PROTOCOL HL192-PD-CA-P101

[redacted] **Protocol Number: 230119**

A Randomized, Phase 1 Study to Assess the Safety, Tolerability, Pharmacokinetics of Single and Multiple Doses as Well as the Food Effect of Orally Administered ATH-399A in Healthy Adult Participants

Sponsor:	HanAll Pharmaceutical International Inc. 1 Church St. Suite 103 Rockville, MD 20850, USA HanAll Biopharma Co., Ltd. DaeWoong Building 3F. 12 Bongeunsa-ro 114-gil Gangnam-gu, Seoul Republic of Korea 06170
Investigational Product:	ATH-399A, HL192
Release Date:	26-SEP-2024 **Version Number:** Amendment IV
Contract Research Organization:	[redacted]

CONFIDENTIALITY STATEMENT

1 PROTOCOL HISTORICAL FILE

Version	Brief description/summary of changes	Date
Final	Version submitted to the Independent Ethics Committee (IEC).	17-JUL-2023
Amendment I	Modifications made following Health Canada's Request for Additional Information and other changes.	30-AUG-2023
Amendment II	Integrations of modifications made in Protocol Clarification Letters. Addition of PK timepoints in SAD part and other associated changes.	20-NOV-2023
Amendment III	Addition of PK blood sample collections in MAD.	30-NOV-2023
Amendment IV	See summary of changes list below.	26-SEP-2024

To perform future analysis of biomarkers on residual samples, changes included in Amendment IV are brought to:

- Section 11.8.1
    - Part 2. Included wording to perform future research and analysis of biomarkers with samples collected from the Additional Cohort. The following sentences were added:
        - "In the additional cohort of participants >55-80 years of age (inclusive), future research and analysis of biomarkers may be performed using the residual samples originally collected for PK analysis required in this study. These analyses will only be performed if participants provided specific additional consent."

SPONSOR APPROVAL

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6 Good Clinical Practice.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

The undersigned has reviewed the content of the protocol and approved for issuance.

INVESTIGATOR'S STATEMENT

I have read and agree to the conduct of protocol HL192-PD-CA-P101. I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control who will be involved in the study.

_____ _____

Investigator signature Date

_____

Investigator printed name

_____

Name of clinical facility

_____

Location of facility
(city, state, country)

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3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
Ae_{0-t}	cumulative urinary excretion from time zero to time t
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AQ	amodiaquine
AR	accumulation ratio
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-inf}	area under the concentration-time curve from time zero to infinity (extrapolated)
AUC_{0-t}	area under the concentration-time curve from time zero until the last observed concentration
$AUC_{0-\tau}$	area under the concentration-time curve for one dosing interval (τ) at steady-state
BBB	bundle branch block
BID	*bis in die* (twice a day)
BMI	body mass index
BUN	blood urea nitrogen
C_{avg}	average plasma concentration
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
Cl/F	apparent clearance
Cl_R	renal clearance
C_{max}	maximal observed concentration
C_{min}	minimal observed concentration
CQ	Chloroquine
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia Suicidality Severity Rating Scale
CTA	Clinical Trial Application
CV	coefficient of variation
CYP	cytochrome P450

DA	Dopamine
DLT	dose limiting toxicity
DMP	data management plan
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
eGFR	estimated glomerular filtration rate
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EOS	end of study
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Gla	Glafenine
GLM	general linear model
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HAMD-7	7-item Hamilton depression rating scale
HbA1c	Hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HED	human equivalent doses
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
HPFB	Health Products and Food Branch
IB	Investigator's Brochure
IBBB	incomplete bundle branch block
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IM	Intramuscular

INR	international normalized ratio
IP	Intraperitoneal
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	Intravenous
IVCD	intraventricular conduction delay
K_{el}	terminal elimination rate constant
λz (Lambda-z)	individual estimate of the terminal elimination rate constant
LBD	ligand-binding domain
LDL-C	low-density lipoprotein cholesterol
L-DOPA	L-3,4-dihydroxyphenylalanine
LH	luteinizing hormone
LLN	lower limit of normal
MAD	multiple ascending dose
MAOI	monoamine oxidase inhibitor
Max	Maximum
MCH	mean cell hemoglobin
MCHC	mean cell hemoglobin concentration
MCV	mean cell volume
mDA	midbrain dopamine
MDMA	3,4-methylenedioxymethamphetamine
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MRSD	maximum recommended starting dose
NOAEL	no observed adverse effect level
NOL	No Objection Letter
OTC	over-the-counter
PAD	pharmacologically active dose
PCP	Phencyclidine
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PO	*per os* (oral administration)
PR	PR interval
PRN	as needed

PSA	prostate-specific antigen
PT	prothrombin time
QA	quality assurance
QC	quality control
QD	*quaque die* (once a day)
QT	QT interval
QTcF	Fridericia's corrected QT interval
RBC	red blood cell
R_{max}	maximal rate of urinary excretion
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SAR	structure-activity relationship
SAS	statistical analysis system
SD	standard deviation
SoA	Schedule of Assessments
SOC	System Organ Class
SOP	standard operation procedure
SRC	Safety Review Committee
S-STS	Sheehan suicidality tracking scale
SUSAR	suspected, unexpected, serious adverse reaction
$T_{½\ el}$	terminal elimination half-life
T3	Triiodothyronine
T4	Thyroxine
THC	Tetrahydrocannabinol
TID	*ter in die* (three times a day)
T_{lag}	time of observation prior to the first observation with a measurable (non-zero) concentration
T_{max}	time when the maximal concentration is observed
T_{Rmax}	time of maximal urinary excretion
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
V_z/F	apparent volume of distribution
WBC	white blood cell
WOCBP	woman of childbearing potential

4 SYNOPSIS

Name of Sponsor/Company: HanAll Pharmaceutical International Inc/ HanAll Biopharma Co. Ltd.		
Name of Investigational Product: ATH-399A, HL192 (Nurr1 Activator), hereafter referred to as ATH-399A		
Protocol Number: HL192-PD-CA-P101	**Phase:** 1	**Region:** Canada
Title of Study: A Randomized, Phase 1 Study to Assess the Safety, Tolerability, Pharmacokinetics of Single and Multiple Doses as Well as the Food Effect of Orally Administered ATH-399A in Healthy Adult Participants		

Objectives and Endpoints:

Objectives	Endpoints
Part 1a	
Primary	
To assess the single dose safety and tolerability of ATH-399A in healthy male and female participants in up to 5 different ascending dose level groups.	Safety and tolerability will be assessed by changes in vital signs, ECGs, clinical laboratory tests, telemetry, physical examination, neurological examination, Columbia Suicidality Severity Rating Scale (C-SSRS), and the overall incidence of adverse events (AEs) and serious adverse events (SAEs).
Secondary	
To evaluate the single dose plasma pharmacokinetics (PK) of ATH-399A in healthy male and female participants in up to 5 different ascending dose level groups.	Plasma PK parameters will include: • AUC_{0-t} • AUC_{0-inf} • C_{max} • T_{max} • λ_z • $t_{½ el}$
To determine concentration of ATH-399A and identify its metabolites in blood and urine in healthy male and female participants after a single dose in up to 5 different ascending dose level groups.	Concentrations of ATH-399A and identification of its major metabolites in blood and urine.
Part 1b	
Primary	
To assess the single dose safety and tolerability of ATH-399A in healthy male and female participants under fasted and fed conditions.	Safety and tolerability will be assessed by changes in vital signs, ECGs, clinical laboratory tests, telemetry, physical examination, neurological examination, C-SSRS, and the overall incidence of AEs and SAEs.
Secondary	
To evaluate the single dose plasma PK of ATH-399A in healthy male and female participants under fasted and fed conditions.	Plasma PK parameters will include: • AUC_{0-t} • AUC_{0-inf} • C_{max} • T_{max} • λ_z • $t_{½ el}$

Part 2	
Primary	
To assess the safety and tolerability of multiple doses of ATH-399A in up to 2 ascending dose groups in healthy male and female participants.	Safety and tolerability will be assessed by changes in vital signs, ECGs, clinical laboratory tests, telemetry, physical examination, neurological examination, C-SSRS, and the overall incidence of AEs and SAEs.
Secondary	
To assess the plasma PK of multiple doses of ATH-399A in 2 ascending dose groups in healthy male and female participants.	Plasma PK parameters will include: • AUC_{0-t} • AUC_{0-inf} • C_{max} • $C_{max, ss}$ • C_{min} • C_{avg} • T_{max} • $T_{max, ss}$ • $AUC_{0-\tau}$ (AUC_{0-24}, Day 12 dose) • AUC_{0-24} (Day 1 dose) • λ_z • $t_{½ el}$ • AR
AR=accumulation ratio; AUC=area under the curve; $AUC_{0-\tau}$ = area under the curve for the defined dosing interval; C_{avg}= average plasma concentration; C_{max} = maximum plasma concentration; C_{min}= minimum plasma concentration; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; λ_z = terminal elimination rate constant; PK = pharmacokinetics; $t_{½ el}$ = terminal elimination half-life; T_{max}=time to maximum plasma concentration	

Study Design:

This study is a randomized, Phase 1 three-part study:

- Part 1a is a placebo-controlled, double-blind, single ascending dose (SAD) safety, tolerability, and PK evaluation of ATH-399A.
- Part 1b is an open-label, single dose, food-effect, safety, tolerability, and PK evaluation of ATH-399A.
- Part 2 is a placebo-controlled, double-blind, multiple ascending dose (MAD) safety, tolerability, and PK evaluation of ATH-399A, in 2 different age groups.

Part 1a: (SAD)

After assessing eligibility during a 4-week screening period, approximately 40 healthy participants will participate in Part 1a. Each eligible participant will be assigned to 1 of 5 cohorts (8 participants per cohort) to evaluate up to 5 single ascending dose levels. Proposed dose levels are:

Cohort 1: 5 mg

Cohort 2: 10 mg

Cohort 3: 20 mg

Cohort 4: 40 mg

Cohort 5: 80 mg

The starting dose will be 5 mg. Following completion of each dose level, a Safety Review Committee (SRC) will review the safety and tolerability data through the follow-up visit of a minimum of 6 evaluable participants. The SRC will also review PK data for up to 48 hours post-dose in at least 6 evaluable participants in order to make decisions whether to escalate to the next planned dose level, decrease the next dose level, repeat a dose level, or to not evaluate any additional dose. The determination of the highest dose level for this study will be based on

emerging safety/tolerability and PK data, as recommended by the SRC, but will not exceed the maximum dose currently outlined in the protocol.

For each dose level, 6 participants will receive ATH-399A and 2 participants will receive placebo. Each cohort will utilize sentinel dosing, with one participant receiving ATH-399A and one participant receiving placebo. Provided no clinically significant safety issues are noted in the 48 hours after dosing the initial 2 participants in the cohort, the 6 remaining participants in the cohort will be dosed. Before dosing the rest of the cohort, the Investigator will initiate a discussion via e-mail with the Sponsor's Medical Monitor (MM) or representative to review the available safety and tolerability data of the sentinel participants in order to make a decision regarding continuation of the study with the remaining 6 non-sentinel participants. In the case of clinically significant safety issues or a sentinel stopping rule is present, then an ad hoc SRC meeting and/or a MM call can be necessary.

Participants will be admitted to the clinical unit on the day before study drug administration (Day -1) for baseline assessments and to confirm eligibility. Participants will be dosed in the fasted state and will be required to fast for a minimum of 10 hours prior to dosing and 4 hours following dosing. Except for water given with the study drug, no fluids will be allowed from 1 hour before dosing until 1 hour after dosing. Participants will stay in the clinical unit for 4 days (3 nights), from Day -1 until Day 3. Blood samples for PK analysis for Cohorts 1, 2, and 3 will be collected pre-dose and at specified time points up to Day 3 (48 hours) post-dose and blood samples for PK analysis for Cohorts 4 and 5 will be collected pre-dose and at specified time points up to Day 5 (96 hours) post-dose. Urine samples for PK analysis will be collected from pre-dose and during specified time intervals up to Day 3 (48 hours post-dose). PK blood samples for Cohorts 4 and 5 will be collected at outpatient visits on Day 4 (72 hours post-dose) and Day 5 (96 hours post-dose). All participants in each cohort will return for a follow-up visit on Day 8 (between Day 8 and Day 11).

Physical and neurological examinations, safety labs (including drug screen, cotinine test, and alcohol breath test), vital signs, electrocardiogram (ECG), and telemetry will be performed at specified time points. AEs will be recorded throughout the study. For details regarding the timing of specific procedures, see Table 1.

Part 1b: Food Effect

Part 1b is a 2-period, 2-sequence, crossover study part to evaluate the effect of food on ATH-399A safety, tolerability, and PK.

After assessing eligibility during a 4-week screening period, approximately 12 healthy participants (with a minimum of 3 of each gender) will be randomized to one of the 2 sequences AB or BA and will receive the following study treatments in each period:

- **Treatment A:** Single dose of ATH-399A after a high-calorie, high-fat breakfast.

  After a supervised fast of at least 10 hours, participants will be served a high-fat, high-calorie meal. Drug administration will occur approximately 30 minutes after the meal has been started. Except for fluids provided with the breakfast and water given with the study drug, no fluids will be allowed from 1 hour before until 1 hour after dosing.

- **Treatment B:** Single dose of ATH-399A after fasting.

  No food will be allowed from at least 10 hours before until at least 4 hours after dosing. Except for water given with the study drug, no fluids will be allowed from 1 hour before until 1 hour after dosing.

Eligible participants will be admitted to the clinical unit on the day before (first) administration (Day -1) of the study drug, for baseline assessments and to confirm eligibility. Participants will stay in the clinical unit for 2 periods of 3 nights each with a washout period of at least 7 days (the washout period may be adjusted based on PK data derived from Part 1a). Participants will be discharged from the clinical unit on Day 3 following completion of all assessments. Participants will then return to the clinical unit for PK blood sample collection on Day 4 (72 hours post-dose) and Day 5 (96 hours post-dose). After completing the washout period of at least 7 days, the participants will return to the clinical unit to begin their second study period, receive the study drug on Day 1 (of the second period) and remain in the clinic through completion of their Day 3 (of the second period) assessments. Participants will then return to the clinical unit for PK blood sample collection on Day 4 (72 hours post-dose of the second period) and Day 5 (96 hours post-dose of the second period). An outpatient follow-up visit will take place on Day 8 in Period 2.

Selection of the dose to be administered in Part 1b will depend on the results of Part 1a. [redacted]

Blood samples for PK will be collected pre-dose and at specified time points post-dose. Vital signs, ECG, telemetry, safety lab (including drug screen, cotinine, and alcohol breath test), and physical and neurologic examinations will be performed at specified times. AEs will be recorded throughout the study. For details regarding the timing of specific procedures, see Table 2.

Part 2 (MAD):

Part 2 is the MAD part of the study. After assessing eligibility during the 4-week screening period, approximately 16 participants (with a minimum of 2 of each gender per dose level cohort) will be enrolled in 2 sequential cohorts. Eligible participants in each cohort will come to the clinical unit on the day before the first study drug administration (Day -1), for baseline assessments and to confirm eligibility and will stay in the clinical unit for 14 days (13 nights), from Day -1 until Day 13. Participants will return to the clinical unit for outpatient PK blood sample collections on Day 15 (72 hours post-last dose), and Day 16 (96 hours post-last dose) as well as an outpatient follow-up visit that will take place 7 days after receiving the last dose of study drug, on Day 19 (between Day 19 and Day 22).

Each cohort will include 8 participants, 6 participants will receive ATH-399A and 2 participants will receive placebo. Dose levels of ATH-399A will be based on data from Part 1 (Part 1a and 1b) and recommendation from the SRC. Additionally, [redacted] From Day 1 to Day 12, participants will receive either ATH-399A or placebo once daily (QD) for a total of twelve (12) consecutive days. On Days 1 and 12, participants will fast for a minimum of 10 hours prior to dosing and 4 hours following dosing. From Days 2 to 11, participants will fast for a minimum of 2 hours prior to dosing and 2 hours following dosing.

Following completion of each dose level (both cohorts), an SRC will review the safety and tolerability data, as well as available PK data, (assessed for up to at least 24 hours post-dose) of the previous dose level in at least 6 evaluable participants in order to make decisions whether to escalate to the next planned dose level, decrease the next dose level, repeat a dose level, or to not evaluate any additional dose. The time interval when escalating the dose from the first dosing of Cohort 1 of the MAD to the first dosing of Cohort 2 of the MAD will be approximately 3.5 weeks.

Blood samples for PK will be collected pre-dose and at specified time points up to 96 hours post-Day 12 dose. Vital signs, ECG, telemetry, safety lab (including drug screen, cotinine, and alcohol breath test), C-SSRS, and physical and neurologic examinations will be performed at specified times. AEs will be recorded throughout the study. For details regarding the timing of specific procedures see Table 3.

Additional Cohort*:* Following assessment of MAD dosing in participants, an additional cohort of approximately 8 participants will be evaluated at a dose level determined to be safe by the SRC. After assessing eligibility during the 4-week screening period, 8 participants (approximately equal numbers of males and females, with a minimum of 2 of each gender), aged >55-80 years, inclusive, will be enrolled. The study drug will be administered once daily (QD) in the fasted state for a total of twelve (12) consecutive days. On Days 1 and 12, participants will fast for a minimum of 10 hours prior to dosing and 4 hours following dosing. From Days 2 to 11, participants will fast for a minimum of 2 hours prior to dosing and 2 hours following dosing. Six participants will receive ATH-399A and 2 participants will receive placebo once daily (QD).

Eligible participants in this additional cohort will come to the clinical unit on the day before the first study drug administration (Day -1), for baseline assessments and to confirm eligibility and will stay in the clinical unit for 14 days (13 nights), from Day -1 until Day 13.

Blood samples for PK will be collected pre-dose and at specified time points up to 96 hours post-Day 12 dose. Vital signs, ECG, telemetry, safety lab (including drug screen, cotinine, and alcohol breath test), C-SSRS, and physical and neurologic examinations will be performed at specified times. Adverse events will be recorded throughout the study. Participants will return to the clinical unit for outpatient PK blood sample collections on Day 15 (72 hours post-last dose), and Day 16 (96 hours post-last dose) as well as an outpatient follow-up visit that will take place 7 days after receiving the last dose of study drug, on Day 19 (between Day 19 and Day 22). For details regarding the timing of specific procedures see Table 3.

Safety Review Committee (SRC) and Dose Escalation Criteria:

The study will be monitored by an SRC. The SRC is intended to ensure that treatment does not pose undue risk to participants. The SRC will be composed of at least the Investigator, one medically qualified Sponsor representative and an independent Medical Monitor (MM). SRC meetings will be held after safety and tolerability data through follow-up visit for at least 6 dosed participants from a same cohort and PK data up to at least 48 hours post-dose (Day 3 for Parts 1a and 1b) and 24 hours post-last dose (Day 13 for Part 2) from a same cohort are available. The SRC will consider the data on a cohort basis, but also on the basis of cumulative information across cohorts as the study progresses. The SRC recommendations should be based on results from a minimum of 6 evaluable participants in each dosing cohort.

Safety/tolerability data through the final follow-up visit for each of the 6 evaluable participants in a cohort along with PK data up to at least 48 hours post-dose in Part 1a and 1b (or 24 hours post-last dose in Part 2) will be assessed by the SRC prior to:

a. Ascending from one dose-level cohort to the next higher dose level cohort in Parts 1a and 2,
b. Prior to transitioning from Part 1a to Parts 1b and 2.

The SRC will stop dose escalation or descend to a dose level lower than the planned next higher dose level if any of the following criteria are met:

- One participant per cohort who receives ATH-399A experiences a serious adverse event (SAE) which is considered to be related to the study medication.
- Two participants per cohort who receive ATH-399A have QTc prolongation, defined as an average absolute (regardless of baseline value) QTcF >500 msec or an increase of QTcF > 60 msec above baseline, confirmed by repeating after 5 minutes, and determined post-dose.
- Two participants per cohort who receive ATH-399A exhibit hypotension, defined as resting supine diastolic blood pressure <40 mmHg persisting for at least 10 minutes on repeated assessment, or an asymptomatic or symptomatic fall in systolic blood pressure to below 80 mmHg, persisting for at least 10 minutes on repeated assessment.
- Two participants per cohort who receive ATH-399A exhibit hypertension, defined as an increase in resting systolic blood pressure to above 180 mmHg, persisting for at least 10 minutes, or an increase in resting diastolic blood pressure to above 105 mmHg, persisting for at least 10 minutes.
- Two participants per cohort who receive ATH-399A exhibit tachycardia, defined as resting supine heart rate >130 beats per minute, persisting for at least 10 minutes.
- Two participants per cohort who receive ATH-399A exhibit symptomatic bradycardia, defined as heart rate <40 beats per minute, or asymptomatic bradycardia, defined as resting supine heart rate <30 beats per minute while awake, persisting for at least 10 minutes, or clinically significant arrhythmia.
- One participant per cohort who receives ATH-399A exhibits abnormal liver tests defined as:
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5X upper limit of normal (ULN).
  - AST or ALT >3X ULN along with one of the following criteria:
    - sustained for more than 2 weeks or
    - total bilirubin level >2X ULN or
    - international normalized ratio (INR) time >1.5X ULN or
    - the appearance of fatigue, nausea, vomiting, right upper abdominal pain or tenderness, fever, rash, and/or eosinophilia (>5%).
  - Alkaline phosphatase (ALP) >3X ULN.
  - ALP >2.5X ULN and total bilirubin >2X ULN.

- ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right upper abdominal pain or tenderness, fever, rash, and/or eosinophilia (>5%).

- One participant per cohort who reaches a plasma AUC_{0-24} of ≥ 1,800 h*ng/mL.
- Two participants per cohort who receive ATH-399A exhibit renal toxicity, defined as serum creatinine ≥1.5X ULN (confirmed by repeating within 24 hours).
- Two participants per cohort who receive ATH-399A exhibit hematologic toxicity, defined as one or more of the following (confirmed by repeating within 24 hours):
  - Leukocyte count <2.5 x 10^9/L
  - Neutrophils < 1.3 x 10^9/L and < 1.0 x 10^9/L for Afro-American participants
  - Platelet count <75 x 10^9/L

In addition, the SRC may stop dose escalation or descend to a dose level lower than the planned next higher dose level at any time if the SRC determines that dose escalation would pose undue risk to participants. If dose escalation is not stopped, the SRC may recommend ascending to the planned next higher dose level cohort, ascending to a dose level lower than the planned next higher dose level, or may repeat dosing at the current dose level.

Initially, for Parts 1a and 2, the safety and any available PK data will be reviewed by the SRC in a blinded manner (e.g., without participant identifiers or using reblinded participant numbers), but if the SRC considers it necessary due to a safety concern, individual participant data or an entire cohort's data may be unblinded to the SRC to enable decision-making. Before any such unblinding, the reason for unblinding should be documented.

Number of participants (planned):

It is planned to enroll approximately 76 healthy adult males and females for participation in this study:

Part 1a: approximately 40 healthy male and female participants, aged between 18-55 (inclusive) years.

Part 1b: approximately 12 healthy male and female participants, aged between 18-55 (inclusive) years with a minimum of 3 participants of each gender.

Part 2: approximately 16 healthy male and female participants, aged between 18-55 (inclusive) years with a minimum of 2 participants of each gender per cohort. And additional cohort of approximately 8 healthy male and female participants, aged between >55-80 (inclusive) years with a minimum of 2 participants of each gender.

Criteria for Inclusion:

1. Healthy, as determined by the Investigator based on a medical evaluation including medical history, physical examination, neurological examination, laboratory tests and cardiac monitoring. A participant with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included only if, in the opinion of the Investigator, the finding is:
   a) not clinically significant according to the Investigator judgement
   b) unlikely to introduce additional risk to the participant,
   c) will not interfere with study procedures or confound study results, and
   d) is not otherwise exclusionary.
2. Population (Section 13.4):
   a) Part 1a and 1b: Men and women, age 18-55 years inclusive at date of screening.
   b) Part 2: Men and women aged 18-55 years inclusive at date of screening. Additional cohort: Participants of the additional cohort will be of approximately equal numbers of males and females, with a minimum of 2 of each gender, aged >55-80 years, inclusive.
3. Women of childbearing potential (WOCBP) including those who had bilateral tubal ligation must be non-pregnant and non-lactating. They must use and commit to continuing to use a double barrier contraception method with acceptable, highly effective contraception methods from screening until study completion, including at least 90 days following the last study drug administration. WOCBP must have a negative pregnancy test result before administration of study drug and must agree not to donate ova (or egg) for at least 30 days after the last dose of study drug administration. Total abstinence from heterosexual intercourse is accepted (when this is in line with the preferred and usual lifestyle of the subject) for at least 6 months before screening and until at least 90 days following the last study drug administration.

4. Postmenopausal women must have had ≥12 months of spontaneous amenorrhea (with follicle-stimulating hormone [FSH] ≥40 mIU/mL).
5. Surgically sterile women are defined as those who have had a hysterectomy and/or bilateral oophorectomy. Women who are surgically sterile must provide verbal confirmation. See Section 13.4.
6. Male participants who are sexually active with WOCBP (see Section 13.4) must:
    a) Agree to use condoms to protect their partners from becoming pregnant during the study (including washout periods) and not to donate sperm for at least 90 days after the last dose of study drug, *and*
    b) Agree to ensure that they and their partners are routinely using a medically approved contraceptive method. It is important that male participants not impregnate others while in the study.
7. Body weight ≥50.0 kg for men and ≥45.0 kg for women and body mass index within the range of 18.0-30.0 kg/m^2 (inclusive).
8. Participants participating in Part 1b must be willing and able to consume the entire high-fat, high--calorie breakfast in the designated timeframe.
9. Participants must understand the nature of the study, must be willing to participate in the study, and must provide signed and dated written informed consent in accordance with local regulations before the conduct of any study-related procedures.
10. Participants must be, in the opinion of the Investigator, able to participate in all scheduled evaluations, likely to complete all required tests, and likely to be compliant.
11. Participants must be fluent in English or French.
12. Participants must agree not to post any personal medical data related to the study or information related to the study on any website or social media site (e.g., Facebook, Twitter, etc.).

Criteria for Exclusion:

1. A positive urine cotinine, drug screen, or alcohol breath test at screening or Day -1.
2. Any history of psychiatric disorders, including substance use disorders, according to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5) criteria that requires current treatment with psychiatric medications. Participants with mild anxiety or depression which is stable for >6 months are permitted.
3. History of drug abuse within 1 year prior to screening or recreational use of soft drugs (such as marijuana) within 1 month or hard drugs (such as cocaine, phencyclidine [PCP], crack, opioid derivatives including heroin, and amphetamine derivatives) within 3 months prior to screening.
4. A diagnosis of intellectual disability (intellectual developmental disorder) or mental retardation.
5. A serious mental illness, dementia, or other neuropsychiatric disorder that would interfere with participation in the trial, or ability to provide informed consent in the opinion of the Investigator.
6. Acute suicidality as indicated by the C-SSRS or history of suicidal behavior within the 12 months prior to screening. Participants who answer "yes" to item 4 or 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening or Day -1, or who answer "yes" to any suicidal behavior item (excluding non-suicidal self-injurious behavior) will not be eligible.
7. A positive Hepatitis B surface antigen or positive Hepatitis C antibody result at screening.
8. A positive test at screening for human immunodeficiency virus (HIV) antigen or antibody or a history of positive test.
9. Alanine aminotransferase or aspartate aminotransferase levels greater than 1.2 times the ULN at screening or Day -1.
10. Frequently used any tobacco-containing (e.g., cigar, cigarette or snuff) or nicotine-containing product (e.g., nicotine chewing gum, nicotine plasters, or other product used for smoking cessation) within 30 days prior to first dose administration. Frequent use is defined as >5 cigarettes per week. Use of any tobacco- or nicotine-containing product is prohibited within 2 weeks of first dose administration through

completion of the in-clinic stay for the SAD (Parts 1a and 1b) and until after the final study visit for the MAD (Part 2).

11. History of alcohol abuse within 1 year prior to screening or regular use of alcohol within 6 months prior to screening that exceeds 10 units for women or 15 units for men of alcohol per week (1 unit = 340 mL of beer 5%, 140 mL of wine 12%, or 45 mL of distilled alcohol 40%).
12. Regularly consumed (e.g., more days than not) excessive quantities of xanthine-containing beverages (e.g., more than 2 cups of coffee or the equivalent per day) within 1 week prior to screening or between screening and first dose administration, or unwillingness to refrain from xanthine-containing beverages during the in-clinic stay.
13. Received or used an investigational product (including placebo) or device within the following time period prior to the first dosing day in the current study: 30 days or 5 half-lives (whichever is longer). For biological products, administration of a biological product within 90 days prior to the first dosing, or concomitant participation in an investigational study involving no drug or device administration.
14. Other than those medications outlined in the protocol body and those allowed in the MAD additional cohort, use of prescription or non-prescription drugs, herbal, and dietary supplements (including St John's Wort) within 7 days (or 28 days if the drug is a potential hepatic enzyme inducer) or 5 half-lives (whichever is longer) prior to first dose administration, unless in the opinion of the Investigator and Medical Monitor, the medication will not interfere with the study procedures or compromise participant safety.
15. History of clinically significant sensitivity to any of the study drugs, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.
16. Donation of plasma within 7 days prior to the first dosing or donation or loss of 500 mL or more of whole blood within 8 weeks prior to the first dosing.
17. A positive pregnancy test or lactation.
18. A history or presence of any disease, condition, or surgery likely to affect drug absorption, distribution, metabolism, or excretion. Participants with a history of cholecystectomy should be excluded.
19. A history or presence of a clinically significant hepatic, renal, gastrointestinal, cardiovascular, endocrine, pulmonary, ophthalmologic, immunologic, hematologic, dermatologic, or neurologic abnormality. Participants with fully resolved childhood asthma with no hospitalizations or recurrence in adulthood are permitted to enroll. For the additional cohort in Part 2, any of the above are acceptable where the condition is stable for >6 months and, in the opinion of the Investigator, it does not impact participant safety.
20. A clinically significant abnormality on physical examination, neurological examination, ECG, or laboratory evaluations at screening and Day -1
21. A QT interval measurement corrected according to the Fridericia rule (QTcF) > 450 msec during controlled rest at screening and Day -1, or family history of long QT syndrome.
22. Any clinically significant abnormalities in rhythm, conduction, or morphology of the resting ECG and any abnormalities in the 12-lead ECG that, in the judgement of the Investigator or Medical Monitor, may interfere with the interpretation of QTc interval changes, including abnormal ST-T-wave morphology or left ventricular hypertrophy.
    a) PR (PQ) interval shortening < 120 msec (PR < 120 msec but > 110 msec is acceptable if there is no evidence of ventricular pre-excitation).
    b) PR (PQ) interval prolongation (>220 msec), intermittent second-degree (Wenckebach block while asleep or in deep rest is not exclusionary) or third-degree AV block.
    c) Persistent or intermittent complete bundle branch block (BBB), incomplete bundle branch block (IBBB), or intraventricular conduction delay (IVCD) with QRS > 120 msec.

    Note: at the Investigator's discretion, if an abnormal ECG is observed, the assessment may be repeated.
23. A clinically significant vital sign abnormality at screening or between screening and first dose administration. This includes, but is not limited to, the following in the supine position:

a) systolic blood pressure < 90 or >140 mmHg,
b) diastolic blood pressure <50 or > 90 mmHg, or
c) heart rate < 45 or >100 beats per minute.
d) decrease in systolic blood pressure of 20 mmHg or higher, decrease in diastolic blood pressure of 10 mmHg or higher, or increase in heart rate of 30 bpm or higher within 2 to 3 minutes after passing from a supine to a standing position.

Note: at the Investigator's discretion, if a single abnormal vital sign is observed, the assessment may be repeated.

24. Significant (> 5%) weight loss or gain within 30 days prior to screening or between screening and first dose administration.
25. A history of seizures. Occurrence of a single febrile seizure is not exclusionary.
26. A history of head trauma, including closed head injury with loss of consciousness. Concussions which did not lead to hospitalization or loss of consciousness, and for which there are no ongoing issues, are not exclusionary.
27. A history of symptomatic orthostatic hypotension (i.e., postural syncope).
28. A history of neuroleptic malignant syndrome.
29. A history of chronic urinary tract infections (≥2 times per year).
30. The participant is, in the opinion of the Investigator or Medical Monitor, unlikely to comply with the protocol or is unsuitable for any reason.
31. Currently employed by NurrOn Pharmaceuticals, Inc., HanAll Pharmaceutical Inc., or HanAll Biopharma Co. Ltd., or by a clinical trial site participating in this study, or a first-degree relative of an NurrOn Pharmaceuticals, Inc. or HanAll Pharmaceutical Inc., or HanAll Biopharma Co. Ltd. employee or of an employee at a participating clinical trial site.
32. Unsatisfactory venous access.
33. Unable to swallow oral capsules.
34. Positive result to a COVID-19 PCR test at screening or on Day-1.
35. COVID-19 or flu vaccination within 30 days prior to study drug administration or any other vaccination which is judged by the investigator to potentially affect eligibility.
36. Presence of fever (body temperature >37.5°C) (e.g., a fever associated with a symptomatic viral or bacterial infection) within 2 weeks prior to first dosing.

Investigational product, dosage, and mode of administration: ATH-399A (capsules containing 5 mg or 20 mg ATH-399A active doses with no excipients). Oral administration with a glass of water.

Duration of treatment: Participants in Part 1a will receive a single dose of study drug and will be on-study for approximately 9 days, including Day -1. Participants in Part 1b will receive 2 doses of study drug and will be on-study for approximately 18 days, including Day -1. Participants in Part 2 will receive QD dosing of study drug from Day 1 to Day 12 and will be on-study for approximately 20 days, including Day -1.

Reference product, dosage, and mode of administration: Placebo capsules with inert filler (Avicel) will visually match the active capsules and will be administered orally with a glass of water.

Criteria for evaluation:

Safety:

Safety and tolerability will be assessed by changes in vital signs, ECGs, clinical laboratory tests, telemetry, C-SSRS, physical examination, and neurological examination, and the occurrence of AEs.

Pharmacokinetics:

Part 1a: Blood sampling for ATH-399A plasma concentrations will be performed pre-dose and at specified time points until Day 3 post-dose for Cohorts 1, 2, and 3 and until Day 5 post-dose for Cohorts 4 and 5. Urine sampling will be conducted on Day 1 pre-dose and 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, and 24-48 hours post-dose for all cohorts.

Part 1b: Blood sampling for ATH-399A plasma concentrations will be performed pre-dose and at specified time points until Day 5 post-dose for each study period.

Part 2: Blood samples to determine ATH-399A plasma concentrations will be taken pre-dose and post-dose from Day 1 to Day 16 at specified time points.

Statistical methods:

A Statistical Analysis Plan (SAP) will be finalized prior to database lock.

Safety and tolerability

Safety and tolerability data will be listed individually and summarized using descriptive statistics and frequency tables.

Pharmacokinetic

Individual plasma and urine concentrations, concentrations in plasma derived PK parameters will be listed individually, displayed in appropriate graphics, and summarized using descriptive statistics.

4.1 Schedules of Assessments (SoA)

Table 1: Schedule of Assessments (Part 1a)

	Screening	Treatment				Outpatient Visits (Cohorts 4 and 5 only)		Follow-Up[1]
	D-28 to -2	D-1	D1	D2	D3 (Discharge[2] or early termination)	D4	D5	D8 (between Days 8 and 11)
Informed consent	X							
Height and BMI	X							
Weight	X	X			X			
Inclusion/Exclusion Criteria	X	X[3]	X					
Demographics[4]	X							
Medical History		X						
Concomitant Medications		Continuously						
Physical and Neurological Examination	X	X			X			X
Vital Signs including orthostatic vital signs, 12-lead ECG, Body Temperature[5]	X	X	X	X	X			X
12-Lead Telemetry[6]			X	X	X			
Hematology, Clinical Chemistry, HbA1c, and Urinalysis[7]	X	X	X	X	X			X
Thyroid Panel	X	X			X			X
Coagulation Tests	X	X			X			
Drug Screening, Alcohol Breath, and Urine Cotinine Test	X	X						
COVID-19 PCR	X	X						
Virus Serology	X							
Study Drug Administration			X					
PK Blood Sampling[8]			X	X	X	X	X	
PK Urine Sampling[9]			X	X	X			
FSH Test in Post-Menopausal Participants[10]	X							
Pregnancy Test[11]	X	X			X			
C-SSRS	X	X						X
Adverse Events		Continuously						
Outpatient Visits	X					X	X	X
Residence in Clinic				X				

D=day; ECG=electrocardiogram; PK=pharmacokinetic

1. Follow-up examination will take place on Day 8 (or between Day 8 and 11).
2. Discharge after completion of all study 48-hour assessments.
3. Continuous eligibility assessments on Day -1 including continuous medical history on Day -1 and prior to dosing on Day 1.
4. Including sex, date of birth, race, and ethnicity.
5. Will be performed at Screening, at admission on Day –1, Day 1 pre-dose (up to 60 min pre-dose), and 1 (±20 min), 2 (±20 min), 4 (±20 min), 8 (±60 min), 12 (±60 min), and 16 (±60 min) hours post-dose, at Day 2 (24 and 36 [±60 min] hours post-dose), on Day 3 (48 [±60 min] hours post-dose), and at Follow-up. Orthostatic vital signs will be measured at Screening and at admission on Day -1 only.
6. Will be started approximately 1-2 hours pre-dose at Day 1 and will be continued to approximately 48 hours post-dose.
7. Will take place at Screening (in fasted state, i.e., participants should fast for 4 hours prior to sample collection), at Day -1 (in fasted state), Day 1 at 8 hours post-dose (in not-fasted state), at Day 2 (in fasted state), at Day 3 (in fasted state), and at Follow-up (in fasted state). HbA1c will be performed at Screening.
8. Will take place at pre-dose (within 2 hours of dosing) and at 0.25 (±2 min), 0.5 (±2 min), 1 (±5 min), 1.5 (±5 min), 2 (±5 min), 3 (±10 min), 4 (±10 min), 6 (±10 min), 8 (±10 min), 12 (±10 min), 16 (±30 min), 24 (±30 min), 36 (±30 min), and 48 (±30 min) hours post-dose for Cohorts 1-5, and at 72 (± 1 hr), and 96 (±1 hr) hours post-dose for Cohorts 4 and 5.
9. Will be collected on Day 1 pre-dose and 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, and 24-48 hours post-dose.
10. In potential post-menopausal women only to confirm the post-menopausal status.
11. Women of childbearing potential (only) will have a urine pregnancy test at Screening and at discharge on Day 3, and a serum pregnancy test on Day –1.

Table 2: Schedule of Assessments (Part 1b)

	Screening[1]	Treatment (Each Period: Periods 1 and 2)[2]				Outpatient Visits		Follow-Up[3]
	D-28 to -2	D-1	D1	D2	D3 (Discharge[2] or Early Termination)	D4	D5	D16 (or between Day 16 and 19)
Informed consent	X							
Height and BMI	X							
Weight	X	X			X			
Inclusion/Exclusion Criteria[4]	X	X	X					
Demographics[5]	X							
Medical History		X[4]						
Concomitant Medications		Continuously						
Physical and Neurological Examination	X	X			X			X
Vital Signs including orthostatic vital signs, 12-lead ECG, Body Temperature[6]	X	X	X	X	X			X
12-Lead Telemetry[7]			X	X	X			
Hematology, Clinical Chemistry, HbA1c, and Urinalysis[8]	X	X	X	X	X			X
Thyroid Panel	X	X			X			X
Coagulation Tests	X	X			X			
Drug Screening, Alcohol Breath, and Urine Cotinine Test	X	X						
COVID-19 PCR	X	X						
Virus Serology	X							
Study Drug Administration[9]			X					
PK Blood Sampling[10]			X	X	X	X	X	
FSH Test in Post-Menopausal Participants[11]	X							
Pregnancy Test[12]	X	X			X			
C-SSRS	X	X						X
Adverse Events		Continuously						
Outpatient Visits	X					X	X	X
Residence in Clinic		X						

D=day; ECG=electrocardiogram; PK=pharmacokinetic.

1. Participants will not be rescreened before the subsequent treatment.
2. Discharge after completion of all study 48-hour assessments (Day 3 of each period). There will be outpatient visits on Days 4 and 5 (of each period). There will be a washout period of at least 7 days for individual participants between treatments.
3. Follow-up outpatient examination will take place 7 days after the last dose of the last treatment period (i.e., between Day 16 and 19).

4. Continuous eligibility assessments on Day -1 will be done only during Period 1, and continuous medical history on Day -1 and prior to dosing on Day 1 of each period.
5. Including sex, date of birth, race, and ethnicity.
6. Will be performed at Screening, at the admission of each period (Day –1), for each period: on Day 1 pre-dose (up to 60 minutes pre-dose), and 1 (±20 min), 2 (±20 min), 4 (±20 min), 8 (±60 min), 12 (±60 min), and 16 (±60 min) hours post-dose; on Day 2 (24 [±60 min] hours post-dose); on Day 3 (48 [±60 min] hours post-dose), and at Follow-up. Orthostatic vital signs will be measured at Screening and at admission on Day -1 only.
7. Will be started approximately 1-2 hours pre-dose at Day 1 of each period and will be continued to approximately 48 hours post-dose.
8. Will take place at Screening (in fasted state, i.e., participants should fast for 4 hours prior to sample collection), and in each period: on Day -1 (in fasted state), Day 1 at 8 hours post-dose (in not-fasted state), at Day 2 (in fasted state), at Day 3 (in fasted state), and at Follow-up (in fasted state). HbA1c will be performed at Screening.
9. Participants receiving Treatment A will be required to consume a high-calorie, high-fat meal 30 minutes prior to study drug administration. Participants receiving Treatment B will be administered the study drug under fasted state.
10. Will take place at pre-dose (within 2 hours of dosing) and at 0.25 (±2 min), 0.5 (±2 min), 1 (±5 min), 1.5 (±5 min), 2 (±5 min), 3 (±10 min), 4 (±10 min), 6 (±10 min), 8 (±10 min), 12 (±10 min), 16 (±30 min), 24 (±30 min), 36 (±30 min), 48 (±30 min), 72 (± 1 hr), and 96 (±1 hr) hours post-dose.
11. In potential post-menopausal women only to confirm the post-menopausal status.
12. Women of childbearing potential (only) will have a urine pregnancy test at Screening and at discharge on Day 3, and a serum pregnancy test on Day –1 of each period.

Table 3: Schedule of Assessments (Part 2)

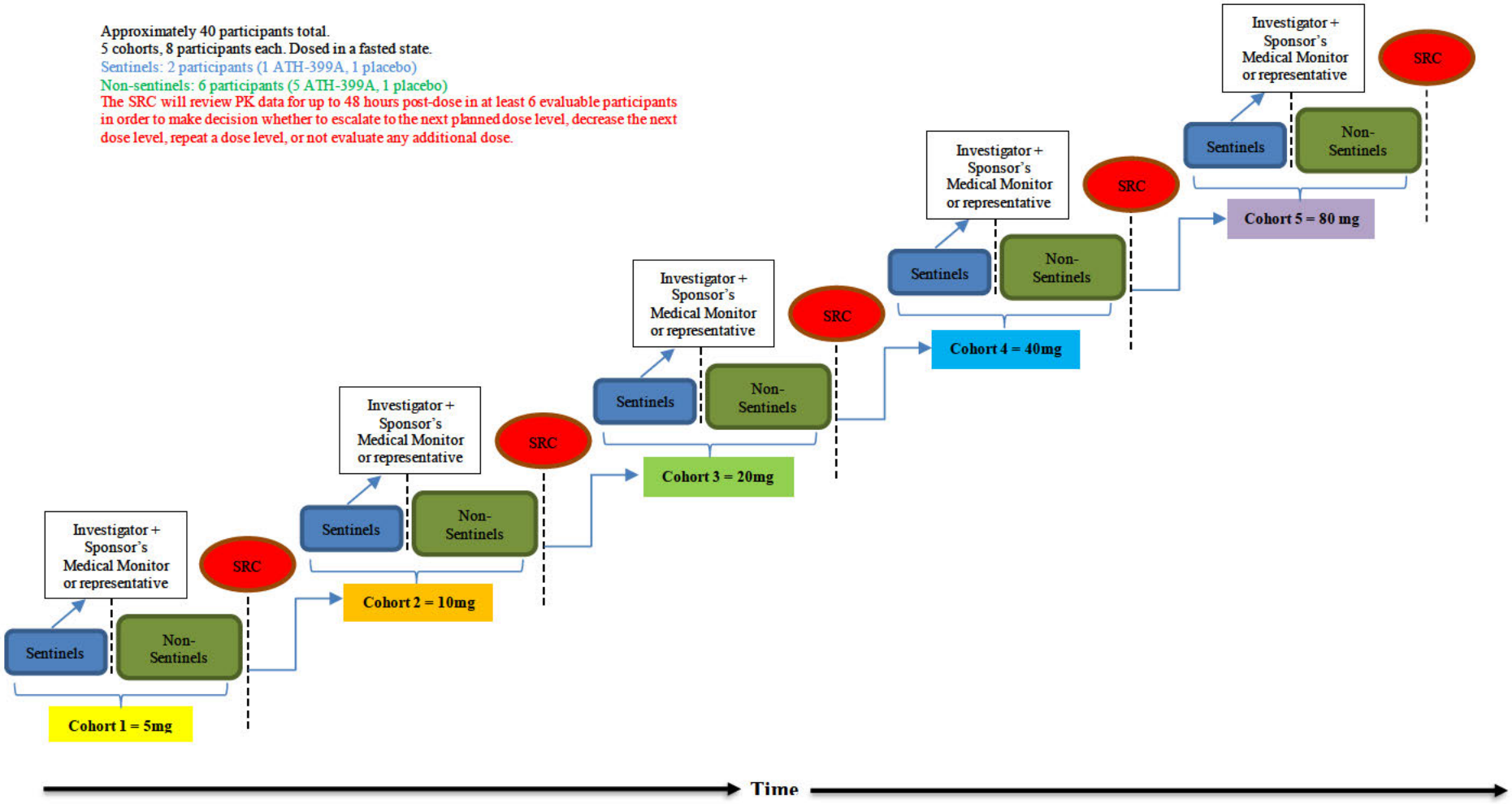
	Screening	Treatment						Outpatient Visits		Follow-Up[1]
	D-28 to -2	D-1	D1	D2	D3-11	D12	D13 (Discharge[2] or early termination)	D15	D16	D19 (or between Day 19 and Day 22)
Informed consent	X									
Height and BMI	X									
Weight	X	X					X			
Inclusion/Exclusion Criteria	X	X[3]	X[3]							
Demographics[4]	X									
Medical History		X[3]								
Concomitant Medications		Continuously								
Physical and Neurological Examination	X	X					X			X
Vital Signs including orthostatic vital signs, 12-lead ECG, Body Temperature[5]	X	X	X	X	X	X	X			X
12-Lead Telemetry[6]			X	X		X	X			
Hematology, Clinical Chemistry, HbA1c, and Urinalysis[7]	X	X	X	X	X		X			X
Thyroid Panel[8]	X	X			X		X			X
Coagulation Tests	X	X					X			
Drug Screening, Alcohol Breath, and Urine Cotinine Test	X	X								
COVID-19 PCR	X	X								
Virus Serology	X									
Study Drug Administration			X	X	X	X				
PK Blood Sampling[9]			X	X	X	X	X	X	X	
FSH Test in Post-Menopausal Participants[10]	X									
Pregnancy Test[11]	X	X					X			
C-SSRS	X	X					X			
Adverse Events		Continuously								
Outpatient Visits	X							X	X	X
Residence in Clinic		X								

D=day; ECG=electrocardiogram; PK=pharmacokinetic

1. Follow-up examination will take place 7 days after the last dose, on Day 19 or between Day 19 and Day 22.
2. Discharge after completion of all study 36-hour post-Day 12 dose assessments.
3. Continuous eligibility assessments on Day -1 and Day 1 prior to dosing.
4. Including sex, date of birth, race, and ethnicity.
5. Will take place at Screening, at admission on Day -1, on Day 1 pre-dose (up to 60 minutes pre-dose) and 1 (±20 min), 2 (±20 min), 4 (±20 min), 6 (±60 min), 8 (±60 min), 12 (±60 min); on Days 2-11 on pre-dose (up to 60 minutes pre-dose) and 4 (±20 min) hours post-dose; on Day 12, pre-dose (up to 60 minutes pre-dose) and 1 (±20 min), 2 (±20 min), 4 (±20 min), and 8 (±60 min) hours post-dose; on Day 13 (in the morning); and at Follow-up. Orthostatic vital signs will be measured at Screening and at admission on Day -1 only.
6. Will be started on Day 1 and Day 12: approximately 1-2 hours pre-dose and will be continued to approximately 24 hours post-dose.
7. Will be performed at Screening (in fasted state, i.e., participants should fast for 4 hours prior to sample collection), Day -1 (in fasted state), on Day 1 at 8 hours post-dose (in not fasted state) and on Days 2, 6, 13 (in fasted state), and Follow-up (in fasted state). HbA1c will be performed at Screening.
8. A thyroid panel (TSH, FT3, and FT4) will be performed at Screening, on Day -1, on Day 6, Day 13, and at the Follow-up Visit.
9. Will take place:
   - on Day 1: pre-dose (within 2 hours of dosing) and 0.25 (±2 min), 0.5 (±2 min), 1 (±5 min), 1.5 (±5 min), 2 (±5 min), 3 (±10 min), 4 (±10 min), 6 (±10 min), 8 (±10 min), 12 (±10 min), and 16 (±30 min) hours post-Day 1 dose,
   - on Day 2: at 24 hours (±30 min) and 36 hours (±30 min) post-Day 1 dose,
   - on Day 9: pre-dose (within 2 hours of dosing),
   - on Day 10: pre-dose (within 2 hours of dosing),
   - on Day 11: pre-dose (within 2 hours of dosing),
   - on Day 12: pre-dose (within 2 hours of dosing) and 0.25 (±2 min), 0.5 (±2 min), 1 (±5 min), 1.5 (±5 min), 2 (±5 min), 3 (±10 min), 4 (±10 min), 6 (±10 min), 8 (±10 min), 12 (±10 min), and 16 (±30 min) hours post-Day 12 dose and
   - on Day 13: at 24 hours (±30 min) and 36 hours (±30 min) post-Day 12 dose.
   - on Day 15: at 72 (± 1 hr) hours post-Day 12 dose (outpatient visit), and
   - on Day 16: at 96 (±1 hr) hours post-Day 12 dose (outpatient visit).
10. In potential post-menopausal women only to confirm the post-menopausal status.
11. Women of childbearing potential (only) will have a urine pregnancy test at Screening and at discharge on Day 13, and a serum pregnancy test on Day -1.

4.2 Study Schema

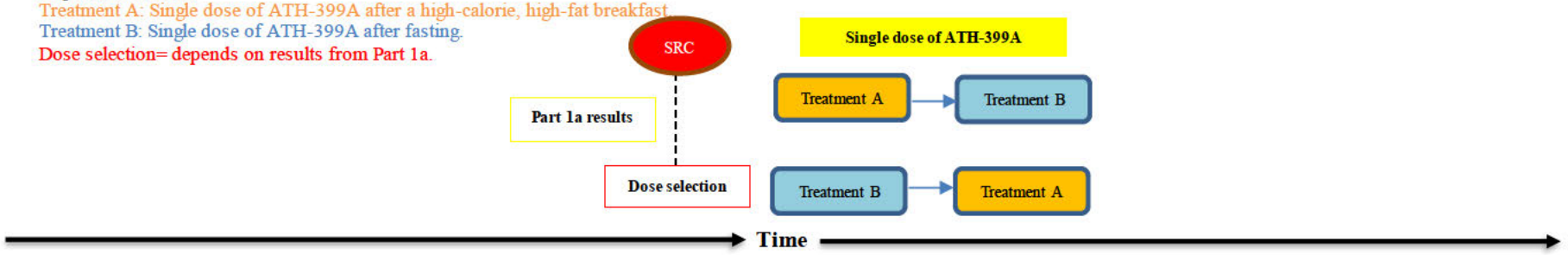
Single Ascending Dose (SAD) Part 1a



SRC=Safety Review Committee

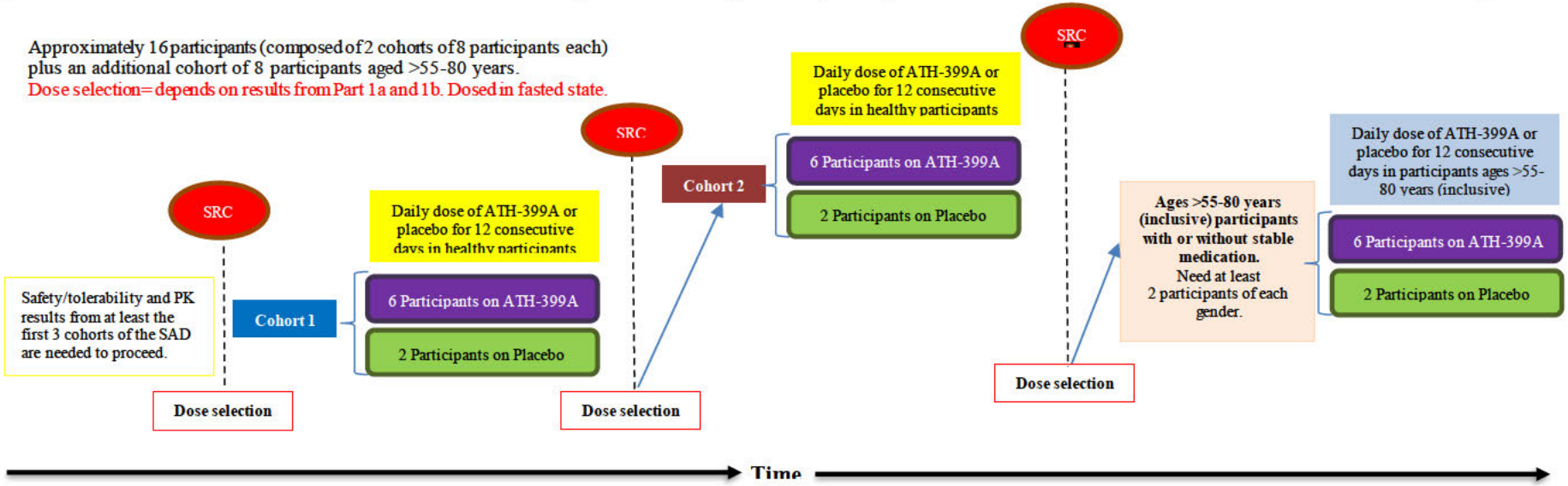
Part 1b (open-label, food effect)

12 participants total, crossover.
Sequences: AB, BA
Treatment A: Single dose of ATH-399A after a high-calorie, high-fat breakfast.
Treatment B: Single dose of ATH-399A after fasting.
Dose selection= depends on results from Part 1a.



Multiple Ascending Dose (MAD) Part 2

Approximately 16 participants (composed of 2 cohorts of 8 participants each) plus an additional cohort of 8 participants aged >55-80 years.
Dose selection= depends on results from Part 1a and 1b. Dosed in fasted state.



5 INTRODUCTION

5.1 Background

Parkinson's Disease (PD) is primarily caused by the selective degeneration of midbrain dopamine (mDA) neurons and is the most prevalent movement disorder, affecting 1% to 2% of the global population over the age of 65 (Dauer 2003; Meissner 2011; Obeso 2010). Currently available pharmacological treatments (e.g., L-3,4-dihydroxyphenylalanine [L-DOPA], Apomorphine, Totigotine) are largely symptomatic and lose their efficacy over time, with accompanying severe side effects such as dyskinesia. Thus, there is an unmet medical need to develop mechanism-based and/or disease-modifying treatments (Meissner 2011; Obeso 2010). NurrOn Pharmaceuticals and HanAll Pharmaceuticals, Inc. are co-developing ATH-399A/HL192 (hereafter referred to as ATH-399A), an orally administered first-in-class small molecule targeting the Nurr1 nuclear receptor for the treatment of PD.

Nurr1 is a key regulator of mDA neurons and is essential not only for development but also for maintenance of mDA neurons in adult brains (American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). (American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

Castillo 1998; Saucedo-Cardenas 1998; Zetterström 1997; Kadkhodaei 2009).

Nurr1 is the merging control point of two major signaling pathways, Shh and Wnt1, during mDA neuron development. Nurr1 heterozygous null mice display behavior seen in animal models of PD, as they exhibit a significant decrease in both rotarod performance and locomotor activities associated with decreased levels of dopamine (DA) in the striatum and decreased number of A9 DA neurons (Jiang 2005).

Nurr1 regulates many critical dopaminergic function genes such as tyrosine hydroxylase (Kim 2003), aromatic amino acid decarboxylase, dopamine transporter, vesicular monoamine transporter, and GDNF receptor c-Ret genes, which maintain the DA neurotransmitter phenotype and survival of the mDA neuron. Nurr1 protects mDA neurons in part by suppressing neurotoxic mediators in microglia and astrocytes (Glass 2010).

Post-mortem findings revealed that Nurr1 expression is significantly diminished in the substantia nigra of PD patients (Chu 2006; Moran 2007), positing Nurr1 as a potential target for developing novel and mechanism-based therapeutics for PD (Decressac 2013; Kim 2016; Dong 2016). In addition, a recent study demonstrated that Nurr1 plays critical roles in both microglia and astrocytes to repress proinflammatory genes and protects mDA neurons from inflammation-induced death (Saijo 2009).

Although Nurr1 is a promising drug target for therapeutic development for PD, the prevailing dogma in this research field was that it is a constitutively active, ligand-independent transcription factor. This dogma is based on previous studies showing that the structure of Nurr1's ligand-binding domain (LBD) looks like it is agonist-bound, in a transcriptionally active conformation and that its LBD lacks a "classical" binding pocket due to the presence of bulky hydrophobic

side chain residues (Wang 2003). However, NurrOn has demonstrated that Nurr1 is an "adopted" nuclear receptor with ligand.

[redacted]

This study will be a first-in-human evaluation of the safety and pharmacokinetics of single and multiple doses of ATH-399A in healthy adults in the 18-55 year age range, multiple doses in healthy participants in the >55-80 year age range, and will also evaluate the effect of food on ATH-399A.

5.2 Study Rationale

The study design meets the objectives of pharmacokinetic profile and food effect assessments and the evaluation of safety, tolerability and exposure profile resulting from single and multiple dose administration, required in Phase 1 studies. Part 2 will initially evaluate the safety of multiple doses in participants aged 18 – 55 years. Once safety is established, the study will evaluate dosing in healthy participants of either gender in the >55-80 year age range to match the approximate age range of the target PD population. A typical crossover design is adopted for the evaluation of food effect. The single and multiple ascending dose stages are randomized, double-blind, and placebo-controlled. The number of participants is based on standard practices of clinical pharmacology and clinical development.

5.3 Benefit/Risk Assessment

There have been no clinical studies of ATH-399A conducted to date; therefore, assessment of potential risks of ATH-399A administration are based on non-clinical data to date.

[redacted]

As this first-in-human study is being conducted in healthy participants, there is no anticipated personal medical benefit.

6 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Part 1a	
Primary	
To assess the single dose safety and tolerability of ATH-399A in healthy male and female participants in up to 5 different ascending dose level groups.	Safety and tolerability will be assessed by changes in vital signs, ECGs, clinical laboratory tests, telemetry, physical examination, neurological examination, C-SSRS, and the overall incidence of AEs and SAEs.
Secondary	
To evaluate the single dose plasma pharmacokinetics (PK) of ATH-399A in healthy male and female participants in up to 5 different ascending dose level groups.	Plasma PK parameters will include: • AUC_{0-t} • $AUC_{0-\infty}$ • C_{max} • T_{max} • λ_z • $t_{½\ el}$
To determine concentration of ATH-399A and identify its metabolites in blood and urine in healthy male and female participants after a single dose in up to 5 different ascending dose level groups.	Concentrations of ATH-399A and identification its major metabolites in blood and urine.
Part 1b	
Primary	
To assess the single dose safety and tolerability of ATH-399A in healthy male and female participants under fasted and fed conditions.	Safety and tolerability will be assessed by changes in vital signs, ECGs, clinical laboratory tests, telemetry, physical examination, neurological examination, C-SSRS, and the overall incidence of AEs and SAEs.
Secondary	
To evaluate the single dose plasma PK of ATH-399A in healthy male and female participants under fasted and fed conditions.	Plasma PK parameters will include: • AUC_{0-t} • AUC_{0-inf} • C_{max} • T_{max} • λ_z • $t_{½\ el}$

Objectives	Endpoints
Part 2	
Primary	
To assess the safety and tolerability of multiple doses of ATH-399A in up to 2 ascending dose groups in healthy male and female participants.	Safety and tolerability will be assessed by changes in vital signs, ECGs, clinical laboratory tests, telemetry, physical examination, neurological examination, C-SSRS, and the overall incidence of AEs and SAEs.
Secondary	
To assess the plasma PK of multiple doses of ATH-399A in up to 2 ascending dose groups in healthy male and female participants.	Plasma PK parameters will include: • AUC_{0-t} • AUC_{0-inf} • C_{max} • $C_{max, ss}$ • C_{min} • C_{avg} • T_{max} • $T_{max, ss}$ • $AUC_{0-\tau}$ (AUC_{0-24}, Day 12 dose) • AUC_{0-24} (Day 1 dose) • λ_z • $t_{½ el}$ • AR
AR=accumulation ratio; AUC = area under the curve; $AUC_{0-\tau}$ = area under the curve for the defined dosing interval; C_{avg} = average plasma concentration; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; λ_z = terminal elimination rate constant; PK = pharmacokinetics; $t_{½ el}$ = terminal elimination half-life; T_{max} = time to maximum plasma concentration	

7 STUDY DESIGN

7.1 Overall Design

This study is a randomized, Phase 1 three-part study:

- Part 1a is a placebo-controlled, double-blind, SAD, safety, tolerability, and PK evaluation of ATH-399A.
- Part 1b is an open-label, single dose, food-effect, safety, tolerability, and PK evaluation of ATH-399A.
- Part 2 is a placebo-controlled, double-blind, MAD, safety, tolerability, and PK evaluation of ATH-399A, in 2 different age groups.

7.1.1 Part 1a (SAD)

After assessing eligibility during a 4-week screening period, approximately 40 healthy participants will participate in Part 1a. Each eligible participant will be assigned to 1 of 5 cohorts (8 participants per cohort) to evaluate a total of up to 5 single ascending dose levels. Proposed dose levels are:

Cohort 1: 5 mg

Cohort 2: 10 mg

Cohort 3: 20 mg

Cohort 4: 40 mg

Cohort 5: 80 mg

The starting dose will be 5 mg. Following completion of each ascending dose level, an SRC will review the safety and tolerability data through the follow-up visit of a minimum of 6 evaluable participants. The SRC will also review PK data for up to 48 hours post-dose in at least 6 evaluable participants in order to make decisions whether to escalate to the next planned dose level, decrease the next dose level, repeat a dose level, or to not evaluate any additional dose. The determination of the highest dose level for this study will be based on emerging safety/tolerability and PK data, as recommended by the SRC, but will not exceed the maximum dose currently outlined in the protocol.

For each dose level, 6 participants will receive ATH-399A and 2 participants will receive placebo. Each cohort will utilize sentinel dosing, with one participant receiving ATH-399A and one participant receiving placebo. Provided no clinically significant safety issues are noted in the 48 hours after dosing the initial 2 participants in the cohort, the 6 remaining participants in the cohort will be dosed. Before dosing the rest of the cohort, the Investigator will initiate a discussion via e-mail with the Sponsor's Medical Monitor (MM) or representative to review the available safety and tolerability data of the sentinel participants in order to make a decision regarding continuation of the study with the remaining 6 non-sentinel participants. In the case of

clinically significant safety issues or a sentinel stopping rule is present, then an ad hoc SRC meeting and/or a MM call can be necessary.

Participants will be admitted to the clinical unit on the day before study drug administration (Day -1) for baseline assessments, and to confirm eligibility. Participants will be dosed in the fasted state and will be required to fast for a minimum of 10 hours prior to dosing and 4 hours following dosing. Except for water given with the study drug, no fluids will be allowed from 1 hour before dosing until 1 hour after dosing. Participants in Study Part 1a will stay in the clinical unit for 4 days (3 nights), from Day -1 until Day 3. Blood samples for PK analysis for Cohorts 1, 2, and 3 will be collected pre-dose and at specified time points up to Day 3 (48 hours) post-dose and blood samples for PK analysis for Cohorts 4 and 5 will be collected pre-dose and at specified time points up to Day 5 (96 hours) post-dose. Urine samples for PK analysis will be collected from pre-dose and during specified time intervals up to Day 3 (48 hours post-dose). PK blood samples for Cohorts 4 and 5 will be collected at outpatient visits on Day 4 (72 hours post-dose) and Day 5 (96 hours post-dose). All participants in each cohort will return for a follow-up visit on Day 8 (between Day 8 and Day 11).

Physical and neurological examinations, safety labs (including drug screen, cotinine test, and alcohol breath test), vital signs, ECG, and telemetry will be performed at specified time points. AEs will be recorded throughout the study. For details regarding the timing of specific procedures, see Table 1.

7.1.2 Part 1b (Food Effect)

Part 1b is a 2-period, 2-sequence, crossover study part to evaluate the effect of food on ATH-399A safety, tolerability, and PK.

After assessing eligibility during a 4-week screening period, approximately 12 healthy participants (with a minimum of 3 of each gender) will be randomized to one of the 2 sequences AB or BA and will receive the following study treatments in each period:

- Treatment A: Single dose of ATH-399A after a high-calorie, high-fat breakfast.

  After a supervised fast of at least 10 hours, participants will be served a high-fat, high-calorie meal. Drug administration will occur approximately 30 minutes after the meal has been started. Except for fluids provided with the breakfast and water given with the study drug, no fluids will be allowed from 1 hour before until 1 hour after dosing.
- Treatment B: Single dose of ATH-399A after fasting.

  No food will be allowed from at least 10 hours before until at least 4 hours after dosing. Except for water given with the study drug, no fluids will be allowed from 1 hour before until 1 hour after dosing.

Eligible participants will be admitted to the clinical unit on the day before (first) administration (Day -1) of the study drug, for baseline assessments and to confirm eligibility. Participants will stay in the clinical unit for 2 periods of 3 nights each with a washout period of at least 7 days (the washout period may be adjusted based on PK data derived from Part 1a). Participants will be discharged from the clinical unit on Day 3 following completion of all assessments. Participants will then return to the clinical unit for PK blood sample collection on Day 4 (72 hours post-dose)

and Day 5 (96 hours post-dose). After completing the washout period of at least 7 days, the participants will return to the clinical unit to begin their second study period, receive the study drug on Day 1 (of the second period) and remain in the clinic through completion of their Day 3 (of the second period) assessments. Participants will then return to the clinical unit for PK blood sample collection on Day 4 (72 hours post-dose of the second period) and Day 5 (96 hours post-dose of the second period). An outpatient follow-up visit will take place on Day 8 in Period 2.

Selection of the dose to be administered in Part 1b will depend on the results of Part 1a. [redacted]

Blood samples for PK will be collected pre-dose and at specified time points post-dose. Vital signs, ECG, telemetry, safety lab (including drug screen, cotinine, and alcohol breath test), and physical and neurologic examinations will be performed at specified times. AEs will be recorded throughout the study. For details regarding the timing of specific procedures, see Table 2.

7.1.3 Part 2 (MAD)

Part 2 is the MAD part of the study. After assessing eligibility during the 4-week screening period, approximately 16 participants (with a minimum of 2 of each gender per dose level cohort) will be enrolled in 2 sequential cohorts. Eligible participants in each cohort will come to the clinical unit on the day before the first study drug administration (Day -1), for baseline assessments and to confirm eligibility and will stay in the clinical unit for 14 days (13 nights), from Day -1 until Day 13. Participants will return to the clinical unit for outpatient PK blood sample collections on Day 15 (72 hours post-last dose), and Day 16 (96 hours post-last dose) as well as an outpatient follow-up visit that will take place 7 days after receiving the last dose of study drug, on Day 19 (between Day 19 and Day 22).

Each cohort will include 8 participants, 6 participants will receive ATH-399A and 2 participants will receive placebo. Dose levels of ATH-399A will be based on data from Part 1 (Part 1a and 1b) and recommendation from the SRC. Additionally, [redacted] From Day 1 to Day 12, participants will receive either ATH-399A or placebo once daily (QD) for a total of twelve (12) consecutive days. On Days 1 and 12, participants will fast for a minimum of 10 hours prior to dosing and 4 hours following dosing. From Days 2 to 11, participants will fast for a minimum of 2 hours prior to dosing and 2 hours following dosing.

Following completion of each dose level (both cohorts), an SRC will review the safety and tolerability data through the follow-up visit of a minimum of 6 evaluable participants. The SRC will also review PK data for up to 24 hours post-last dose in at least 6 evaluable participants in

order to make decisions whether to escalate to the next planned dose level, decrease the next dose level, repeat a dose level, or to not evaluate any additional dose. The time interval when escalating the dose from the first dosing of Cohort 1 of the MAD to the first dosing of Cohort 2 of the MAD will be approximately 3.5 weeks.

Blood samples for PK will be collected pre-dose and at specified time points up to 96 hours post-Day 12 dose. Vital signs, ECG, telemetry, safety lab (including drug screen, cotinine, and alcohol breath test), C-SSRS, and physical and neurologic examinations will be performed at specified times. AEs will be recorded throughout the study. For details regarding the timing of specific procedures see Table 3.

Additional Cohort: Following assessment of MAD dosing in participants, an additional cohort of approximately 8 participants will be evaluated at a dose level determined to be safe by the SRC. After assessing eligibility during the 4-week screening period, 8 participants (approximately equal numbers of males and females, with a minimum of 2 of each gender), aged >55-80 years, inclusive, will be enrolled. The study drug will be administered once daily (QD) in the fasted state for a total of twelve (12) consecutive days. On Days 1 and 12, participants will fast for a minimum of 10 hours prior to dosing and 4 hours following dosing. From Days 2 to 11, participants will fast for a minimum of 2 hours prior to dosing and 2 hours following dosing. Six participants will receive ATH-399A and 2 participants will receive placebo once daily (QD).

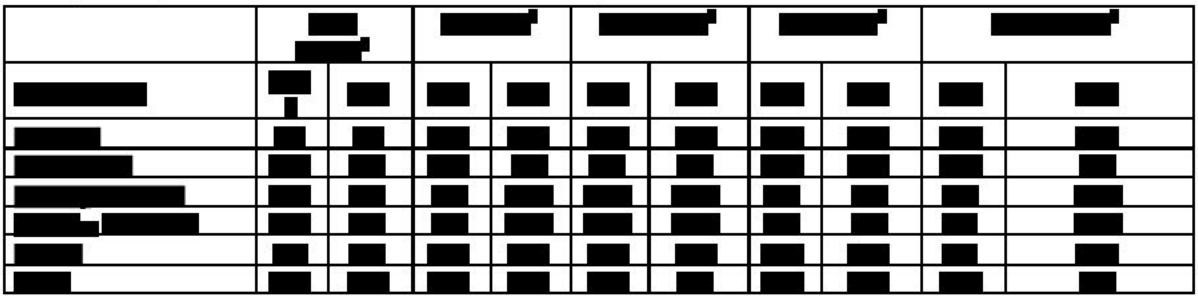
Eligible participants in this additional cohort will come to the clinical unit on the day before the first study drug administration (Day -1), for baseline assessments and to confirm eligibility and will stay in the clinical unit for 14 days (13 nights), from Day -1 until Day 13.

Blood samples for PK will be collected pre-dose and at specified time points up to 96 hours post-Day 12 dose. Vital signs, ECG, telemetry, safety lab (including drug screen, cotinine, and alcohol breath test), C-SSRS, and physical and neurologic examinations will be performed at specified times. Adverse events will be recorded throughout the study. Participants will return to the clinical unit for outpatient PK blood sample collections on Day 15 (72 hours post-last dose), and Day 16 (96 hours post-last dose) as well as an outpatient follow-up visit that will take place 7 days after receiving the last dose of study drug, on Day 19 (between Day 19 and Day 22). For details regarding the timing of specific procedures see Table 3.

7.2 Justification for Dose

[redacted]

[redacted]



[redacted]

7.3 Safety Review Committee and Dose Escalation Criteria

The study will be monitored by an SRC. The SRC is intended to ensure that treatment does not pose undue risk to participants. The SRC will be composed of at least the Investigator, one medically qualified Sponsor representative and an independent MM. SRC meetings will be held after safety and tolerability data through follow-up visit for at least 6 dosed participants from a same cohort and PK data up to at least 48 hours post-dose (Day 3 for Parts 1a and 1b) and 24 hours post-last dose (Day 13 for Part 2) from a same cohort are available. The SRC will consider the data on a cohort basis, but also on the basis of cumulative information across cohorts as the

study progresses. The SRC recommendations should be based on results from a minimum of 6 evaluable participants in each dosing cohort.

Safety/tolerability data through the final follow-up visit for each of the 6 evaluable participants in a cohort along with PK data up to at least 48 hours post-dose in Part 1a and 1b (or 24 hours post-last dose in Part 2) will be assessed by the SRC prior to:

a. Ascending from one dose-level cohort to the next higher dose level cohort in Parts 1a and 2,
b. Prior to transitioning from Part 1a to Parts 1b and 2.

The SRC will stop dose escalation or descend to a dose level lower than the planned next higher dose level if any of the following criteria are met:

- One participant per cohort who receives ATH-399A experiences a serious adverse event (SAE) which is considered to be related to the study medication.
- Two participants per cohort who receive ATH-399A have QTc prolongation, defined as an average absolute (regardless of baseline value) QTcF >500 msec or an increase of QTcF > 60 msec above baseline, confirmed by repeating after 5 minutes, and determined post-dose.
- Two participants per cohort who receive ATH-399A exhibit hypotension, defined as resting supine diastolic blood pressure <40 mmHg persisting for at least 10 minutes on repeated assessment, or an asymptomatic or symptomatic fall in systolic blood pressure to below 80 mmHg, persisting for at least 10 minutes on repeated assessment.
- Two participants per cohort who receive ATH-399A exhibit hypertension, defined as an increase in resting systolic blood pressure to above 180 mmHg, persisting for at least 10 minutes, or an increase in resting diastolic blood pressure to above 105 mmHg, persisting for at least 10 minutes.
- Two participants per cohort who receive ATH-399A exhibit tachycardia, defined as resting supine heart rate >130 beats per minute, persisting for at least 10 minutes.
- Two participants per cohort who receive ATH-399A exhibit symptomatic bradycardia, defined as heart rate <40 beats per minute, or asymptomatic bradycardia, defined as resting supine heart rate <30 beats per minute while awake, persisting for at least 10 minutes, or clinically significant arrhythmia.
- One participant per cohort who receives ATH-399A exhibits abnormal liver tests defined as:
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5X upper limit of normal (ULN).
  - AST or ALT >3X ULN along with one of the following criteria:
    - sustained for more than 2 weeks or
    - total bilirubin level >2X ULN or
    - international normalized ratio (INR) time >1.5X ULN or
    - the appearance of fatigue, nausea, vomiting, right upper abdominal pain or tenderness, fever, rash, and/or eosinophilia (>5%).
  - Alkaline phosphatase (ALP) >3X ULN.
  - ALP >2.5X ULN and total bilirubin >2X ULN.

  - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right upper abdominal pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- One participant per cohort who reaches a plasma AUC_{0-24} of ≥ 1,800 h*ng/mL.
- Two participants per cohort who receive ATH-399A exhibit renal toxicity, defined as serum creatinine ≥1.5X ULN (confirmed by repeating within 24 hours).
- Two participants per cohort who receive ATH-399A exhibit hematologic toxicity, defined as one or more of the following (confirmed by repeating within 24 hours):
  - Leukocyte count <2.5 x 10^9/L
  - Neutrophils < 1.3 x 10^9/L and < 1.0 x 10^9/L for Afro-American participants
  - Platelet count <75 x 10^9/L

In addition, the SRC may stop dose escalation or descend to a dose level lower than the planned next higher dose level at any time if the SRC determines that dose escalation would pose undue risk to participants. If dose escalation is not stopped, the SRC may recommend ascending to the planned next higher dose level cohort, ascending to a dose level lower than the planned next higher dose level, or may repeat dosing at the current dose level.

Initially, for Parts 1a and 2, the safety and any available PK data will be reviewed by the SRC in a blinded manner (e.g., without participant identifiers or using reblinded participant numbers), but if the SRC considers it necessary due to a safety concern, individual participant data or an entire cohort's data may be unblinded to the SRC to enable decision-making. Before any such unblinding, the reason for unblinding should be documented.

Unblinding to validate treatment group where stopping criteria is met will be determined by SRC members. Subsequent dose escalation or descent will depend on if stopping criteria was met by participants who received ATH-399A as opposed to placebo.

7.4 End-of-Study Definition

The study will be completed when all participants have completed their Final Study Visit assessments. On completion of the study, data will be reconciled, and the database will be locked for analysis.

8 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

8.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Healthy, as determined by the Investigator based on a medical evaluation including medical history, physical examination, neurological examination, laboratory tests and cardiac monitoring. A participant with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included only if, in the opinion of the Investigator, the finding is:
    a. not clinically significant according to the Investigator judgement
    b. unlikely to introduce additional risk to the participant,
    c. will not interfere with study procedures or confound study results, and
    d. is not otherwise exclusionary.
2. Population (see Section 13.4):
    a. Part 1a and 1b: Men and women, age 18-55 years inclusive at date of screening.
    b. Part 2: Men and women aged 18-55 years inclusive at date of screening. Additional cohort: Participants of the additional cohort will be of approximately equal numbers of males and females, with a minimum of 2 of each gender, aged >55-80 years, inclusive.
3. Women of childbearing potential (WOCBP) including those who had bilateral tubal ligation must be non-pregnant and non-lactating. They must use and commit to continuing to use a double barrier contraception method with acceptable, highly effective contraception methods from screening until study completion, including at least 90 days following the last study drug administration. WOCBP must have a negative pregnancy test result before administration of study drug and must agree not to donate ova (or egg) for at least 30 days after the last dose of study drug administration. Total abstinence from heterosexual intercourse is accepted (when this is in line with the preferred and usual lifestyle of the subject) for at least 6 months before screening and until at least 90 days following the last study drug administration.
4. Postmenopausal women must have had ≥12 months of spontaneous amenorrhea (with follicle-stimulating hormone [FSH] ≥40 mIU/mL).
5. Surgically sterile women are defined as those who have had a hysterectomy and/or bilateral oophorectomy. Women who are surgically sterile must provide verbal confirmation. See Section 13.4.
6. Male participants who are sexually active with WOCBP (see Section 13.4) must:
    a. Agree to use condoms to protect their partners from becoming pregnant during the study (including washout periods) and not to donate sperm for at least 90 days after the last dose of study drug, *and*

b. Agree to ensure that they and their partners are routinely using a medically approved contraceptive method. It is important that male participants not impregnate others while in the study.

7. Body weight ≥50.0 kg for men and ≥45.0 kg for women and body mass index within the range of 18.0-30.0 kg/m^2 (inclusive).
8. Participants participating in Part 1b must be willing and able to consume the entire high-fat, high-calorie breakfast in the designated timeframe.
9. Participants must understand the nature of the study, must be willing to participate in the study, and must provide signed and dated written informed consent in accordance with local regulations before the conduct of any study-related procedures.
10. Participants must be, in the opinion of the Investigator, able to participate in all scheduled evaluations, likely to complete all required tests, and likely to be compliant.
11. Participants must be fluent in English or French.
12. Participants must agree not to post any personal medical data related to the study or information related to the study on any website or social media site (e.g., Facebook, Twitter, etc.).

8.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. A positive urine cotinine, drug screen, or alcohol breath test at screening or Day -1.
2. Any history of psychiatric disorders, including substance use disorders, according to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5) criteria that requires current treatment with psychiatric medications (Am. Psych. Association). Participants with mild anxiety or depression which is stable for >6 months are permitted.
3. History of drug abuse within 1 year prior to screening or recreational use of soft drugs (such as marijuana) within 1 month or hard drugs (such as cocaine, phencyclidine [PCP], crack, opioid derivatives including heroin, and amphetamine derivatives) within 3 months prior to screening.
4. A diagnosis of intellectual disability (intellectual developmental disorder) or mental retardation.
5. A serious mental illness, dementia, or other neuropsychiatric disorder that would interfere with participation in the trial, or ability to provide informed consent in the opinion of the Investigator.
6. Acute suicidality as indicated by the C-SSRS or history of suicidal behavior within the 12 months prior to screening. Participants who answer “yes” to item 4 or 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening or Day -1, or who answer “yes” to any suicidal behavior item (excluding non-suicidal self-injurious behavior) will not be eligible.
7. A positive Hepatitis B surface antigen or positive Hepatitis C antibody result at screening.

8. A positive test at screening for human immunodeficiency virus (HIV) antigen or antibody or a history of positive test.
9. Alanine aminotransferase or aspartate aminotransferase levels greater than 1.2 times the ULN at screening or Day -1.
10. Frequently used any tobacco-containing (e.g., cigar, cigarette or snuff) or nicotine-containing product (e.g., nicotine chewing gum, nicotine plasters, or other product used for smoking cessation) within 30 days prior to first dose administration. Frequent use is defined as >5 cigarettes per week. Use of any tobacco- or nicotine-containing product is prohibited within 2 weeks of first dose administration through completion of the in-clinic stay for the SAD (Parts 1a and 1b) and until after the final study visit for the MAD (Part 2).
11. History of alcohol abuse within 1 year prior to screening or regular use of alcohol within 6 months prior to screening that exceeds 10 units for women or 15 units for men of alcohol per week (1 unit = 340 mL of beer 5%, 140 mL of wine 12%, or 45 mL of distilled alcohol 40%).
12. Regularly consumed (e.g., more days than not) excessive quantities of xanthine-containing beverages (e.g., more than 2 cups of coffee or the equivalent per day) within 1 week prior to screening or between screening and first dose administration, or unwillingness to refrain from xanthine-containing beverages during the in-clinic stay.
13. Received or used an investigational product (including placebo) or device within the following time period prior to the first dosing day in the current study: 30 days or 5 half-lives (whichever is longer). For biological products, administration of a biological product within 90 days prior to the first dosing, or concomitant participation in an investigational study involving no drug or device administration.
14. Other than those medications outlined in the protocol body and those allowed in the MAD additional cohort, use of prescription or non-prescription drugs, herbal, and dietary supplements (including St. John's Wort) within 7 days (or 28 days if the drug is a potential hepatic enzyme inducer) or 5 half-lives (whichever is longer) prior to first dose administration, unless in the opinion of the Investigator and Medical Monitor, the medication will not interfere with the study procedures or compromise participant safety.
15. History of clinically significant sensitivity to any of the study drugs, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.
16. Donation of plasma within 7 days prior to the first dosing or donation or loss of 500 mL or more of whole blood within 8 weeks prior to the first dosing.
17. A positive pregnancy test or lactation.
18. A history or presence of any disease, condition, or surgery likely to affect drug absorption, distribution, metabolism, or excretion. Participants with a history of cholecystectomy should be excluded.
19. A history or presence of a clinically significant hepatic, renal, gastrointestinal, cardiovascular, endocrine, pulmonary, ophthalmologic, immunologic, hematologic, dermatologic, or neurologic abnormality. Participants with fully resolved childhood

asthma with no hospitalizations or recurrence in adulthood are permitted to enroll. For the additional cohort in Part 2, any of the above are acceptable where the condition is stable for >6 months and, in the opinion of the Investigator, it does not impact participant safety.

20. A clinically significant abnormality on physical examination, neurological examination, ECG, or laboratory evaluations at screening and Day -1.
21. A QT interval measurement corrected according to the Fridericia rule (QTcF) > 450 msec during controlled rest at screening and Day -1, or family history of long QT syndrome.
22. Any clinically significant abnormalities in rhythm, conduction, or morphology of the resting ECG and any abnormalities in the 12-lead ECG that, in the judgement of the Investigator or Medical Monitor, may interfere with the interpretation of QTc interval changes, including abnormal ST-T-wave morphology or left ventricular hypertrophy.
    a) PR (PQ) interval shortening < 120 msec (PR < 120 msec but > 110 msec is acceptable if there is no evidence of ventricular pre-excitation).
    b) PR (PQ) interval prolongation (>220 msec), intermittent second-degree (Wenckebach block while asleep or in deep rest is not exclusionary) or third-degree AV block.
    c) Persistent or intermittent complete bundle branch block (BBB), incomplete bundle branch block (IBBB), or intraventricular conduction delay (IVCD) with QRS > 120 msec.

    Note: at the Investigator's discretion, if an abnormal ECG is observed, the assessment may be repeated.
23. A clinically significant vital sign abnormality at screening or between screening and first dose administration. This includes, but is not limited to, the following in the supine position:
    a) systolic blood pressure < 90 or >140 mmHg,
    b) diastolic blood pressure <50 or > 90 mmHg, or
    c) heart rate < 45 or >100 beats per minute.
    d) decrease in systolic blood pressure of 20 mmHg or higher, decrease in diastolic blood pressure of 10 mmHg or higher, or increase in heart rate of 30 bpm or higher within 2 to 3 minutes after passing from a supine to a standing position.

    Note: at the Investigator's discretion, if a single abnormal vital sign is observed, the assessment may be repeated.
24. Significant (> 5%) weight loss or gain within 30 days prior to screening or between screening and first dose administration.
25. A history of seizures. Occurrence of a single febrile seizure is not exclusionary.
26. A history of head trauma, including closed head injury with loss of consciousness. Concussions which did not lead to hospitalization or loss of consciousness, and for which there are no ongoing issues, are not exclusionary.
27. A history of symptomatic orthostatic hypotension (i.e., postural syncope).
28. A history of neuroleptic malignant syndrome.

29. A history of chronic urinary tract infections (≥2 times per year).
30. The participant is, in the opinion of the Investigator or Medical Monitor, unlikely to comply with the protocol or is unsuitable for any reason.
31. Currently employed by NurrOn Pharmaceuticals, Inc., HanAll Pharmaceutical Inc., or HanAll Biopharma Co. Ltd., or by a clinical trial site participating in this study, or a first-degree relative of an NurrOn Pharmaceuticals, Inc., HanAll Pharmaceutical Inc., or HanAll Biopharma Co. Ltd. Employee or of an employee at a participating clinical trial site.
32. Unsatisfactory venous access.
33. Unable to swallow oral capsules.
34. Positive result to a COVID-19 PCR test at screening or on Day-1.
35. COVID-19 or flu vaccination within 30 days prior to study drug administration or any other vaccination which is judged by the investigator to potentially affect eligibility.
36. Presence of fever (body temperature >37.5°C) (e.g., a fever associated with a symptomatic viral or bacterial infection) within 2 weeks prior to first dosing.

8.3 Lifestyle Guideline

8.3.1 Meals, Dietary, and Lifestyle Restrictions

- Consumption of red wine, Seville oranges, grapefruit, pomegranate, pineapple or grapefruit juice, are prohibited from 4 days prior to admission to the clinical unit until the final study visit.
- Consumption of poppy seeds (e.g., orange and poppy seed muffin, poppy seed bread) 48 hours before screening and admission (e.g., each time a drugs of abuse test is done) is prohibited.
- During in-clinic stay, participants will consume only standardized meals and snacks provided to them. Prune juice during mealtimes is allowed and will be provided by the clinic to treat constipation, if needed.
- For participants receiving study drug in the fasted state, they will be required to fast for a minimum of 10 hours prior to dosing and 4 hours following dosing.
- For participants receiving study drug in the fed state, participants will consume a standardized high fat, high calorie meal (in accordance with FDA Guidance for Industry, Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations, June 2022). Participants are to eat the meal in 30 minutes or less and study drug will be administered 30 minutes (±2 minutes) after the start of the meal. The timing of the meal with respect to drug administration should be recorded, along with the amount of food consumed. Participants should then fast for 4 hours following dosing.
- Approximately 240 to 340 mL water will be given to each participant at the time of administration of the study medication. At least 240 mL of water should be swallowed with the study drug.

- Except for water provided for study drug administration and fluids given with the high fat high calorie breakfast (food-effect cohort), no fluids will be allowed from 1 hour before until 1 hour after dosing.
- The complete dose should be administered within a maximum of 5 minutes (for situations of multiple capsule administration).
- No unaccustomed exercise 48 hours before every visit where blood samples are to be collected.
- Participants should not receive a COVID-19 or flu vaccination within 30 days prior to study drug administration through the final study visit or any other vaccination which is judged by the investigator to potentially affect eligibility.

8.3.2 Caffeine, Alcohol, Drugs, and Tobacco

- Soft or hard drugs from screening and throughout the study are prohibited;
- During each in-clinic stay, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate).
- Food or beverages containing xanthine derivatives or xanthine-related compounds (coffee, black/green tea, chocolate) or energy drinks from 48 hours prior to dosing until discharge from the clinical site. Consumption of quinine, caffeine and xanthine containing beverages is not allowed throughout the clinical stay and until after the final study visit.
- Participants should not consume alcohol or alcohol-based products for 24 hours prior to admission to the clinical unit and until after the final study visit.
- Participants who use tobacco products in excess of 5 cigarettes per week in the last 30 days preceding screening are excluded from participation in this study. Use of any tobacco or nicotine-containing products is prohibited within 2 weeks of the first dose of study drug through the completion of the in-clinic stay for the SAD (Parts 1a and 1b) and until after the final study visit for the MAD (Part 2).

8.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once.

9 STUDY TREATMENTS AND CONCOMITANT THERAPY

9.1 Study Treatments Administered

Study treatments to be administered in this study are provided in Table 5.

Table 5: Study Treatments Administered

Treatment Name	ATH-399A	Placebo
Type	Drug	Drug
Dose Formulation	Capsule	Capsule with inert filler (Avicel)
Unit Dose Strength(s)	5 and 20 mg	N/A
Dosage Level(s)	5 mg to not more than 80 mg	N/A
Route of Administration	Oral	Oral
Use	Experimental	Placebo
IMP or NIMP	IMP	NIMP
Sourcing	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	Study treatment will be provided in HDPE bottles with child-resistant caps. Each bottle will be labeled as required per country requirement.	Study treatment will be provided in HDPE bottles with child-resistant caps. Each bottle will be labeled as required per country requirement.

IMP=Investigational Medicinal Product; N/A=not applicable; NIMP=Non-Investigational Medicinal Product; TBD=to be determined

9.2 Study Drug Packaging and Labeling

Study drug will be packaged and labeled according to current Good Manufacturing Practice and GCP guidelines and applicable local laws and/or regulations.

9.3 Study Drug Storage

The Investigator (or designee) is responsible for the safe and proper storage of the study drug and placebo at the study site.

The drug product is stable when stored at the recommended storage conditions at room temperature ranging around 15-25°C (59-77°F). Placebo should be stored similarly.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received, and any discrepancies are reported to the Sponsor and resolved before use of the study drug.

9.4 Study Drug Administration

Study drug will be administered at study site according to the Schedules of Assessments (SoA).

The study drug will be administered to each participant with at least 240 mL of water and a mouth check will be performed to ensure consumption of the study drug.

Time of dosing will be set equal to the time when the first capsule is administered to the participants.

For the fed period of Part 1b, after a supervised fast of at least 10 hours, participants will be served a high-fat, high-calorie meal of approximately 800 to 1000 calories (approximately ≥50% of total caloric content of the meal derived from fat). This meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. Participants should start the meal approximately 30 minutes prior to drug administration. Participants will be required to completely eat the meal in 30 minutes or less. No food will be allowed until at least 4 hours post-dose. The total volume of water administered for dosing in the fasting period will be recorded and the same volume will be used for dosing in the fed period.

For Part 2, each study drug administration will be separated by approximately 24 hours and should be done at approximately the same time every day. On Days 1 and 12, no food will be allowed from at least 10 hours before until at least 4 hours after dosing. No food will be allowed from at least 2 hours before until at least 2 hours after dosing for all other doses.

Except for water given with the study drug and fluids provided with the high-fat, high-calorie meal, no fluids will be allowed from 1 hour before until 1 hour after each dosing. Water will be provided ad libitum at all other times.

9.5 Study Drug Accountability

The Investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated study personnel must maintain study drug accountability records throughout the study. Further details will be provided in the Pharmacy Manual**.**

The study drugs will be stored at the clinical site pharmacy as per applicable requirements in a locked, temperature-controlled medication room with restricted access. Container(s) will be labeled according to applicable regulations.

Individual doses for each participant will be dispensed at the clinical site pharmacy, as per appropriate SOP and according to the randomization scheme, in appropriate envelopes/containers that will be identified with at least the protocol number and the participant randomization number.

Study drug intended for the study cannot be used for any purpose other than that described in this protocol.

9.6 Study Drug Handling and Disposal

Periodically and/or after completion of the study, all used, unused, damaged, and/or expired study drug must be reconciled and destroyed at the site if the site has an appropriate standard operating procedure; otherwise, remaining study drug to be shipped to location specified by Sponsor for destruction.

9.7 Assignment to Study Treatment

Participants will be assigned sequentially to study part and cohort, and randomized within their assigned part/cohort of the study. Participants will be numbered during screening and study procedures according to the site SOP.

For each cohort in Parts 1a, 1b and 2, eligible participants for participation will be randomized (on Day 1) to receive either the active or placebo. Participants in Part 1a and Part 2 will be randomized in a 3:1 ratio, for a total of 6 participants per cohort receiving ATH-399A and 2 participants receiving the placebo in each dose level. In Part 1a, two sentinel participants will be dosed initially (1 active and 1 placebo). The remaining 6 participants (5 actives and 1 placebo) will be dosed at least 48 hours later after sentinels have been evaluated. Participants in Part 1b will be randomized in one of the 2 arms to receive study treatments in the sequence AB or BA. If PK data analyzed from Parts 1a and 1b demonstrate a potential accumulation of ATH-399A, a sentinel approach similarly used in Part 1a will be considered for the dosing of Part 2 where sentinels will be dosed on Day 1 and the remaining participants will be dosed at least 96 hours later, which would allow safety assessment of the sentinel subjects after steady-state has been attained. One randomization scheme will be produced for each cohort separately.

Participants may be automatically replaced if they withdraw/discontinue after randomization but prior to any dosing. Replacement of participants who withdraw/discontinue post dose will be at the discretion of the Sponsor. Procedures will be performed according to the site's SOP.

9.8 Blinding

This is a randomized, double-blind (Parts 1a and 2) study using active drug (ATH-399A) and placebo control. Part 1b is randomized and open-label. Randomization to treatment group will be performed after participants have been deemed eligible for study participation. Blinding will be used in Parts 1a and 2 to reduce potential bias during data collection and evaluation of clinical endpoints. The participants and the clinical personnel involved in the collection, monitoring, revision, or evaluation of AEs, or personnel who could have an impact on the outcome of the study will be blinded with respect to the participant's treatment assignment (active or placebo). Blinding will be maintained until at least the clinical phase of the study is completed, i.e., when reporting and evaluation of all AEs have been completed for all cohorts.

Designated unblinded pharmacy personnel at the clinical site not directly involved with the clinical aspects of the study will prepare, store, and dispense the study drug in a blinded manner, according to the randomization scheme. ATH-399A and placebo will have the same visual appearance in order to avoid compromising the study blinding.

Participants will be randomized to treatments on Day 1. For Parts 1a and 2 (SAD and MAD, respectively), participants will be randomized 3:1 to active:placebo. In Part 1a, the first two participants in each cohort will be sentinel participants and will be randomized 1:1 to active:placebo. For Part 1b (food effect) participants will be randomized to 1 of 2 ATH-399A treatment condition sequences (AB or BA).

The study blind should not be broken for an individual participant except in a medical emergency (where knowledge of the study drug/dose level administered would affect the treatment of the emergency) or regulatory requirement.

The clinical site will be provided with code break envelopes for emergency unblinding. Separate code breaks will be provided for replacement numbers. The decision to break the blind for a participant will be made on a case-by-case basis, at the discretion of the Sponsor and/or Investigator or designee. In the event of a medical emergency for an individual participant for whom knowledge of the study treatment is critical, the Investigator may break the blind immediately for that participant and a notification will be made to the Sponsor within 24 hours. If the blind is broken, the date, time and reason must be recorded on the electronic Case Report Form (eCRF) and any associated adverse event (AE) reported.

Blinded PK data will be available during the course of the study. The results will be reported without revealing the participant's treatment assignment.

9.9 Study Treatment Compliance

Administration of study drug will be performed under the supervision of the Investigator at the clinical site. The investigator will be at the clinical unit on the first day of dosing for each participant and will remain in the clinical unit for 8 hours (based on T_{max} data) post-dose for safety monitoring of the participants in the event an AE and/or SAE emerges.

Compliance with study drug is defined as the participant receiving 100% of the planned dosage. Drug administration will be recorded and any discrepancies with the dosing regimen must be documented and explained in the eCRF.

9.10 Treatment of Overdose

For this study, any dose of ATH-399A greater than the assigned dose for that cohort will be considered an overdose.

In the event of an overdose, the Investigator should:

- Evaluate the participant to determine, in consultation with the Medical Monitor, if possible, whether study treatment should be interrupted (Parts 1b and 2 only).
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.

9.11 Concomitant Therapy

Use of prescription or non-prescription drugs, herbal, and dietary supplements (including St. John's Wort) within 7 days (or 28 days if the drug is a potential hepatic enzyme inducer) or 5 half-lives (whichever is longer) prior to first dose administration and throughout the duration of study participation is prohibited for Part 1 of the study and Part 2 for participants aged 18-55 years, with the exception of paracetamol (acetaminophen) up to 2000 mg daily.

In Part 2 of the study, for the additional cohort of participants >55-80 years of age, the use of cholesterol medications, antihypertensives, hormone replacement therapy, asthma medications, thyroid medications, non-steroidal anti-inflammatory drugs, proton pump inhibitors, and antihistamines are permitted according to the medical judgement of the Investigator, as long as the participant is on a stable dose for at least 14 days prior to the first study drug dose. As needed, paracetamol up to 2000 mg per day is permitted.

Hormonal contraceptives may be allowed if deemed to not interact with the study drug PK.

Prune juice during mealtimes is allowed and will be provided by the clinic to treat constipation, if needed.

10 DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 13.1.10.

10.1 Study Stopping Criteria

In the event of a life-threatening or fatal AE, the SRC will urgently convene to assess the event and determine if it is related to study drug. In the meantime, all dosing must be suspended until a decision has been made by the CRS. If the determination is made that the AE is related to study drug, the study will be suspended. Continuation of the study would require approval by the appropriate regulatory authority(ies).

Data from any participant in the sentinel groups with significant safety issues will be reviewed by an ad hoc SRC, and all dosing must be suspended until a decision is made, prior to dosing the remaining non-sentinel participants in each cohort:

- One participant per cohort who receives ATH-399A experiences a SAE which is considered to be related to the study medication.
- Two participants per cohort who receive ATH-399A have QTc prolongation, defined as an average absolute (regardless of baseline value) QTcF >500 msec or an increase of QTcF > 60 msec above baseline, confirmed by repeating after 5 minutes, and determined post-dose.
- Two participants per cohort who receive ATH-399A exhibit hypotension, defined as resting supine diastolic blood pressure <40 mmHg persisting for at least 10 minutes on repeated assessment, or an asymptomatic or symptomatic fall in systolic blood pressure to below 80 mmHg, persisting for at least 10 minutes on repeated assessment.
- Two participants per cohort who receive ATH-399A exhibit hypertension, defined as an increase in resting systolic blood pressure to above 180 mmHg, persisting for at least 10 minutes, or an increase in resting diastolic blood pressure to above 105 mmHg, persisting for at least 10 minutes.
- Two participants per cohort who receive ATH-399A exhibit tachycardia, defined as resting supine heart rate >130 beats per minute, persisting for at least 10 minutes.
- Two participants per cohort who receive ATH-399A exhibit symptomatic bradycardia, defined as heart rate <40 beats per minute, or asymptomatic bradycardia, defined as resting supine heart rate <30 beats per minute while awake, persisting for at least 10 minutes, or clinically significant arrhythmia.
- One participant per cohort who receives ATH-399A exhibits abnormal liver tests defined as:
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5X upper limit of normal (ULN).
  - AST or ALT >3X ULN along with one of the following criteria:
    - total bilirubin level >2X ULN or
    - international normalized ratio (INR) time >1.5X ULN or

        - the appearance of fatigue, nausea, vomiting, right upper abdominal pain or tenderness, fever, rash, and/or eosinophilia (>5%).
    - Alkaline phosphatase (ALP) >3X ULN.
    - ALP >2.5X ULN and total bilirubin >2X ULN.
    - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right upper abdominal pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- One participant per cohort who reaches a plasma AUC_{0-24} of ≥ 1800 ng*h/mL
- Two participants per cohort who receive ATH-399A exhibit renal toxicity, defined as serum creatinine ≥1.5X ULN (confirmed by repeating within 24 hours).
- Two participants per cohort who receive ATH-399A exhibit hematologic toxicity, defined as one or more of the following (confirmed by repeating within 24 hours):
    - Leukocyte count <2.5 x 10^9/L
    - Neutrophils < 1.3 x 10^9/L and < 1.0 x 10^9/L for Afro-American participants
    - Platelet count <75 x 10^9/L

10.2 Discontinuation of Study Treatment

In rare instances, it may be necessary for a participant to permanently discontinue study treatment. If study treatment is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for safety. See the SoA for data to be collected at the time of discontinuation of study treatment and follow-up and for any further evaluations that need to be completed.

10.3 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, significant protocol deviations, or compliance reasons.
- A participant may be withdrawn at any time for positive pregnancy test, drug screen, cotinine test, or alcohol breath test.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the SoA. The participant will be permanently discontinued from the study treatment and the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- A PK blood draw may be collected at the time of withdrawal.

10.4 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, followed by a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

11 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoAs (Table 1, Table 2, and Table 3).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the Informed Consent Form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.
- At time points when vitals, ECGs, and blood collections coincide, the order for conducting assessments should be ECGs first, then vital signs, and then blood sample collection. Sample collections done outside the pre-defined time windows will not be considered as protocol deviations since actual post-dose sampling times will be used for PK and statistical analyses. Actual collection times should be recorded on the eCRF.
- Blood and urine samples will be collected and processed as per the Analytical Methodology Information Sheet.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. The maximum amount of blood collected from each participant over the duration of the study, including that collected for eligibility and safety purposes and any extra assessments that may be required, will not exceed 250 mL for Part 1a and 350 mL for Parts 1b and Part 2.

11.1 Informed Consent

Voluntary written informed consent must be obtained before any study procedures are performed, in accordance with International Council for Harmonisation (ICH) guidelines and requirements of informed consent (Title 21 CFR Parts 50.20 and 50.25) (Section 13.1.3).

11.2 Height, Weight, and BMI

Height (cm) and weight (kg) will be collected at the time points specified in the SoAs (Table 1, Table 2, and Table 3). Based on these, body mass index (BMI) will be calculated.

11.3 Demographics

Participant demographics will be obtained during screening and include sex, date of birth, race, and ethnicity.

11.4 Medical History

A complete medical and surgical history will be obtained during screening by the Investigator or a qualified designee. Surgical and medical history of current and clinically significant conditions will be recorded.

11.5 Prior and Concomitant Medications and Treatment Medications

The Investigator or qualified designee will review past and current medication use. All medications taken by the participant within 3 months of signing the ICF through the Follow-up Visit, including prescription medications, over-the-counter medications, vitamins, herbal therapies and supplements will be recorded. Hormonal contraceptives may be allowed if deemed to not interact with the study drug PK. Treatment Medications are medications used for the treatment of SAEs.

11.6 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1, Table 2, and Table 3).

11.6.1 Physical and Neurological Examinations

A complete physical examination will be performed at screening, at the admission and at the discharge and will include assessments of the following: head, eyes, ears, nose, throat (HEENT), neck, chest, lungs, abdomen, musculoskeletal, dermatological, cardiovascular/peripheral vascular, and general neurological examination.

A brief physical examination will be performed at all other times, and will include assessments of the following: HEENT, chest, lungs, abdomen, dermatological, cardiovascular/peripheral vascular, and areas of note elicited from the participant.

11.6.2 Vital Signs

The Investigator or qualified designee will assess vital signs as noted in the SoA. Vital signs include temperature, blood pressure, pulse rate, and respiratory rate. The participant will be instructed to rest in the supine position for at least 5 minutes before vital signs are assessed.

11.6.3 Electrocardiograms

12-Lead ECGs will be performed in triplicate, at least 1 minute apart, all within 10 minutes, and will be performed and interpreted according to the site's standard operating procedures. Average

values should be recorded. The ECGs will be performed after the participant has been resting in a supine position for at least 5 minutes. The ECG will electronically measure and calculate ventricular heart rate and the PR, RR, QRS, QT, and QTcF intervals. The QTcF interval will be used for clinical evaluations.

If a clinically significant abnormality is detected, the abnormality should be documented as an AE and followed until resolution with additional ECGs as medically indicated.

11.6.4 12-Lead Telemetry

12-Lead telemetry for evaluation of cardiac arrhythmias will be conducted at the time points noted in the SoAs.

11.6.5 Clinical Safety Laboratory Tests

- See Section 13.2 for the list of clinical laboratory tests to be performed and the SoA (Section 4.1) for the timing and frequency.
- The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents (Section 10.1).
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or MM.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
    - All protocol-required laboratory tests, as defined in Section 13.2, must be conducted in accordance with the site's standard procedures or SOPs.
    - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

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

The C-SSRS is a validated instrument to prospectively assess suicidal ideation and behavior (http://www.cssrs.columbia.edu). There are versions of the questionnaire designed for use at screening (Baseline/Screening version) and at baseline and visits throughout the study (Since Last Visit version). All versions of the C-SSRS include a series of screening questions related to suicidal ideation and suicidal behavior. Participant responses of "yes" to one or more screening questions will prompt additional questions that evaluate frequency and intensity of suicidal ideation and/or behavior. Participants with active suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal

ideation with specific plan and intent) based on the C-SSRS in the 12 months before screening based on the C-SSRS will not be eligible to participate. If the Investigator determines that a participant is at risk of suicide or self-harm, appropriate measures to ensure the participant's safety and obtain mental health evaluation must be implemented: refer to the family physician and/or to the nearest hospital. A complete evaluation and medical care should be provided rapidly.

The C-SSRS will be administered and scored by the Investigator or qualified clinical unit personnel.

11.7 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 13.3.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following AEs to resolution and/or stabilization. This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 13.3.

11.7.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected continuously from time of informed consent until the Follow-up Visit (Section 4.1).

Medical occurrences that begin after obtaining informed consent will be recorded as AEs.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 13.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on new AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

11.7.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

11.7.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 10.4). Further information on follow-up procedures is provided in Section 13.3.

11.7.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/ Ethics Committees (ECs), and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/EC, if appropriate, according to local requirements.

11.7.5 Pregnancy

- Details of all pregnancies in female participants and, if possible, female partners of male participants will be collected after the start of study treatment and until the end of the study.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any female participant who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.

11.7.6 Adverse Events of Special Interest

There are currently no known adverse events of special interest for ATH-399A.

11.8 Pharmacokinetics

11.8.1 Plasma Pharmacokinetics

Plasma concentrations of ATH-399A (and metabolite identification only in Part 1a) will be determined by validated method(s).

Parts 1a and 1b PK parameters:

- AUC_{0-t}: Area under the concentration-time curve from time zero until the last observed concentration
- AUC_{0-inf}: Area under the concentration-time curve from time zero to infinity (extrapolated)
- Residual area: Percentage of AUC_{0-inf} due to extrapolation from the time of the last observed concentration to infinity, calculated as $[1 – (AUC_{0-t}/AUC_{0-inf})] \times 100$
- C_{max}: Maximal observed concentration
- T_{max}: Time when the maximal concentration is observed
- For Part 1b only: T_{lag}: Time of observation prior to the first observation with a measurable (non-zero) concentration.
- $t_{½\ el}$: Terminal elimination half-life
- λ_z: Terminal elimination rate constant
- Cl/F: Apparent clearance
- V_z/F: Apparent volume of distribution

Part 2 PK parameters:

For Day 1, the following PK parameters will be calculated:

- AUC_{0-24}: Area under the concentration-time curve from time zero to time 24 hours
- C_{max}: Maximal observed concentration
- T_{max}: Time when the maximal concentration is observed

For Day 12, the following PK parameters will be calculated:

- $AUC_{0-\tau}$: Area under the concentration-time curve for one dosing interval (τ) at steady-state. In this study, τ = 24 hours (AUC_{0-24})
- AUC_{0-t}: Area under the concentration-time curve from time zero until the last observed concentration
- AUC_{0-inf}: Area under the concentration-time curve from time zero to infinity (extrapolated)
- $C_{max\ ss}$: Maximal observed concentration at steady-state
- $T_{max\ ss}$: Time when the maximal concentration is observed at steady-state
- $C_{min\ ss}$: Minimal observed concentration at steady-state
- Residual area: Percentage of AUC_{0-inf} due to extrapolation from the time of the last observed concentration to infinity, calculated as $[1 – (AUC_{0-t}/AUC_{0-inf})] \times 100$
- $t_{½\ el}$: Terminal elimination half-life
- λ_z: Terminal elimination rate constant
- Cl_{ss}/F: Apparent clearance at steady-state
- $V_{z\ ss}/F$: Apparent volume of distribution at steady-state
- AR=accumulation ratio

Blood PK sample collection will be performed at the timepoints in Table 6.

Table 6: Pharmacokinetic Blood Sample Collection Timepoints

Visit Day	Timepoint	Part 1a	Part 1b	Part 2
Day 1 of each Period/Cohort	Pre-dose (within 2 hours of dosing)	X	X	X
	0.25 hours (±2 min) post-Day 1 dose	X	X	X
	0.5 hours (±2 min) post-Day 1 dose	X	X	X
	1 hour (±5 min) post-Day 1 dose	X	X	X
	1.5 hour (±5 min) post-Day 1 dose	X	X	X
	2 hours (±5 min) post-Day 1 dose	X	X	X
	3 hours (±10 min) post-Day 1 dose	X	X	X
	4 hours (±10 min) post-Day 1 dose	X	X	X
	6 hours (±10 min) post-Day 1 dose	X	X	X
	8 hours (±10 min) post-Day 1 dose	X	X	X
	12 hours (±10 min) post-Day 1 dose	X	X	X
	16 hours (±30 min) post-Day 1 dose	X	X	X
Day 2 of each Period/Cohort	24 hours (±30 min) post-Day 1 dose	X	X	X
	36 hours (±30 min) post-Day 1 dose	X	X	X
Day 3 of each Period/Cohort	48 hours (±30 min) post-Day 1 dose	X	X	
Day 4 of each period	72 hours (±1 hour) post-Day 1 dose (outpatient visit)	X (Cohorts 4 and 5 only)	X	
Day 5 of each period	96 hours (±1 hour) post-Day 1 dose (outpatient visit)	X (Cohorts 4 and 5 only)	X	

Visit Day	Timepoint	Part 1a	Part 1b	Part 2
Day 9 of each Cohort	Pre-dose (within 2 hours of dosing)			X
Day 10 of each Cohort	Pre-dose (within 2 hours of dosing)			X
Day 11 of each Cohort	Pre-dose (within 2 hours of dosing)			X
Day 12 of each Cohort	Pre-dose (within 2 hours of dosing)			X
	0.25 hours (±2 min) post-Day 12 dose			X
	0.5 hours (±2 min) post-Day 12 dose			X
	1 hour (±5 min) post-Day 12 dose			X
	1.5 hour (±5 min) post-Day 12 dose			X
	2 hours (±5 min) post-Day 12 dose			X
	3 hours (±10 min) post-Day 12 dose			X
	4 hours (±10 min) post-Day 12 dose			X
	6 hours (±10 min) post-Day 12 dose			X
	8 hours (±10 min) post-Day 12 dose			X
	12 hours (±10 min) post-Day 12 dose			X
	16 hours (±30 min) post-Day 12 dose			X
Day 13 of each Cohort	24 hours (±30 min) post-Day 12 dose			X
	36 hours (±30 min) post-Day 12 dose			X
Day 15 of each Cohort	72 hours (±1 hour) post-Day 12 dose			X
Day 16 of each Cohort	96 hours (±1 hour) post-Day 12 dose			X

An additional aliquot may be collected at each time point and stored for future evaluation of ATH-399A metabolites. Any blood samples drawn beyond the specified window period will be noted as early or late draws and will be recorded appropriately as a protocol deviation. A comment and explanation should be provided in the source documents. The exact collection time will be recorded in the source documents.

For Part 2: plasma concentration observed before treatment administrations (C_{trough}) during repeated dosing (Day 9, Day 10, Day 11 and Day 12) will be presented. In the additional cohort of participants >55-80 years of age (inclusive), future research and analysis of biomarkers may be performed using the residual samples originally collected for PK analysis required in this study. These analyses will only be performed if participants provided specific additional consent.

Refer to the Analytical Methodology Information Sheet (AMIS) for the collection, processing, and shipping of PK samples.

11.8.2 Urine Pharmacokinetics

In Part 1a, urine samples will be collected for analysis of ATH-399A concentrations and identification of metabolites at pre-dose, and at the following time intervals: 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, and 24-48 hours post-dose.

If a participant cannot void their bladder within 30 minutes before dosing, a urine sample from an earlier morning urine collection may be used as the pre-dose sample. Voids that occur within the time interval will be pooled, and participants will be asked to void their bladder within 30 minutes before the end of each collection interval, so that each new interval will begin with an empty bladder. Any urine voided by participants at the intersection (within 10 minutes) of two intervals will be included in the earlier sample. Any urine voided by participants but not collected will be documented. If a participant is unable to void at the end of a collection interval, the unsuccessful attempt will be documented.

Refer to the AMIS for the collection, processing, and shipping of urine samples.

For Part 1a, the following PK parameters will be calculated for [ATH-399A and metabolite(s), if applicable] urine concentrations:

- Ae_{0-t}: Cumulative urinary excretion from time zero to time t, calculated as the sum of the amounts excreted over each collection interval
- R_{max}: Maximal rate of urinary excretion, calculated by dividing the amount of drug excreted in each collection interval by the time over which it was collected
- T_{Rmax}: Time of maximal urinary excretion, calculated as the midpoint of the collection interval during which R_{max} occurred
- Cl_R: Renal clearance, calculated as Ae_{0-t}/AUC_{0-t}

Additional PK parameters may be calculated.

12 STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan (SAP) will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses.

12.1 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

- The Safety Population includes all participants who received at least one dose of study medication, ATH-399A or placebo.
- The Pharmacokinetic (PK) Population includes all participants who received at least one dose of ATH-399A, and provided at least one plasma or urine concentration measure.

12.2 General Considerations

All collected data will be reported using summary tables and figures, as appropriate. Data summaries will be presented separately by part, dose, cohort, and overall. Tabulations will be produced for appropriate disposition, demographic, baseline, safety, and PK parameters. Categorical variables will be summarized by frequency distributions (number and percentages of participants) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). As appropriate, a 95% confidence interval (CI) will be presented. Graphical displays will be presented, as appropriate. All data will be provided in by-participant listings.

Baseline is defined as the last value prior to the first dose and will be flagged for all necessary analyses.

12.3 Disposition and Baseline Characteristics

Participant disposition will be tabulated by part, cohort, treatment assignment, and dose. Disposition will include the number and percent of participants who are enrolled, those who receive treatment, discontinue early, with reasons for discontinuation, and completers. Summary statistics will be reported for baseline characteristics by cohort, part, treatment assignment, and dose.

12.4 Safety Analyses

Safety and tolerability of ATH-399A will be evaluated through the assessment of AEs (i.e., seriousness, severity, relationship to the study drug, outcome, duration, and management), vital signs, 12-lead ECGs, clinical laboratory tests, and physical examinations. AEs will be coded using the latest version of the MedDRA dictionary.

Demographic parameters will be summarized descriptively.

Safety and tolerability analysis will be performed for all participants in the safety population. No inferential statistical analysis of safety data is planned.

AEs and SAEs, will be tabulated by treatment. Changes from baseline values in vital signs, 12-lead ECGs, and clinical laboratory tests will be evaluated. Safety and tolerability data will be reported using descriptive statistics.

12.5 Pharmacokinetic Analyses

Plasma and urine concentrations of ATH-399A will be tabulated descriptively by sampling time-point. Plasma pharmacokinetic parameters will be calculated by non-compartmental methods. Descriptive statistics (n, arithmetic mean, SD, minimum, median, maximum, coefficient of variation [CV], geometric mean and geometric CV) of the plasma PK parameters will be provided by part, dose, and cohort. Individual and mean plasma concentration-time profiles will be presented graphically on both linear and semi-logarithmic scales for each dose level using nominal time points.

For Part 1a, summary statistics will be used to describe the PK profile of [ATH-399A and metabolite(s), if applicable] for each dose level. The power model approach will be performed on $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} data to assess the dose-proportionality. An ANOVA will also be performed on the untransformed T_{max}, $t_{½\ el}$, and λ_z data.

Part 1b (food effect) will be evaluated by analysis of variance, with terms for participant, sequence, period, treatment as fixed effects and participant within sequence as a random effect for the ATH-399A parameters C_{max} and $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$. The exposure measurements (AUCs and C_{max}) will be log-transformed prior to analysis. The 90% CI for the ratio of population geometric means between test (fed) and reference products (fasting) will be provided for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ and C_{max}. Intra- and inter-subject CV will also be estimated.

For Part 2, summary statistics will be used to describe the PK profile of [ATH-399A and metabolite(s), if applicable] for each dose level. The power model approach will be performed on C_{max}, $AUC_{0\text{-}tau}$, $C_{max\ ss}$, $C_{min\ ss}$, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ data to assess the dose-proportionality. An ANOVA will also be performed on the untransformed T_{max}, $T_{max\ ss}$, $t_{½\ el}$, and λ_z data. Repeated measures analysis will be carried out on ln transformed pre-dose concentrations (Days 9 to 12) to determine attainment of steady-state. Comparisons between Day 1 and Day 12 PK parameters: $AUC_{0\text{-}24}$ versus $AUC_{0\text{-}\tau}$, C_{max} versus $C_{max\ ss}$, and T_{max} versus $T_{max\ ss}$ will be done by ANOVA. Ratios (Day 12/Day1) and 90% geometric CI will be computed for AUC and C_{max}.

12.6 Interim Analyses

There are no planned interim analyses for this study. Safety and PK summaries will be available for SRC meetings.

12.7 Sample Size Determination

The sample size for each stage was determined based on standard practice in Phase 1 food effect, SAD and MAD studies empirically and was not powered for statistical significance. Cohort sizes were selected based on those commonly utilized in similar Phase 1 studies and thus generally considered sufficient to assess safety, tolerability, and estimate PK parameters.

13 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

13.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

13.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
    - Applicable ICH GCP guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/EC by the Investigator and reviewed and approved by the IRB/EC before the study is initiated.
- Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
    - Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, and all other applicable local regulations

13.1.2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

13.1.3 Informed Consent Process

The Investigator agrees to provide the IEC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), IB, and any other written information provided to study participants. The trial will not begin until the Investigator have obtained the IEC favourable written approvals for the above-mentioned study documents. A properly executed written ICF shall be read, signed, and dated by each participant prior to entering the trial or prior to performing any study procedure. The original signed and dated ICF will be kept at the clinical site and a copy will be given to the participant.

In the event that the protocol is amended, the revised protocol must be approved by the IEC prior to its implementation, unless the changes involve only logistical or administrative aspects of the trial. If a revised ICF is introduced during the study, each participant's further consent must be obtained. The new version of the ICF must be approved by the IEC, prior to subsequently obtaining each participant's consent.

The Investigator and the Sponsor's representative must sign the protocol and its amendments (if any) before initiating the study.

It is the Sponsor's responsibility to submit the protocol and its amendments (if any), and the ICFs to regulatory authorities when necessary.

13.1.4 Data Protection

- Randomized participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.
- The contract between Sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

13.1.5 Committees Structure

13.1.5.1 Safety Review Committee

An SRC will be established to review safety and any available PK data and to oversee the overall conduct of the study with the primary purpose of protecting the safety of participants participating in the study. Details concerning the specific objectives, roles, responsibilities, and data review procedures of the SRC are documented in a separate SRC Charter document. The SRC will be composed of at least the Investigator, one medically qualified Sponsor representative and an independent MM.

The SRC may consult with or add members that include, but are not limited to, physician(s) scientists, biostatisticians, or other subject matter experts.

The SRC will meet as soon as is feasible, upon the occurrence of safety signals and after completion of dosing a given cohort to recommend acceptability of continued dosing, as well as escalation, de-escalation, or whether to add additional participants at the current dose level.

All data (reports) that are provided and reviewed by the SRC, including any minutes and decisions from the meetings, will be archived. The minutes will document clearly any questions posed and decisions reached and whether these decisions were unanimous.

SRC meetings will be held after safety and tolerability data up to at least 48 hours post-dose (Day 3) are available for at least 6 evaluable dosed participants from a same cohort for the SAD part, and after safety and tolerability data up to at least 24 hours post-last dose (Day 12) are available for all dosed evaluable participants from a same cohort for the MAD part. PK data up to 24 hours post-dose (post-last dose for the MAD part) will also be reviewed to evaluate if PK parameters in humans are as anticipated. The SRC will consider the data on a cohort basis, but also on the basis of cumulative information across cohorts as the study progresses.

The potential decisions of the SRC are:

- Escalate to the next planned dose level;
- Continue the study with a more conservative approach, such as decreasing to a dose-level lower than the planned next higher dose level, descending from a higher dose level to a lower dose level, repeating a dose level, or exploring an alternative dosing regimen in the MAD part (not exceeding the total daily dose planned in the protocol for that given cohort);
- Suspend dose escalation until further review of study data can be made, allowing the SRC to determine whether predefined stopping rules have been met. Dose escalation may resume once the SRC concludes that no stopping rules have been met;
- Stop dose escalation;
- Terminate the study.

The SRC will conduct a blinded review of the data; however the blind may be broken for individual participants if judged necessary, prior to making a decision on dose escalation. Dose escalation may occur only following mutual agreement between the SRC members. The SRC may recommend to modify the PK sample collection schedule based on emerging data, including shortening or lengthening the total collection interval by up to 48 hours, and may add up to two additional PK samples, if necessary. Decisions taken by the SRC will be documented and submitted to the IEC overseeing the study, if required, along with supportive data.

13.1.6 Confidentiality and Retention of Study Records

This document contains trade secrets and commercial information that is confidential and may not be disclosed to third parties. Persons to whom this study protocol is disclosed must be informed that all the information herein is confidential and may not be further divulged. These restrictions will apply as well to all future communications if deemed privileged or confidential. Publication of the study results may only be allowed with written permission from the Sponsor.

All information on a participant obtained during the conduct of the study will be kept confidential. Participants will be identified by an anonymized identifier on all samples and study records provided to the Sponsor or designee. In compliance with ICH GCP, the Sponsor's authorized representatives, monitor(s), auditor(s), IEC, and regulatory authority(ies) will be granted direct access to the participant's original trial-related records for verification of clinical trial procedures and/or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations. Consent from the participant for disclosure of such information will be obtained in writing in the ICF. In addition, should a participant require medical care or hospitalization during the course of the study, the clinical site may contact the treating physician with the participant's consent, except that consent may not be requested if there is an emergency situation. If the results of the study are published, the participant's identity will remain confidential.

The clinical sites will maintain adequate study records according to applicable regulatory requirements. The Sponsor will be notified prior to the destruction of study records.

13.1.7 Compliance

This study will be conducted in compliance with the protocol, GCP, all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), and any IEC requirements relative to clinical studies. The study will also be conducted in compliance with the recommendations laid down in the most recent version of the Declaration of Helsinki, with the exception that registration of such Phase 1 trials in a publicly accessible database is not mandatory. As required by the Canadian regulatory agency, a Clinical Trial Application (CTA) will be submitted before the beginning of the study and a No Objection Letter (NOL) must be received prior to dosing.

13.1.8 Data Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data. When applicable, quality assurance procedures will be performed according to the site SOPs.

The study will be monitored according to the site monitoring plan and SOP to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements. The Sponsor is entitled to access information about the status of the study and to review the original documents of the study.

The Sponsor may arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, SOPs, GCP, and all applicable regulatory requirements. In such case, audits will be independent of and separate from the routine monitoring and quality control functions.

- All participant data relating to the study will be recorded on electronic CRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Completion Guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the study monitoring plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

13.1.9 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

13.1.10 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the first participant signs informed consent.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study treatment development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the ECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should ensure appropriate participant follow-up.

13.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the local laboratory at the time points specified in the SoAs.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 7: Protocol-required Safety Laboratory Tests

Serum or urine pregnancy:	β-human chorionic gonadotropin (β-hCG); urine pregnancy test at screening and follow-up, and serum pregnancy test on Day -1 for WOCBP; in the absence of 12 months of amenorrhea, confirmation with at least one FSH measurement (≥40 IU/L or mIU/mL or per local threshold for defining postmenopausal state is required.
Hematology:	Hematocrit, hemoglobin, platelet count, RBC count, RBC distribution width, WBC count and differential: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils
Clinical Chemistry:	Albumin, Alkaline phosphatase, ALT, AST, calcium, chloride, creatinine, creatine kinase, estimated glomerular filtration rate (eGFR, calculated using the MDRD equation), gamma-glutamyl transferase, glucose, phosphorus, potassium, sodium, total, direct and indirect bilirubin, total protein, urea (BUN).
Thyroid Panel:	TSH, FT3, FT4
Coagulation:	Prothrombin time (PT, unless not available due to local laboratory reporting standards), activated partial thromboplastin time (aPTT), and international normalized ratio (INR)
Urinalysis:	macroscopic examination, pH, specific gravity, protein, glucose, ketones, bilirubin, occult blood, nitrite, urobilinogen, and leukocytes. Unless otherwise specified, microscopic examination will be performed on abnormal findings.
Serology:	HIV antigen/antibody, HbsAg, HCV antibody, COVID-19 PCR
Urine Drug Screen:	Amphetamines, methamphetamines, methadone, barbiturates, benzodiazepines, cocaine, opiates, methyl-enedioxy methamphetamine (MDMA), methadone, phencyclidine, and tetrahydrocannabinol
Breath Test:	Alcohol
Other:	HbA1c (Only at screening)

Investigators must document their review of each laboratory safety report.

13.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

13.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after the informed consent is signed even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>not</u> Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

13.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life-threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias, convulsions not resulting in hospitalization, or development of treatment dependency or treatment abuse.

13.3.3 Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the EDC tool.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study per CTCAE v5.0 grading criteria:

- Grade 1: Mild, asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- Grade 2: Moderate, minimal, local or non-invasive treatment indicated; limiting age-appropriate instrumental activities of daily life.
- Grade 3: Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily life.
- Grade 4: Life-threatening consequences; urgent treatment indicated.
- Grade 5: Death related to AE.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- All AEs will be assigned a causality attribution as follows:
    - Related: There is a reasonable likelihood of a causal relation between study drug and the AE.

- Not related: There is reasonable certainty that the cause of the AE is another etiology such as concomitant medication, disease progressions or other medical conditions and not related to study treatment.

- For causality assessment, the Investigator will also consult the IB and/or product information for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always assesses causality for every event before the initial transmission of the SAE data.
- The Investigator may change their opinion of causality based on follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor (or designee) within 24 hours of investigator learning about the event.

13.3.4 Reporting of SAEs

Serious Adverse Event Reporting to the Sponsor

The site will enter the SAE data into the electronic system as soon as it becomes aware of the event. Any SAE will be reported to the Sponsor (or representative) within 24 hours of learning of the event, and then a written report will be completed and provided as soon as possible, but no later than 7 calendar days of first knowledge of the event. The notification must be directed to:

[redacted]

Information on SAEs will be recorded on the SAE Report Form. Blank copies are included in the study Investigator's file. It is not acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor company or its representative in lieu of completion of

the appropriate AE eCRF page or SAE Report Form. However, there may be instances when copies of medical records for certain cases are requested by the Sponsor or its representative. In this instance, all subject identifiers will be blinded on the copies of the medical records before submission to the Sponsor or its representative.

The completed SAE Form and SAE cover sheet should be sent via fax or e-mail immediately upon completion to [redacted]. If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before completing and sending the form.

Additional relevant information or clinical follow-up should be sent via fax or e-mail to [redacted] as soon as it becomes available. The Investigator should follow the subject with the event until resolution or stabilization of the condition. Follow-up reports (as many as required) should be completed and faxed/e-mailed following the same procedure above.

A final report is required once the condition is resolved or stabilized and no more information about the event is expected. The final report should be completed and faxed/e-mailed following the same procedure above.

The Investigator must keep a copy of all documentation related to the event in the clinical site files.

If the Investigator learns of any SAE, including death, at any other time after a subject completes the study, and he/she considers the event reasonably related to the study drug, the Investigator will promptly notify the Sponsor/Medical Monitor.

Serious Adverse Event Reporting to the IEC and Regulatory Agency(ies)

It is the responsibility of the clinical site to report suspected, unexpected, serious adverse reactions (SUSARs) to the IEC responsible for the study per their policies. Report of fatal or life threatening SUSARs must be made as soon as possible, but no later than 7 calendar days after first knowledge of the event. Report of SUSARs that are neither fatal nor life threatening must be made as soon as possible, but no later than 15 calendar days after first knowledge of the event.

The Sponsor (or representative) is responsible for notifying the regulatory agency(ies) of SUSARs observed during the study conduct per their regulations, as soon as possible but no later than 7 calendar days after becoming aware of the information when fatal or life-threatening, or 15 calendar days when neither fatal nor life-threatening. The Sponsor (or representative) is responsible to comply with any other applicable regulatory requirement(s) related to the reporting of SAE to other regulatory authority(ies).

13.4 Appendix 4: Contraceptive and Barrier Guidance

Males

1. Male participants, who agree to remain abstinent (when this is in line with the preferred and usual lifestyle of the participants) for the duration of the study (from first study treatment administration until 90 days following the last dose):

   CONTRACEPTION REQUIRED: Abstinence (sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant).

   If the situation changes post-dose during the study, participants must use an acceptable method of contraception (see Section 13.4).

2. Male participants, who anticipate being sexually active during the study period (from first study treatment administration until 90 days following the last dose) with a woman who is either a woman of childbearing potential (WOCBP), a woman who is pregnant and/or breast feeding:

   CONTRACEPTION REQUIRED (see Section 13.4): From the first day of dosing until 90 days following the last dose. Documentation can be obtained from the site personnel's review of the participant's medical records or verbal confirmation at medical history interview. Acceptable methods are:

   - Surgical sterilisation (vasectomy with documentation of azoospermia) and a barrier method (condom).
   - The participant's female partner uses oral contraceptives (combined hormonal contraception), injectable progesterone, or subdermal implants and a barrier method (condom).
   - The participant's female partner uses medically prescribed topically-applied transdermal contraceptive patch and a barrier method (condom).
   - The participant's female partner has undergone documented tubal ligation (female sterilisation). In addition, a barrier method (condom) must be used.
   - The participant's female partner has undergone documented placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS) and the use of a barrier method (condom).

   Male participants must use a condom when engaged in intercourse and should not donate sperm during the study and for 90 days after the last dose of study drug.

Females

3. Female participants of non-childbearing potential: Defined as either postmenopausal (must have had ≥12 months of spontaneous amenorrhea with FSH ≥40 mIU/mL), or surgical sterilization (evidence of hysterectomy and/or bilateral oophorectomy).

   CONTRACEPTION REQUIRED: None.

4. Female participants of childbearing potential (WOCBP) who anticipate being sexually active with a male during the study (from one complete menstrual cycle and at least 30 days prior to the first study drug administration until at least 90 days following the final study drug administration):

   CONTRACEPTION REQUIRED: Highly effective double-barrier contraception must be used from screening (with at least 1 method that must have been started one complete menstrual cycle and at least 30 days prior to the first day of dosing) and continue until at least 90 days following the final study drug administration. A condom is required along with another form of highly effective contraception from the day of screening until at least 90 days following the final drug administration. Documentation can be obtained from the site personnel's review of the participant's medical records or verbal confirmation at medical history interview. Highly effective contraception methods for WOCBP include:

   - Progestogen-only hormonal contraception associated with inhibition of ovulation
     - oral
     - injectable
     - implantable
   - Combined hormonal contraception (ie, estrogen- and progestogen-containing)
   - IUS
   - IUD
   - Bilateral tubal occlusion
   - Infertile male partner (eg, vasectomized, permanently sterile following bilateral orchidectomy, or any other documented cause of infertility)

5. Female participants of childbearing potential (WOCBP) who agree to remain abstinent (when this is in line with the preferred and usual lifestyle of the participant) is acceptable from 6 months prior to the first IMP administration until at least 90 days following the final study drug administration):

   CONTRACEPTION REQUIRED: Abstinence (sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse, when this is in line with the preferred and usual lifestyle of the subject, for at least 6 months before screening and until at least 90 days following the last study drug administration). The

reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Calendar, symptothermal and postovulation methods of contraception are not considered to be equivalent to abstinence).

No contraceptive methods are required for participants with same-sex partners.

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