK samples may change based on emerging data. However, the total blood volume collected from each subject will not exceed the maximum limits for the study (575 mL). The actual date and time of collection of each sample will be recorded on the CRF. For blood volume see Section 7.1.

Plasma samples

Venous blood samples will be collected for the determination of concentrations of 18-MC and possible metabolites in plasma will be taken at the intervals indicated in the footnotes of the Schedule of Study Procedures Table. Sample handling and collection will be provided in a laboratory manual.

The back-up plasma samples should be kept at the study site unless requested.

Plasma samples will be shipped to MicroConstants, Inc.

Urine samples

Urine sample for possible PK analysis (if a validated assay becomes available) will be collected at intervals indicated in Table 3. A manual will be provided with instructions for sample handling.

Shipment of PK samples

The plasma and urine samples will be transported frozen, on dry ice (a sufficient amount of dry ice should be used to keep the samples frozen for up to 5 days) to the following address:

MicroConstants, Inc.
9050 Camino Santa Fe
San Diego, CA 92121

The following persons will be notified before dispatch:

Yazmin Alatorre
Senior Project Coordinator
MicroConstants, Inc.
Phone: 858-652-4600
Email: yalatorre@microconstants.com

6.3.2 Determination of Drug Concentration in Pharmacokinetic Samples

Samples for determination of 18-MC concentrations in plasma and urine will be analyzed by MicroConstants, Inc., on behalf of the sponsor, using an appropriate bioanalytical method. Full details of the analytical methods used will be described in a separate bioanalytical report.

For each placebo treatment, only the predose and 0.5 hour sample will be analyzed. Other time points will be analyzed on a 'for cause' basis, eg, if quantifiable concentrations were observed in a volunteer's samples when drug might be expected to be seen.

Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites, or to determine the reproducibility of analytical results. Any results from such analyses may be reported separately from the Clinical Study Report.

6.4 Pharmacodynamics

6.4.1 Digit Symbol Substitution Test (DSST)

The DSST is a paper test in which the participants are provided a sheet that has a key with ten different symbols, and associated with each symbol is a number from 0 to 9. The rest of the sheet is a randomized set of digits and the subject is asked to proceed through the digits and provide the associated symbol for each of the listed digits. The subject is given 90 seconds to complete the substitutions. As there is a learning bias, two pre-dose tests should be performed by the participants as practice on Day -1. On Day 1, the participants will be asked to perform the test before dosing and at the times after dosing. See Table 7 (Appendix A) for the test. Practice tests may be performed at anytime on Day -1, with at least an hour between tests.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of Blood

The approximate total volume of blood that will be drawn from each subject in this study is shown below.

Table 6: Part 1 Volume of Blood to be Drawn From Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Safety	Clinical chemistry	5	7	35
	Glucose	2	7	14
	Coagulation	3	7	21
	Hematology	2	7	14
	Serology	5	1	5
PK samples		10	15	150
Total		n/a	44	232

Table 6: Part 2 Volume of Blood to be Drawn From Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Safety	Clinical chemistry	5	9	45
	Glucose	2	9	18
	Coagulation	3	9	27
	Hematology	2	9	18
	Serology	50	1	5
PK samples		10	32	320
Total		n/a	72	433

The number of samples to be obtained, as well as the volume required for each analysis, may be changed during the study as new data on 18-MC become available. However, the maximum volume to be drawn from each subject should not exceed 575 mL, ie, the same volume as that would be drawn during a regular blood donation.

7.2 Handling, Storage and Destruction of Biological Samples

The samples will be used or disposed of after analyses, or retained for further use, as described in this section.

7.2.1 Pharmacokinetic Samples

Additional analyses will be conducted on the biological samples to investigate the reproducibility of the analytical results in incurred samples. Any results from such analyses will only be used to confirm the reproducibility of the method, and will be reported in a separate table in the bioanalytical study contribution report.

Following the bioanalysis of 18-MC, selected plasma samples from this study will be retained for possible future analysis of metabolites.

7.2.1.1 Sample Processing and Shipping

Samples must be shipped frozen (-20°C or below).

7.3 Labeling and Shipment of Biohazard Samples

The investigator ensures that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria).

Any samples identified as Infectious Category A materials are not shipped, and no further samples will be taken from the subject unless agreed with the sponsor, and appropriate labeling, shipment, and containment provisions are approved.

8. ETHICAL AND REGULATORYREQUIREMENTS

8.1 Ethical Conduct of Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH) Good Clinical Practice (GCP).

8.2 Subject Data Protection

The informed consent form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and Regulatory Review

The Institutional Review Board (IRB) should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the participants. The investigator will ensure the distribution of these documents to the applicable IRB, and to the study site staff.

The opinion of the IRB should be given in writing. The investigator should submit the written approval to the sponsor before enrollment of any subject into the study.

The IRB should approve all advertising used to recruit participants for the study.

The sponsor should approve any modifications to the ICF that are needed to meet local requirements. The IB should be updated and reviewed annually.

The investigator is also responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product.

8.4 Informed Consent

Any incentives for participants who participate in the study as well as any provisions for participants harmed as a consequence of study participation should be described in the ICF that is approved by an IRB.

The investigator will:

- Ensure that each subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure that each subject is notified that they are free to withdraw from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF are stored in the Investigator's Study File
- Ensure copies of the signed ICF are given to the subject

8.5 Changes to Protocol and Informed Consent Forms

Study procedures will not be changed without the mutual agreement of the investigator and sponsor.

If there are any substantial changes to the study protocol, these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol (Revised Protocol).

The sponsor will distribute any subsequent amendments and new versions of the protocol to the investigator. For distribution to the IRB, see Section 8.3.

If a protocol amendment requires a change to the ICF, the sponsor and the IRB should approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by the IRB.

8.6 Audits and Inspections

Authorized representatives of the sponsor, Health Authority, or an IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact the sponsor immediately if contacted by a regulatory agency about an inspection at the center.

9. STUDY MANAGEMENT

9.1 Pre-study Activities

Before the first subject is entered into the study, it is necessary for a representative of the sponsor to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of participants appropriate for the study
- Discuss with the investigator (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of the sponsor or its representatives. This will be documented in a Clinical Study Agreement between the sponsor and the investigator.

9.2 Training of Study Site Personnel

Before the first subject is entered into the study, a sponsor's representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

9.3 Monitoring of Study

During the study, a representative of the sponsor will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the electronic data capture [EDC] system with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating participants. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented and reported to the subject.

The sponsor's representative will be available between visits if the investigator or other staff at the site needs information and advice about the study conduct.

9.3.1 Source Data

Refer to Clinical Study Agreement for location of source data.

9.4 Study Agreements

The investigator should comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of participants, and in all other respects, the terms of the Clinical Study Agreement shall prevail.

Agreements between the sponsor and the investigator should be in place before any study-related procedures can take place or participants are enrolled.

9.4.1 Archiving of Study Documents

The investigator follows the principles outlined in the Clinical Study Agreement.

9.5 Study Timetable and End of Study

The end of the study is defined as "the last visit of the last volunteer undergoing the study."

The study may be terminated if the study procedures are not being performed according to GCP, or if recruitment is slow. The sponsor may also terminate the entire study prematurely if concerns for safety arise within this study, or in any other study with 18-MC.

10. DATA MANAGEMENT BY A DELEGATE

Data management will be performed by Mind Medicine Inc or its delegate.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, and locked, a clean file will be declared. Any treatment-revealing data may thereafter be added and the final database will be locked.

Data storage will be done in accordance with GCP guidelines. The Study Data Management Plan will describe the methods used to collect, check, and process clinical data in detail. It will also clarify the roles and responsibilities for the different functions and personnel involved in the data management process. Furthermore, the Study Data Management Plan will describe the data flow and timelines within the study.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or Derivation of Safety Variable(s)

All AEs will be collected for each subject from the time when informed consent is obtained (Visit 1) until the follow-up visit. Adverse events that occur before dosing will be reported separately.

Change-from-baseline variables will be calculated for the safety variables listed below, as the posttreatment value minus the value at baseline. The baseline values will be as follows:

- Clinical laboratory tests: Day -1
- Vital signs (including supine and standing blood pressure): Day -1
- ECG: predose on Day 1

11.1.1 Other Significant Adverse Events

During the evaluation of the AE data, the sponsor's medically qualified expert will review the list of AEs that were not reported as SAEs or AEs leading to discontinuation. Based on the expert's judgment, significant AEs of particular clinical importance may be considered OAEs and reported as such in the Clinical Study Report. A similar review of other data from laboratory tests, vital signs, ECGs, and other safety assessments will be performed for identification of OAEs.

Examples of these are marked hematological and other laboratory abnormalities, certain events that lead to intervention (other than those already classified as serious), or significant additional treatment.

11.2 Calculation or Derivation of Pharmacokinetic Variables

The PK analyses of the plasma and urine (if a validated assay is available) concentrations of 18-MC will be performed at MicroConstants.

The actual sampling times will be used in the PK parameter calculations. Pharmacokinetic parameters will be derived using noncompartmental methods.

Where possible, the PK parameters listed below will be determined for 18-MC, and if there is a validated assay, for any major metabolites. Major metabolites are defined as any metabolite whose exposure (AUC) is greater than or equal to 10% of the total drug exposure. The total drug exposure is defined as the sum of the exposure (AUC) of the drug and measurable metabolites. If a validated assay is not available for the measurement of observed metabolites, as a substitute, the peak heights in the MS of 18-MC and the metabolites will be substituted as it appears that the peak heights are approximately proportional to the metabolite concentrations in the preclinical studies.

- Maximum plasma concentration (C_{max}, ng/mL) in the sampled matrix, obtained directly from the observed concentration versus time data
- Time to maximum plasma concentration (T_{max}, h), obtained directly from the observed concentration versus time data
- Terminal rate constant (λ_z), if estimable, calculated by log-linear least-squares regression of the terminal part of the plasma concentration versus time curve using at least three data points in the terminal part of the curve. If the goodness-of-fit statistic (Rsq) is less than 0.80, λ_z will not be reported
- Area under the plasma concentration-time curve from zero to the time of the last measurable concentration ($AUC_{(0-t)}$, ng·h/mL), calculated by linear up/log down trapezoidal summation
- Area under the plasma concentration-time curve from zero (predose) extrapolated to infinite time (AUC, µg×h/mL), calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by

the elimination rate constant: $AUC_{(0\text{-last})} + C_{last}/\lambda_z$. If the extrapolated area (C_{last}/λ_z) is greater than 20% of AUC, then AUC will not be reported

- Terminal half-life ($t_{½\lambda z}$, h), calculated by $\ln 2/\lambda_z$. If the Rsq is less than 0.80, $t_{½\lambda z}$ will not be reported
- Apparent plasma clearance (CL/F, L/h), calculated as Dose/AUC (F)
- Apparent volume of distribution at terminal phase (V_z/F, L), calculated by $CL/\lambda_z F$
- Amount of 18-MC and major metabolites excreted in urine from time zero to "t" ($Ae_{(0\text{-t})}$, µg) for each collection interval and each cumulative interval, calculated as the amounts (amount = [urine volume] x [urine concentration] at each interval and summation of the amount at each cumulative interval)
- Fraction of dose excreted into urine ($fe_{(0\text{-t})}$, %), calculated as $A_{e(0\text{-t})}$ divided by dose. $fe_{(0\text{-t})}$ will be calculated for each collection interval and each cumulative interval. The appropriate correction factor to account for the differences in molecular weight of parent drug and metabolites will be employed for this calculation
- Renal clearance (CL_R, L/h), calculated as $Ae_{(0\text{-t})}$ divided by AUC

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- The time interval (h) of the log-linear regression used to determine $t_{½\lambda z}$
- Number of data points included in the log-linear regression analysis
- Rsq for calculation of λ_z
- Percentage of AUC obtained by extrapolation (%AUCex)

Additional PK parameters will be determined if deemed appropriate.

The data from this study may be used to develop a population PK model. The results of such analysis will not form part of the Clinical Study Report for this study.

11.3 Calculation or Derivation of Pharmacodynamic Variables

The collection of the pharmacodynamic variables is exploratory. Among the variables collected will be the number (percentage) of participants with abnormalities on the abbreviated neurologic exam, and for the DSST the number of substitutions attempted in the 90 seconds and the number of correct substitutions. The data will be summarized by using descriptive statistics. In addition, for the DSST, the following may be calculated:

- Area under the effect-time curve from zero to the time of the last test (AUEC)
- Time to maximum increase or decrease in the number of attempted substitution ($T_{max\ attempt}$, h), obtained directly from the observed effect versus time data
- Time to maximum increase or decrease in the number of correct substitution ($T_{max\ correct}$, h), obtained directly from the observed effect versus time data
- Maximum percentage increase or decrease in number of attempted substitution ($E\%_{max\ attempt}$) in the sampled matrix, obtained directly from the effect versus time data

- Maximum percentage increase or decrease in number of correct substitution ($E\%_{max\,correct}$) in the sampled matrix, obtained directly from the effect versus time data

12. STATISTICAL METHODS AND SAMPLE SIZE

12.1 Description of Analysis Sets

12.1.1 General Principles

The analysis of data will be based on different subsets according to the purpose of analysis, ie, for safety and PK, respectively. The decision regarding validity of data for each of the analysis sets will be based on a blind review of data.

The as-treated principle will be applied to all evaluations; ie, participants who receive a treatment other than the one assigned in the randomization list will be analyzed as belonging to the actual treatment group and not that assigned by randomization.

12.1.2 Safety Analysis Set

All participants who receive at least 1 dose of randomized investigational product, 18-MC or placebo, and for whom any postdose data are available, will be included in the safety population. As the number of participants in each cohort who receive placebo is only one subject, all of the participants who receive placebo will be considered as a single group when the data is summarized.

12.1.3 PK Analysis Set

The PK analysis set will include all participants who receive a dose of 18-MC and have at least 1 postdose PK measurement without important protocol deviations or violations thought to significantly affect the PK of the drug. Data from participants with deviations determined to affect PK will be excluded from the PK analysis set. Participants that receive placebo will not be part of the PK analysis set. A strategy for dealing with data affected by protocol violations and deviations will be agreed to by the sponsor, monitor, and pharmacokineticist, prior to clean file and code break. Participants will be analyzed according to the treatment they actually received.

12.1.4 Interim Pharmacokinetic Analysis

Interim PK analyses will be conducted when the PK analysis results from each dose cohort are made available to the SRC to determine dose escalation (see Section 3.1.2). All participants from each dose cohort with 18-MC HCl exposure data will be included in the analysis dataset.

12.1.5 Pharmacodynamic Analysis Set

The PD analysis set will include all participants who receive a dose of 18-MC and have at least 1 postdose PD measurement without important protocol deviations or violations thought to significantly affect the PD of the drug. This will apply when the PD variables in the analysis of the DSST are developed (see Section 11.3).

The same rules of analysis as described in Section 11.1 will be followed, as applicable.

12.2 Methods of Statistical Analyses

12.2.1 General Principles

Given the exploratory nature, no formal statistical hypothesis testing will be performed in this study. The PD effect parameters will be summarized descriptively for all participants who were treated with investigational product according to the protocol.

Data will be presented by actual dose (not by cohort), and participants receiving placebo will be pooled across the dose cohorts for the purposes of summarizing the safety results.

Missing data will result in a reduced sample size for that parameter. Since the statistical analyses will be predominantly presentations in tables and individual data listings, no action will be taken to handle missing data.

A subject who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation.

12.2.2 Subject Characteristics

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum) by treatment/dose group. All of the participants who receive placebo will be grouped together as one group and will be presented as a separate treatment group in the presentation of demographic information and safety information. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment/dose group.

12.2.3 Safety and Tolerability

All safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarized using descriptive statistics (n, mean, SD, minimum, median, and maximum) by treatment/dose group. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment/dose group. Graphical presentations will be used as appropriate. Examples may include line graphs showing individual or mean development over time, and shift plots showing pretreatment values on horizontal axis and posttreatment values on vertical axis.

All AEs will be collected for each volunteer from the time when informed consent is obtained (Visit 1) until the follow-up visit. Adverse events that occur before dosing will be reported separately.

Adverse events will be summarized by preferred term and system organ class using MedDRA vocabulary (version 12.0 or higher) by dose group. Furthermore, listings of SAEs and AEs that led to withdrawal will be made and the number of participants who had any AEs, SAEs, AEs that led to withdrawal, and AEs with severe intensity will be summarized.

Tabulations and listings of data for vital signs, clinical laboratory tests, ECGs, and physical examination findings will be presented. Where applicable, data will be summarized for the absolute value at each scheduled assessment and for the corresponding change from baseline. For clinical laboratory tests, listings of values for each subject will be presented with abnormal or out- of-range values flagged. Clinical laboratory data will be reported in the units provided by the clinical laboratory for the SRC meeting.

Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics but will be included in subject listings. All AEs, ECG outliers, and clinical laboratory outliers that occur following dosing of study medication will be included in the tabulations of AEs and outlier events, including episodes that occur at unscheduled evaluations.

For ECG parameters, the QT correction factor will be based on the Fridericia's formula. Further categorical summaries of absolute QT and QTcF values (< 300 ms, < 320 ms, > 450 ms, > 480 ms, >500 ms) and change from predose values in QT and QTcF values (> 30 ms, > 60 ms) will also be produced.

12.2.4 Pharmacokinetics

A listing of PK blood sample collection times by individual, as well as derived sampling time deviations will be provided. A listing of urine sample collection start and stop times will be provided. A subject listing of all plasma and urine concentration-time data for each treatment will be presented.

Plasma concentrations of 18-MC and major metabolites will be summarized by nominal time point and dose using appropriate descriptive statistics such as N, mean, SD, coefficient of variation (CV), geometric mean, geometric CV (GCV), minimum, median, and maximum. The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The GCV is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the standard deviation of the data on a log scale.

Below quantifiable limit (BQL) values of plasma concentrations will be reported as BQL and not included in the calculation.

Amounts and fractions of 18-MC and major metabolites excreted in urine (if measured) over each collection interval (individuallyand cumulatively) for each dose cohort will be summarized using descriptive statistics.

Plasma and urine PK parameters will be summarized by dose using N, mean, SD, CV%, geometric mean, GCV, minimum, median, and maximum, except that t_{max} will be reported with N, minimum, median, and maximum only.

Figures of geometric mean concentration-time data may be presented for all doses. Individual subject concentration-time data will be graphically presented on linear and semi-logarithmic scales using actual sample times.

Figures of C_{max}, $AUC_{(0-t)}$, and AUC versus dose, showing individual and the geometric mean, will be presented separately, with a linear trend-line through zero in order to visually demonstrate whether dose-proportionality stays within the examined dose range. In addition, individual dose-normalized C_{max} and AUC will be plotted versus dose.

12.2.5 Pharmacodynamics

The data from the DSST will be summarized for the number of substitutions attempted and number correct by dose using N, mean, SD, CV%, mean, minimum, median, and maximum. If a subject attempts the DSST and does not have any recorded response on the answer sheet, the number attempted and correct will be set to zero. Participants that do not attempt any response data will not be included in the summary statistics for the given time point.

12.3 Determination of Sample Size

Due to the exploratory nature of the study, the sample size is not based on formal statistical considerations. The sample size is based on experience from previous similar Phase 1 studies with other compounds.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical Emergencies and Contacts

The investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes an SAE and isto be reported as such (see Section 6.2.4).

In the case of a medical emergency, the investigator may contact the sponsor's physician.

Name	Role in the study	Address & telephone numbers
Scott Freeman	Chief Medical Officer	Mind Medicine, Inc. 1325 Airmotive Way, Suite 175A, Reno, NV, 89502, USA Telephone: + 1 202 494 0284 (mobile)
Scott Freeman	Medical Monitor	Mind Medicine, Inc. 1325 Airmotive Way, Suite 175A, Reno, NV, 89502, USA Telephone: + 1 202 494 0284 (mobile)

13.2 Overdose

There is no human data on overdosing since there were no overdoses in the previous first-time-in-human Phase 1 study with 18-MC HCl. There is no known antidote. In the event of an overdose, the subject should be monitored closely and treated symptomatically.

Use of investigational product in doses in excess of that specified in the protocol should not be recorded in the CRF system as an AE of "Overdose," unless there are associated symptoms or signs. The associated symptoms or signs will be the AE terms documented in the source documents.

An overdose with associated SAE(s) must be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the source documentation and CRF only. An overdose with associated nonserious AEs must be recorded as the AE diagnosis/symptoms on the relevant AE forms in the source documentation and in the CRF. Only overdoses of study medication will be reported.

13.3 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be reported to the sponsor.

13.3.1 Maternal Exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, it should be reported to the sponsor.

13.3.2 Paternal Exposure

Pregnancy of a subject's partner is not considered to be an AE. However, any conception occurring from the date of dosing until 3 months after dosing should be reported to the sponsor and followed up for its outcome.

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15. APPENDIX A

Digital Symbol Substitution Test (DSST)

Table 7: DSST