CLINICAL TRIAL PROTOCOL

THE EFFECT OF FOOD ON THE ORAL BIOAVAILABILITY OF AEF0117 IN HEALTHY VOLUNTEERS

Sponsor:	**Aelis Farma** **Neurocentre Magendie** **146, Rue Léo Saignat** **33 077 Bordeaux, France**
Protocol number:	**AEF0117-105 including amendment 01 dated 01-Dec-2022 and amendment 02 dated 03-Feb-2023**
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

$\%AUC_{extrap}$	percentage of $AUC_{0-\infty}$ due to extrapolation from T_{last} to infinity
AE	adverse event
AEF0117	3ß-(4-methoxybenzyloxy)pregn-5-en-20-one
Aelis	Aelis Farma
AUC	area under the curve
AUC_{0-24}	area under the plasma concentration-time curve from time zero (pre-dose) to 24 hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero (pre-dose) to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time 0 (pre-dose) to the last quantifiable concentration time point, calculated using the linear trapezoid rule
BMI	body mass index
BP	blood pressure
CB1	cannabinoid type 1 receptor
CB1-SSi	signaling specific inhibitor of CB1
CFR	Code of Federal Regulations
CI	confidence interval
C_{last}	last measurable plasma concentration
CL/F	apparent oral clearance
C_{max}	maximum plasma concentration
$C_{min,24h}$	minimum observed (or trough) plasma concentration within 24 hours after dosing
COVID-19	coronavirus disease 2019
CPK	creatine phosphate kinase
C-SSRS	Columbia-Suicide Severity Rating Scale
CTR	clinical trial report
CV	coefficient of variation
ECG	Electrocardiogram
eCRF	electronic case report form
FDA	US Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	investigational medicinal product

IND	investigational new drug
IRB/EC	institutional review board/ethics committee
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram(s)
mL	Milliliter
PCS	potentially clinically significant
PK	pharmacokinetic(s)
PT	preferred term
PV	Pharmacovigilance
QRS	ventricular depolarization on the ECG
QT	QT interval on the ECG
QTc	QT interval corrected
QTcF	corrected QT interval, using Fridericia's formula
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
THC	Δ^9-tetrahydrocannabinol
$T_{½}$	terminal elimination half-life
T_{lag}	the delay in achieving T_{max}
T_{last}	time to last measurable plasma concentration
T_{max}	time to maximum plasma concentration
US	United States (of America)
Vd/F	apparent volume of distribution

SPONSOR SIGNATURE

This clinical trial protocol is approved by:

Date	Signature
	Name: Lasse Steen Ravn, MD
	Title: Head of Clinical Operations
	Institution: Aelis Farma

INVESTIGATOR STATEMENT

I have read and understand the protocol and agree to implement the trial in accordance with the procedures set forth in the protocol and in accordance with the sponsor's guidelines, all applicable government regulations, and the International Council for Harmonisation Good Clinical Practice Guidelines (ICH GCP E6).

I will maintain accurate source documents from which data are transcribed onto case report forms and accurate drug accountability records that show the receipt and disposition of all trial drugs.

I will provide adequate protocol training to my associates, colleagues, and employees assisting in the conduct of the trial.

I will obtain institutional review board/ethics committee (IRB/EC) approval of the protocol and informed consent form (ICF) prior to enrollment of participants in the trial. I understand that any modifications to the protocol made during the trial must first be approved by the IRB/EC prior to implementation, except when such modification is made to remove an immediate hazard to the participant.

I will ensure that a fully executed IRB-approved ICF is obtained from each participant prior to initiation of any trial procedures.

I will report (within 24 hours) any serious adverse event (SAE), regardless of relationship to trial drug, or pregnancy that occurs during the trial, in accordance with the procedures described in section 7.3 of the protocol. I will notify the sponsor if I become aware that a partner of a trial participant becomes pregnant while the participant was receiving this trial drug.

I will allow the sponsor, Aelis Farma (Aelis) and its agents, as well as the United States (US) Food and Drug Administration (FDA) and other regulatory agencies to inspect trial facilities and pertinent records at reasonable times and in a reasonable manner, ensuring participant confidentiality. If I am notified that this trial is to be inspected by a regulatory agency, I will notify the sponsor as soon as possible thereafter (no later than one week).

I am aware that this protocol contains information that is proprietary to Aelis. The information contained herein is provided for the purpose of conducting a clinical trial for Aelis.

I am aware that the contents of this protocol may be disclosed to trial personnel under my supervision and to the IRB/EC with authority for our site. I am aware that the contents of this protocol may not be disclosed to any other parties (unless such disclosure is required by government regulations or laws) without the prior written approval of Aelis.

Date	Signature
	Name: Margaret Haney, Ph.D.
	Title: Professor of Neurobiology (in Psychiatry)
	Institution: Columbia University Irving Medical Center

1 PROTOCOL SUMMARY

1.1 Protocol synopsis

Trial title	The effect of food on the oral bioavailability of AEF0117 in healthy volunteers.
Signatory investigator	Margaret Haney, PhD
Trial site	New York State Psychiatric Institute (NYSPI), Columbia University
Clinical phase	1
Objectives	Primary objective • To determine the bioavailability of orally administered AEF0117 after fed conditions relative to fasting conditions in healthy volunteers. Secondary objectives • To evaluate other pharmacokinetic (PK) parameters of AEF0117 in healthy volunteers. • To evaluate safety and tolerability of a single dose of 1 mg AEF0117 in healthy volunteers. Exploratory objective • To characterize potential metabolites regarding plasma PK.
Trial design	This is a single center, randomized, parallel-group, 2-arm, open-label, single-dose trial in healthy male and female volunteers aged 18–55 years, both inclusive. The total trial duration for an individual participant will be up to 6 weeks (42 days) from screening (up to 28 days prior to dosing) to the final follow-up visit (14 days after dosing). After screening, the trial includes 2 days where the participants are confined at the research facility, and thereafter 7 visits to the site (6 visits and a follow-up visit). Participants will stay in the research facility from the afternoon prior to dosing on Day 1 and until collection of the blood sample 24 hours after dosing (i.e., Day 2) and then be discharged. Participants will be asked to return to the research facility for collection of blood samples each morning on Days 3, 4, 5, 7, 9, and 11, and at the follow-up visit on Day 14. On Day 1, eligible participants will be randomized and receive a single dose of 1 mg AEF0117 in fed or fasting condition, and serial blood samples will be collected up to 312 hours after dose administration.
Number of participants	A total of 32 participants will be randomized 1:1, stratified by sex, into 2 groups. One group of 16 participants will be dosed after fasting for 10 hours, while the other group of 16 participants will be dosed 30 minutes after start of consumption of a standardized high fat breakfast (US Food and Drug Administration [FDA] breakfast).
Inclusion criteria	To be eligible for participation in this trial, the individual participant must meet all the following criteria at screening and/or on admission at Day -1: 1. Healthy, non-smoking male or female of any race, 18 to 55 years old, both inclusive.

	2. Both males and female participants must use highly effective contraception during the entire trial period. Male participants should refrain from donating sperm or planning a pregnancy throughout the trial. Heterosexually active male participants must agree to use double-barrier contraceptive methods: male condoms and spermicide. Heterosexually active females are only eligible if they are documented to be surgically sterile (e.g., hysterectomy, tubal ligation) or post-menopausal (amenorrhea >1 year and follicle-stimulating hormone [FSH] >25.8 mIU/mL) and with a negative pregnancy test. 3. A body mass index (BMI) of 22.0 to <35.0 kg/m^2. 4. Be informed of the nature of the trial and provide signed informed consent to participate in the trial prior to any trial-specific procedures. 5. After being shown the high fat meal, understands and accepts that the entire meal should be consumed within 30 minutes. 6. Be legally competent and able to communicate effectively (in English) with trial personnel.
Exclusion criteria	To be eligible for participation in this trial, participants must not meet any of the following criteria at screening and/or on admission at Day -1: 1. Tobacco cigarette smokers within the last 3 months prior to dosing with trial drug. 2. Any disease or condition that might compromise the cardiovascular, hematologic, renal, hepatic, pulmonary (including chronic asthma), endocrine (e.g., diabetes), central nervous, or gastrointestinal (including an ulcer and cholecystectomy) systems, or any clinical laboratory values assessed as potentially clinically significant by the investigator[1]. 3. Blood pressure outside normal range (140/80 mmHg systolic/diastolic) and considered potentially clinically significant. 4. Congenital long QT syndrome. 5. A corrected QT interval (Fridericia's – QTcF) >450 msec (male) or >470 msec (female). 6. A history of alcoholism or drug addiction within the past 2 years, recent use (in the last month) of any illicit drugs, or positive results from a urine screen for substances of abuse or from an alcohol breath test. 7. A history of or current serious mental illness including active or recent suicidal ideation, severe psychological distress (e.g., active suicidal plans, psychosis, debilitating panic disorder) and/or an abnormal Columbia-Suicide Severity Rating Scale (C-SSRS) result. 8. Severe learning disability, brain damage, or pervasive developmental disorder. 9. A history of difficulty donating blood or inadequate venous access.

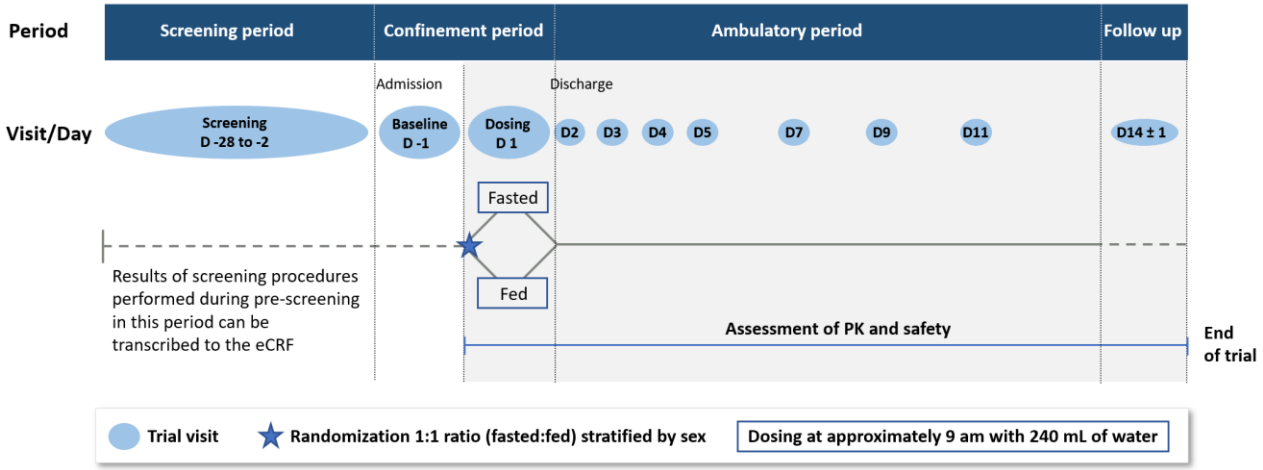
[1] Screening laboratory samples must be collected between Day -28 and -2 and evaluated at the latest on Day -1. Eligibility for randomization is based on the screening results unless abnormal results from the baseline samples collected at Day -1 are available prior to randomization on Day 1.

	10. Clinically significant anemia or low hemoglobin levels (<11.5 g/dL for women and <13 g/dL for men) at screening, donation of >250 mL of blood or plasma or received any blood and plasma for medical/surgical reasons within the 30 days prior to prior to receiving trial drug, or intention to donate blood or plasma within 1 month after receiving trial drug. 11. History of or current HIV or hepatitis B or C. 12. History of COVID-19 within 4 weeks prior to Day -1, or positive COVID-19 test, according to standard procedures at the site, at screening or Day -1. 13. Positive serum pregnancy test (ß-hCG) at screening or positive urine pregnancy test at Day -1 confirmed by a serum pregnancy test result. 14. Allergies to the trial drug and known allergies to pregnenolone or to corn and corn derivatives. 15. Use of any prescription or over-the-counter drug therapy, including psychoactive and/or psychotropic medication, herbal, homeopathic, vitamins, minerals, and nutritional supplements, bodybuilding supplements unapproved by the sponsor, within 2 weeks prior to receiving the trial drug (for drugs with an elimination half-life greater than 10 days, this will be extended to 60 days). 16. Use of a drug therapy, or diet or supplements (e.g., St. John's Wort) food and fruit juices (e.g., grapefruit juice) known to induce or inhibit hepatic drug metabolism within 30 days prior to receiving trial drug or during the trial. 17. Legal status that would interfere with participation. 18. Unable to follow the restrictions outlined in the protocol. 19. Ingestion of an investigational drug or product, or participation in a drug trial within a period of 90 days prior to receiving trial drug.
Investigational medicinal product	The trial drug is AEF0117 (3ß-(4-methoxybenzyloxy)pregn-5-en-20-one). Oral AEF0117 1 mg capsules will be supplied by Aelis Farma. Capsules are 10.oval soft gelatin capsules of 0.5 mL.
Duration of treatment	The participants will receive a single dose of 1 mg AEF0117 orally in the morning of Day 1.
Endpoints	<u>Primary endpoint</u> • Bioavailability of AEF0117 after fed conditions relative to fasting conditions. PK parameters C_{max}, T_{max}, T_{lag}, AUC_{0-t}, $AUC_{0-\infty}$ determined based on plasma concentration in serial blood sample collections up to 312 hours after dosing. <u>Secondary PK endpoints</u> • PK parameters $\%AUC_{extrap}$, $C_{min,24h}$, $t_{½}$, CL/F, and Vd/F determined based on plasma concentration in serial blood sample collections up to 312 hours after dosing. <u>Secondary safety endpoints</u> • Vital signs (blood pressure [BP], heart rate [HR]) and electrocardiogram (ECG). • Adverse events (AEs).

	Exploratory endpoints (will be reported separately) • Identification of metabolites, to the extent feasible, and PK of potential metabolites of AEF0117 in plasma. To the extent concentration in plasma allows, the following PK parameters will be estimated: C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $C_{min,24h}$, and C_{last}.
Trial procedures/ assessments	Screening for this trial should be performed between Day -28 and Day -2. If some of the screening procedures have been completed as part of a general pre-screening procedure at the research facility within this period, those results can be transcribed to the electronic case report form (eCRF) for this trial, provided source documentation is available. Eligible participants will be admitted to the research facility during the afternoon on Day -1. Upon admission, it will be verified that the participants are still eligible according to the inclusion and exclusion criteria, and baseline assessments will be performed. After an overnight stay in the research facility, volunteers will be randomized and dosed in the morning at approximately 9 am with a single oral dose of 1 mg AEF0117 with approximately 240 mL of room temperature water. 16 participants will be dosed after fasting for 10 hours, and 16 participants will be dosed 30 minutes after start of a standardized high fat breakfast, in which 50% of the calories are derived from fat (FDA breakfast). The participants will be divided into smaller cohorts of minimum 2 participants for operational reasons (adjusted to capacity of the research facility) and each cohort will include 1 fasting participant and 1 participant receiving breakfast prior to dosing. Water is not allowed from 1 hour prior to dosing until 2 hours after dosing but is allowed ad libitum thereafter. Food and fluids other than water is not allowed for 4 hours post dose. A standardized lunch and dinner will be served for both groups approximately 4 hours after and 10 hours after the dose, respectively. Snacks will be available and allowed from 4 hours after the dose. Blood samples (6 mL/sample) for determination of AEF0117 in plasma will be collected at the following timepoints during the confinement period: at pre-dose, and 1, 1.5, 2, 3, 4, 5, 6, 8, 11, 14, and 24 hours post dose, and after discharge at visits to the site on Day 3 (48 hours), Day 4 (72 hours), Day 5 (96 hours), Day 7 (144 hours), Day 9 (192 hours), Day 11 (240 hours), and Day 14 (312 hours) after dosing. An additional blood sample (6 mL/sample) will be collected for identification and exploratory analysis of potential metabolites of AEF0117 at the following timepoints during the confinement period: at pre-dose, and 2, 4, 6, 8, 11, and 24 hours post dose, and after discharge at visits to the site on Day 4 (72 hours) and Day 7 (144 hours). The exact timepoints of all samples will be recorded. During the confinement period, an adverse event (AE) assessment by querying with non-leading questions and observation will be performed at the same time as the PK sample collection, i.e., at pre-dose, and at 1, 1.5, 2, 3, 4, 5, 6, 8, 11, 14, and 24 hours after dosing. ECG and vital signs (BP and HR) will be measured at pre-dose and at 1, 2, 4, 8, 11, and 24 hours after dosing. After discharge, AEs will be assessed at each visit, and vital signs (BP and HR) and ECG will be measured on Day 11. At the follow-up visit on Day 14, final safety assessments will be performed including safety blood samples, urinalysis, urine pregnancy test (females only), vital signs, ECG, weight, and a brief physical examination.

Statistical methods	Power calculation The sample size has been chosen based on previous experience in phase 1 studies with AEF0117 where the coefficient of variation (CV) was in the order of 0.3 for C_{max} and AUC after single doses. It is anticipated that food slightly increases the absorption of AEF0117 and a true ratio of 1.25 is assumed. To allow for potential participants who dropout early, i.e., not allowing for estimation of C_{max} and/or AUC_{0-t}, 32 participants should be included. The power for showing that the upper bound of the 2-sided 90% confidence interval (CI) is ≤1.75 is 90% with 14 participants per treatment group and 86% with 12 participants per group. Primary endpoint The primary analysis will be based on a comparison of the ratio between fed and fasting condition for the following parameters: the mean C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of each group. Descriptive statistics will be applied to T_{max} and T_{lag}. PK analysis will consist of a non-compartmental evaluation of AEF0117 plasma concentration-time profiles to determinate PK parameters using a validated program. PK parameters will be tabulated and summarized using descriptive statistics (mean, median, standard deviation (SD), geometric mean, CV%, minimum, and maximum). The relative bioavailability will be estimated by calculating the ratio of the geometric means between fed and fasted conditions, based on log-transformed data, for AUC_{0-t}, $AUC_{0-\infty}$ (when appropriate) and C_{max}. The 90% CI will be provided. The clinical relevance of any differences between fed and fasted conditions will be discussed, especially with respect to an assessment of the CI in relation to the limits. An analysis of variance model will be applied, with sequence, period, and state (fed, fasting) as factors. Secondary endpoints Additional PK parameters of AEF0117, including $C_{min,24h}$, $t_{½}$, $\%AUC_{extrap}$, CL/F, and Vd/F will be calculated using non-compartmental methods and summarized by graphic displays and descriptive statistics as data permit. Individual and summary (means ± SD for each condition i.e., fed/fasting) plasma AEF0117 concentration-time plots will be displayed graphically. Safety analyses Descriptive statistics and mean change from baseline to each post-baseline value will be provided for clinical laboratory tests, vital signs (BP, HR, and oral temperature), and ECG parameters (HR, PR interval, QRS duration, QT, and QTcF). AEs will be tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) and summarized based on severity (mild, moderate, severe) and causality (related or not related). Explorative analysis If the data allow, a PK analysis will consist of a non-compartmental evaluation of the metabolite plasma concentration-time profiles to determine PK parameters using a validated program. PK parameters will be tabulated and plots of plasma concentration as a function of time provided for the 2 conditions (fed/fasting). The results of the explorative measures will be reported separately.
The trial will be conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice (ICH GCP).	

1.2 Trial design diagram



1.3 Schedule of activities

Period	Screening[1]	Confinement period												Ambulatory period						Follow up/ET	Notes
Day	D -28 to -2	D -1	D1										D2	D3	D4	D5	D7	D9	D11	D14 ±1 day	[1] Results of procedures performed during pre-screening in this period can be transcribed to the eCRF
Hours after dosing		Baseline	0	1	1.5	2	3	4	5	6	8	11	14	24	48 ±2h	72 ±2h	96 ±2h	144 ±3h	192 ±3h	240 ±3h	312 ± 24h	
Screening and baseline assessments																					
Trial informed consent	X																				Prior to any trial-specific procedures
Inclusion/exclusion criteria	X	X[2]																			[2] Recheck inclusion/ exclusion criteria
Demographics	X																				
Medical history/ intercurrent disease	X	X																			
Complete physical examination	X																				Section 7.4.3
Height	X																				Section 7.1.2
Calculation of BMI	X	X																			
Weight	X	X	X[3]											X[3]							X	[3] Pre-breakfast weight at Day 1 and Day 2
Medication																					
Prior and concomitant medications assessment	X[4]	X[4]	X	X										X	X	X	X	X	X	X	X	[4] Previous medications within 30 days prior to D 1 Section 6.7.1
Randomization			X																		Pre-dose
Trial drug administration			X																		In fasted or fed condition acc. to randomization. Fed condition: dosing 30 minutes after start of meal

Period	**Screening**[1]	**Confinement period**												**Ambulatory period**						**Follow up/ET**	**Notes**
Day	**D -28 to -2**	**D -1**	**D1**										**D2**	**D3**	**D4**	**D5**	**D7**	**D9**	**D11**	**D14 ±1 day**	[1] Results of procedures performed during pre-screening in this period can be transcribed to the eCRF
Hours after dosing		**Baseline**	**0**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**11**	**14**	**24**	**48 ±2h**	**72 ±2h**	**96 ±2h**	**144 ±3h**	**192 ±3h**	**240 ±3h**	**312 ± 24h**	
Safety assessments																					
Adverse event monitoring and assessment	X	X	←										→	X	X	X	X	X	X	X	X	From signing informed consent for trial participation Section 7.3
Brief physical examination		X												X							X	Section 7.4.3
Blood pressure, heart rate	X	X	X	X		X		X			X	X		X							X	Vital signs in supine position after 5 minutes rest and prior to blood sampling
Oral temperature	X	X												X							X	
12-lead ECG	X	X	X	X		X		X			X	X		X							X	ECG in supine position after 5 minutes rest and prior to blood sampling Section 7.4.4
C-SSRS	X[5]	X[5]												X[6]							X[6]	[5] Baseline/Screening version [6] Since Last Visit version
Laboratory samples (safety, PK)																					
Fasting blood sample for serum chemistry, hematology, coagulation profile	X	X												X							X	No food or drink other than water for 6 hours prior to collection List of safety blood and urine parameters in Appendix 2
Urinalysis	X	X												X							X	
Urine drug screen	X	X												2–3 times randomly distributed								
Pregnancy test (females only)	X	X																			X	Serum test at Screening, urine test at D -1 and D14
COVID-19 test	X	X																				According to the site's standard procedures Additional tests may be performed during the trial

Period	**Screening**[1]	**Confinement period**												**Ambulatory period**						**Follow up/ET**	**Notes**
Day	**D -28 to -2**	**D -1**	**D1**										**D2**	**D3**	**D4**	**D5**	**D7**	**D9**	**D11**	**D14 ±1 day**	[1] Results of procedures performed during pre-screening in this period can be transcribed to the eCRF
Hours after dosing		**Baseline**	**0**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**11**	**14**	**24**	**48 ±2h**	**72 ±2h**	**96 ±2h**	**144 ±3h**	**192 ±3h**	**240 ±3h**	**312 ± 24h**	
Questioning for COVID-19 symptoms		X	X																			
Alcohol breath test	X	X													2–3 times randomly distributed							
Blood samples for determination of plasma AEF0117 [7]			X[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	The exact timepoint of all samples must be recorded [7] Details on processing in Appendix 3 [8] Pre-dose sample, within 60 minutes prior to dosing
Blood samples for determination of potential plasma metabolites [7]			X[8]			X		X		X	X	X		X		X		X				
Administrative procedures																						
Admission to research facility for confinement		X																				
Discharge from confinement at research facility														X								
Ambulatory visit to research facility	X														X	X	X	X	X	X	X	

BMI, body mass index; COVID-19, coronavirus disease 2019; C-SSRS, Columbia-Suicide Severity Rating Scale; D, day; ECG, electrocardiogram; eCRF, electronic case report form; ET, early termination; h, hours; PK, pharmacokinetic(s).

2 INTRODUCTION

2.1 Background

Cannabis is the most widely used illicit drug with approximately 28 million individuals reporting past-month use [1], and 14% of those receiving substance use disorder treatment in the US reporting cannabis as their primary drug of abuse [2]. While psychotherapeutic approaches have some utility for treating Cannabis Use Disorder (CUD) [3, 4, 5, 6], the vast majority of patients have difficulty significantly reducing their use or achieving abstinence. Safe and effective medications to treat CUD are urgently needed [7, 8]. The overall goal of this clinical trial is to contribute to advancing a safe and effective pharmacotherapy for CUD along the FDA approval pipeline.

When the CB1 receptors are over-activated by very high doses of THC, quite higher than the doses of THC used by cannabis abusers, the concentration of the steroid hormone pregnenolone increases in the brain. Pregnenolone then binds to a specific site on the CB1 receptors, distinct for the one of CB1 agonists and THC, and acts as an endogenous signaling specific inhibitor of the CB1 receptors. However, pregnenolone does not modify the binding of CB1 agonists to the CB1 receptor. Despite this restricted molecular action, when pregnenolone is administered prior to the exposure to THC, it inhibits most of the THC-mediated behavioral effects in rodents and THC self-administration in non-human primates. Pregnenolone cannot be used as a pharmacological treatment because it is poorly bioavailable, has a very short half-life and is converted downstream to active steroids. Aelis Farma, in collaboration with researchers from the Institut National de la Santé et de la Recherche Médicale (INSERM), has developed a new pharmacological class, the synthetic signaling specific inhibitor of the CB1 receptor (sCB1-SSi), by modifying pregnenolone's chemical structure to prevent conversion to active steroids, and to increase absorption and biological stability while maintaining THC antagonism.

To date, 3 clinical studies have been completed with AEF0117 including 2 phase 1 studies in healthy volunteers (AEF0117-101 single ascending dose study and AEF0117-102, multiple ascending dose study), and a phase 2a trial in cannabis users (AEF0117-201). The phase 1 studies showed good safety and tolerability of AEF0117 in the dose range tested (0.2 mg as single dose and 0.6–6 mg/day as single and multiple doses) and the phase 2a trial found that the 1 mg/day dose of AEF0117 significantly reduced both the abuse-related subjective effects of cannabis and its self-administration, while the 0.06 mg dose did not. Importantly, AEF0117 was well tolerated in daily cannabis smokers, with no evidence of precipitated withdrawal, physical, or psychological discomfort. There were no SAEs and a limited number of TEAEs. These results confirm preclinical data showing that AEF0117 does not function as an orthosteric antagonist and does not produce any of the adverse effects associated with rimonabant. Thus, AEF0117 is to our knowledge the first medication to safely and robustly attenuate the positive subjective and reinforcing effects of cannabis in participants with CUD. Further details are provided in the current edition of the IB [9].

In the 3 early studies conducted with AEF0117, AEF0117 was administered orally after a light breakfast. AEF0117 showed a good bioavailability and favorable, dose-proportional PK [9]. In this protocol, the effects of food on AEF0117 bioavailability in healthy volunteers will be

investigated by comparing the rate and extent of AEF0117 when 1 mg AEF0117 is administered in fed state versus fasting state.

2.2 Trial rationale

The safety and tolerability of AE0117 has been demonstrated in the clinical studies conducted to date. This trial will provide data on the effect of food on the oral bioavailability of AEF0117 to support the next stage of the clinical development of the drug.

2.3 Risk-benefit assessment

2.3.1 Known and expected potential risks

This protocol represents an early trial of AEF0117 that will be conducted in parallel with an ongoing phase 2b trial; therefore, the long-term risks and benefits in humans are unknown. Safety data from preclinical studies with AEF0117 do not give rise to safety concerns, details can be found in the investigator's brochure [9].

In phase 1 single and multiple ascending dose studies in healthy volunteers, doses in the range of 0.2 to 6 mg were investigated. In total, 18 volunteers received doses of 0.6, 2, or 6 mg once daily for 7 days, and 30 volunteers received single doses of 0.2, 0.6, 2, or 6 mg. There were no SAEs reported in the 2 studies. AEF0117 was considered safe and with a limited number of mild TEAEs (except 2 TEAEs which were moderate) not related to the dose of AEF0117. There were only 2 noticeable TEAEs in 2 different participants. One participant in AEF0117-101 who received the single administration of 2 mg of AEF0117 showed an increase in creatine phosphate kinase (CPK) and myoglobin. One participant in AEF0117-102 developed a skin rash 30 minutes after the first administration of 0.6 mg of AEF0117 and was withdrawn from the trial.

In study AEF0117-201, 26 cannabis users, 0.06 and 1.0 mg AEF0117 was given once daily for 5 days and was also well tolerated.

Because this drug is investigational, all its side effects are not known. There may be rare and unknown side effects. Some of these may be life-threatening.

AEs across the 3 clinical studies performed with AEF0117 seen in 2 or more participants were headache, dizziness, gastrointestinal symptoms (dyspepsia and nausea), thermal burn, and abnormal/increased CPK.

With almost any drug, there is the possibility of having an allergic reaction. Symptoms of an allergic reaction include:

- Swelling, especially of the face and throat
- Difficulty breathing
- Itchy skin, rash, and hives
- Watery eyes
- Runny nose

Pregnancy

This is an experimental compound with unknown risks during conception and pregnancy in humans. Both male and female participants will be asked about adequate method of contraception they are using. We will also discuss with male participants to ensure that whatever adequate method of contraception males are using, their female partners are also using an adequate method of contraception.

Inpatient research designs

There are minor risks of isolation, boredom, and inactivity associated with living in the research facility. In participants tested at the site to date under similar conditions, such problems have been minimal.

Blood drawing

During the screening assessments, venous blood sample will be collected for medical evaluation, and blood samples will be collected for PK assessments. Blood drawing may cause lightheadedness, fainting, bleeding, pain, redness, bruising, blood clots, which may cause inflammation, swelling, irritation or infection at the site of the IV tube or needle site. There may also be some discomfort during the insertion of the IV tube into the arm.

COVID-19

Participants will be asked to exercise caution when traveling in public and follow public health guidelines, such as wearing masks in public and avoiding crowds and to stay informed about public health recommendations and guidelines regarding COVID-19, such as those issued by the Centers for Disease Control (CDC.gov) and local government guidelines and directives.

2.3.2 Known and expected potential benefits

The participants in this trial are not expected to get any immediate benefit of their participation. However, they will contribute to the process of developing a potential new therapy in an area of high unmet need.

2.3.3 Safety management plan / mitigation of risks

In this trial, participants will be closely monitored through AE monitoring, clinical safety laboratory tests, vital signs, 12-lead ECGs, and physical examination assessments according to the schedule of procedures detailed in section 1.3.

After dosing, participants will be monitored closely for AEs until discharge from the clinic, and regular vital signs measurement and ECG recording will be performed. On Day 2 before discharge, safety laboratory tests, brief physical examination, vital signs, and ECG will be performed.

Suicidality will be assessed by use of the C-SSRS before dosing and at discharge.

In emergency situations, the investigator should contact the sponsor's medical monitor, indicated below:

Trial Medical Monitor
Lasse Steen Ravn, MD, PhD
Aelis Farma
Cell: +45 42 80 87 09
Email: l.steenravn@aelisfarma.com

2.3.4 Overall risk-benefit conclusion

Considering the measures taken to minimize risk to participants participating in this trial, the limited potential risks in association with AEF0117 dosing and the trial design are justified by the anticipated benefits of a potential new therapy to treat CUD.

3 TRIAL OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary objective	**Primary endpoints**
To determine the bioavailability of orally administered AEF0117 after fed conditions relative to fasting conditions in healthy volunteers.	Bioavailability of AEF0117 after fed conditions relative to fasting conditions. PK parameters C_{max}, T_{max}, T_{lag}, AUC_{0-t}, $AUC_{0-\infty}$ determined based on plasma concentration in serial blood sample collections up to 312 hours after dosing.
Secondary objectives	**Secondary endpoints**
To evaluate other PK parameters of AEF0117 in healthy volunteers.	PK parameters $\%AUC_{extrap}$, $C_{min,24h}$, $t_{½}$, CL/F, and Vd/F determined based on plasma concentration in serial blood sample collections up to 312 hours after dosing.
To evaluate safety and tolerability of a single dose of 1 mg AEF0117 in healthy volunteers.	Vital signs (BP, HR) and ECG. AEs.
Exploratory objective	**Exploratory endpoints[1]**
To characterize potential metabolites regarding plasma PK.	Identification of metabolites, to the extent feasible, and PK of potential metabolites of AEF0117 in plasma. To the extent concentration in plasma allows, the following PK parameters will be estimated: C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $C_{min,24h}$, and C_{last}.

[1] Exploratory endpoints will be reported separately.

4 TRIAL DESIGN

4.1 Overview

This is a single center, randomized, parallel-group, 2-arm, open-label, single-dose trial in healthy male and female volunteers aged 18–55 years to obtain data on the effect of food on the oral bioavailability of AEF0117.

A total of 32 healthy volunteers are planned to be enrolled. Participants will be randomized in a 1:1 ratio to receive 1 dose of AEF0117 1 mg in fasted condition (16 participants) or fed condition (16 participants). The participants will be divided into smaller cohorts of minimum 2 participants for operational reasons (adjusted to capacity of the research facility) and each cohort will include 1 fasting participant and 1 participant receiving breakfast prior to dosing.

The total trial duration for an individual participant will be up to 6 weeks (42 days) from screening (up to 28 days prior to dosing) to the final follow-up visit (14 days after dosing).

After screening, the trial includes 2 days where the participants are confined at the research facility, and thereafter 7 visits to the site (6 visits and a follow-up visit). Participants will stay in the research facility from the afternoon prior to dosing on Day 1 and until after collection of the blood sample 24 hours after dosing (i.e., Day 2) and then be discharged.

Participants will be admitted to the research facility during the afternoon on Day -1 where it will be verified that the participants are still eligible according to the inclusion and exclusion criteria,

and the baseline assessments will be performed. After an overnight stay in the research facility, participants will be randomized to fasted or fed state and dosed with a single oral dose of 1 mg AEF0117.

Blood samples for determination of AEF0117 and potential metabolites of AEF0117 in plasma will be collected before dosing and repeatedly for up to 2 weeks after dosing.

Safety will be monitored throughout the trial by assessment of AEs, suicidal risk, clinical safety laboratory parameters, pregnancy tests (females only), vital signs, ECGs, and physical examinations.

The schedule of activities summarizing all procedures is provided in section 1.3, and a description of procedures by visit is provided in section 8.1.

4.2 Scientific rationale for the trial design

4.2.1 Justification for design and parameters

This trial will examine the effects of food on AEF0117 bioavailability in healthy volunteers. Standard PK parameters will be calculated, and a high fat meal will be served according to current guidance [10].

A parallel-group design has been chosen since detectable plasma concentration has been observed 2 weeks after discontinuation of multiple dosing of 1 mg/day due to the long elimination half-life of AEF0117 in humans. A crossover design would have required a long washout period with a potential risk of a high dropout rate.

As AEF0117 is a lipophilic compound it is anticipated that intake of a high fat meal will introduce a slight food effect i.e., increase the bioavailability, and the trial has been powered for such an effect. A total of 32 participants will be randomized 1:1 to fed or fasted conditions with an aim to complete 14 in each group. In alignment with FDA guidance [10, 11], at least 12 participants will complete the 72-hour PK sample in each group.

4.2.2 Justification for dose and route

AEF0117 is formulated as a soft capsule for oral administration. In this parallel-group food-effect bioavailability trial, a single dose will be administered to each participant.

The 1 mg dose has been selected since it is considered the highest therapeutic dose and has been shown to reduce the abuse-related subjective effects of cannabis and its self-administration in a phase 2a trial. Once daily administration of 1 mg dose for 5 days in patients with CUD has shown good safety and tolerability. In healthy volunteers, multiple dosing of up to 6 mg once daily for 7 days was considered safe and well tolerated with no SAEs, and only 2 moderate and no severe TEAEs.

4.3 End of trial definition

The end of the trial is defined as the last follow-up visit for the last participant.

5 TRIAL POPULATION

5.1 Rationale for the trial population

Healthy male and female volunteers will be enrolled in this trial in accordance with current guidance for food-effect bioavailability studies [10]. The aim is that at least 30% of the participants will be female.

5.2 Planned sample size and number of trial sites

This will be a single center trial conducted in US.

A total of 32 participants are planned to be randomized to fed or fasted condition.

5.3 Participant selection criteria

5.3.1 Inclusion criteria

To be eligible for participation in this trial, the individual participant must meet all the following criteria at screening and/or on admission at Day -1:

1. Healthy, non-smoking male or female of any race, 18 to 55 years old, both inclusive.
2. Both males and female participants must use highly effective contraception during the entire trial period. Male participants should refrain from donating sperm or planning a pregnancy throughout the trial. Heterosexually active male participants must agree to use double-barrier contraceptive methods: male condoms and spermicide. Heterosexually active females are only eligible if they are documented to be surgically sterile (e.g., hysterectomy, tubal ligation) or post-menopausal (amenorrhea >1 year and FSH >25.8 mIU/mL) and with a negative pregnancy test.
3. A BMI of 22.0 to <35.0 kg/m^2.
4. Be informed of the nature of the trial and provide signed informed consent to participate in the trial prior to any trial-specific procedures.
5. After being shown the high fat meal, understands and accepts that the entire meal should be consumed within 30 minutes.
6. Be legally competent and able to communicate effectively (in English) with trial personnel.

5.3.2 Exclusion criteria

To be eligible for participation in this trial, participants must not meet any of the following criteria at screening and/or on admission at Day -1:

1. Tobacco cigarette smokers within the last 3 months prior to dosing with trial drug.
2. Any disease or condition that might compromise the cardiovascular, hematologic, renal, hepatic, pulmonary (including chronic asthma), endocrine (e.g., diabetes), central nervous, or

gastrointestinal (including an ulcer and cholecystectomy) systems, or any clinical laboratory values assessed as potentially clinically significant by the investigator[2].

3. Blood pressure outside normal range (140/80 mmHg systolic/diastolic) and considered potentially clinically significant.
4. Congenital long QT syndrome.
5. A corrected QT interval (Fridericia's – QTcF) >450 msec (male) or >470 msec (female).
6. A history of alcoholism or drug addiction within the past 2 years, recent use (in the last month) of any illicit drugs, or positive results from a urine screen for substances of abuse or from an alcohol breath test.
7. A history of or current serious mental illness including active or recent suicidal ideation, severe psychological distress (e.g., active suicidal plans, psychosis, debilitating panic disorder) and/or an abnormal C-SSRS result.
8. Severe learning disability, brain damage, or pervasive developmental disorder.
9. A history of difficulty donating blood or inadequate venous access.
10. Clinically significant anemia or low hemoglobin levels (<11.5 g/dL for women and <13 g/dL for men) at screening, donation of >250 mL of blood or plasma or received any blood or plasma for medical/surgical reasons within the 30 days prior to receiving trial drug, or intention to donate blood or plasma within 1 month after receiving trial drug.
11. History of or current HIV or hepatitis B or C.
12. History of COVID-19 within 4 weeks prior to Day -1, or positive COVID-19 test, according to standard procedures at the site, at screening or Day -1.
13. Positive serum pregnancy test (ß-hCG) at screening or positive urine pregnancy test at Day -1 confirmed by a serum pregnancy test result.
14. Allergies to the trial drug and known allergies to pregnenolone or to corn and corn derivatives.
15. Use of any prescription or over-the-counter drug therapy, including psychoactive and/or psychotropic medication, herbal, homeopathic, vitamins, minerals, and nutritional supplements, bodybuilding supplements unapproved by the sponsor, within 2 weeks prior to receiving the trial drug (for drugs with an elimination half-life greater than 10 days, this will be extended to 60 days).
16. Use of a drug therapy, or diet or supplements (e.g., St. John's Wort) food and fruit juices (e.g., grapefruit juice) known to induce or inhibit hepatic drug metabolism within 30 days prior to receiving trial drug or during the trial.
17. Legal status that would interfere with participation.
18. Unable to follow the restrictions outlined in the protocol.

[2] Screening laboratory samples must be collected between Day -28 and -2 and evaluated at the latest on Day -1. Eligibility for randomization is based on the screening results unless abnormal results from the baseline samples collected at Day -1 are available prior to randomization on Day 1.

19. Ingestion of an investigational drug or product, or participation in a drug trial within a period of 90 days prior to receiving trial drug.

5.3.3 Dosing day exclusion criteria

Participants who at the time of randomization on Day 1 (i.e., pre-dose) meet one of the following criteria must not be dosed with the trial drug and should not be randomized but will be considered screening failures:

- If, in the investigator's medical judgment, further participation would be injurious to the participant's health or well-being.
- AEs or laboratory abnormalities occurring that in the opinion of the investigator may constitute a potential risk for continued participation by the participant.
- Major protocol deviation as discussed and agreed upon between the sponsor and investigator.
- The participant withdraws consent to participate.

5.4 Premature discontinuation of participants or trial

5.4.1 Participant discontinuation

Participants will be informed that they have the right to withdraw from the trial at any time for any reason, without prejudice to their medical care. Participants who withdraw their consent prior to dosing will not receive any AEF0117. Participants who withdraw their consent after dosing will be offered all follow-up safety assessments.

The investigator also has the right to withdraw participants from the trial for any of the following reasons:

- Participant non-adherence to trial drug or protocol requirements.
- Participant unwillingness to continue in the trial.
- Medical judgment of the investigator.

If a participant is noncompliant in the opinion of the investigator, the sponsor should be consulted for instruction on handling the participant. If a participant is withdrawn from the trial, the trial monitor and the sponsor's clinical trial manager must be notified with 24 hours.

All participants must be followed for safety until the time of the follow-up evaluation or until trial drug-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Participants who are discontinued from the trial prior to completion, regardless of reason, should have the assessments planned for the follow-up visit/early termination visit (see section 8.1.6) performed at the time of discontinuation. Reasonable efforts should be made to have the participant return for an early termination visit.

The date of discontinuation and the specific reason for discontinuation, such as withdrawn due to AE, will be recorded in the eCRF. This information will be used to summarize the reasons for trial discontinuation.

Participant withdrawal of consent

If a participant withdraws his/her consent, no further data will be obtained. However, already recorded data may be used and obtained samples may be analyzed. This will be described in the ICF.

5.4.2 Treatment discontinuation

In this trial, the 2 randomized groups may be divided into smaller cohorts of minimum 2 participants that are dosed sequentially for operational reasons. Administration of trial drug to participants scheduled to be dosed should be discontinued, at least temporarily, until a thorough evaluation of safety and relationship to trial drug has been performed, for any of the following reasons:

- Trial drug-related SAE in 1 participant in a cohort, or 2 or more trial drug-related SAEs of the same character across cohorts.
- Trial drug-related severe AE in 1 participant and AEs of the same character but less severe in the other participants in a dosing cohort (or severe AEs of the same character in one third of participants across at least 3 cohorts).
- Findings that, at the discretion of the investigator and/or sponsor, indicate that trial drug administration should be discontinued.

In case of unresolved relationship to trial drug for SAEs or severe AE in 1 participant and AEs of the same character but less severe in the other participants in a cohort (or SAEs of the same character across cohorts, or severe AEs of the same character in one third of participants across at least 3 cohorts), the trial may be temporarily interrupted/further dosing postponed. Except in cases of emergency, it is recommended that the investigator consult with the sponsor medical monitor (or other representative of the sponsor) before temporarily interrupting the trial. The investigator must obtain approval from the sponsor medical monitor before restarting dosing of the next cohort.

All patients who have been dosed with AEF0117 will be encouraged to continue to attend trial center visits through the 2-week post treatment follow-up visit to have safety assessments performed as scheduled.

5.4.3 Site discontinuation

The trial site can be terminated prematurely by the sponsor if:

- The trial site deviates significantly from the protocol without prior approval from the sponsor and regulatory authorities.
- Failure of the investigator to enroll participants at an acceptable rate.
- Insufficient adherence to the protocol requirements including GCP standards and regulatory requirements.

5.4.4 Trial termination

If the investigator, the sponsor, or the sponsor's medical monitor discovers conditions arising during the trial that suggest the trial should be terminated, this can happen only after appropriate consultation between the relevant parties.

Conditions that may warrant trial termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the participants enrolled in ongoing trials.
- A decision on the part of the sponsor to suspend or discontinue development of AEF0117.
- Termination of the trial by the FDA, local health or regulatory authority, or IRB/EC.

Both the sponsor and the investigator reserve the right to terminate the trial, according to the terms specified in the trial contract.

The investigator must notify the IRB/EC in writing of the trial completion or early termination and send a copy of the notification to the sponsor or designee and retain one copy for the site trial regulatory file.

5.4.5 Lost to follow up

A participant will be considered lost to follow up if he or she fails to return for the scheduled visits and is unable to be contacted by the trial site staff.

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

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the trial.
- Before a participant is deemed lost to follow up, the investigator or designee will make every effort to regain contact with the participant. These contact attempts should be documented in the participant's trial file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the trial with a primary reason of lost to follow up.

5.4.6 Replacement of participants

Participants who discontinue prematurely due to safety reasons will not be replaced.

Replacements will take place if more than 4 participants administered trial drug under the same conditions (fasting or fed) drop out for other reasons than safety concern prior to Day 4 (i.e., the 72-hour PK sample).

5.5 Screening failures

Persons who have signed the trial-specific informed consent and who do not meet all inclusion criteria or who meet any of the exclusion criteria at screening may be rescreened once. However,

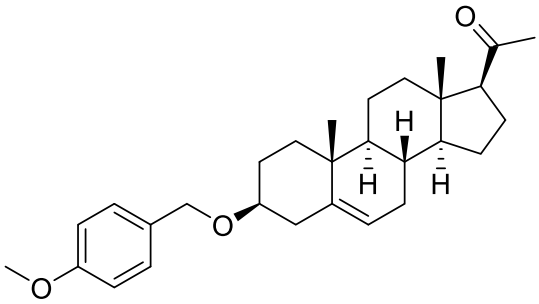
if a person has been rescreened once and still does not meet all entry criteria, the person will remain ineligible for trial participation and will be considered screening failures. Participants who meet a dosing day exclusion criterion on Day 1 prior to randomization are also considered screening failures (see section 5.3.3).

6 TRIAL INTERVENTION AND CONCOMITANT THERAPY

6.1 Trial intervention administered

AEF0117, illustrated in Figure 1 below, is a chemical entity containing 7 chiral centers 3S, 8S, 9S, 10R, 13S, 14S, 17S. The stereochemical configuration at these centers is identical to those of the starting material for pregnenolone. Its molecular formula is $C_{29}H_{40}O_3$ and its relative molecular mass is 436.64 g/mol.

Figure 1 Structure of AEF0117



AEF0117 drug substance is the 3ß-(4-methoxybenzykoxy)pregn-5-en-20-one that is manufactured from pregnenolone. It is a very hydrophobic compound (aqueous solubility <0.1 µg/mL and estimated log P between 5.79 and 7.15). The trial intervention and treatment arms are summarized in Table 1.

Table 1 Description of trial drug

Intervention label	Fed group	Fasted group
Intervention name	AEF0117	AEF0117
Intervention description	One single dose in fed condition	One single dose in fasted condition
Type	Drug	
Dose formulation	Soft capsule	
Unit dose strength	1 mg	1 mg
Dosage level	1 mg as a single dose	1 mg as a single dose
Route of administration	Oral	
Use	Experimental	Experimental
Sourcing	Provided by the sponsor	
Packaging and labeling	Bottles with 21 capsules labeled according to regulatory requirements	
Description of dose and administration in each treatment arm	1 mg AEF0117 with 240 mL of water 30 minutes after start of a high fat meal	1 mg AEF0117 with 240 mL of water in fasting condition

6.1.1 Dosing and administration

All participants in this trial will be dosed with a 1 mg dose of AEF0117.

The principal investigator or designee will administer the trial drug to the trial participants.

Each dose of trial drug will be administered in the morning at approximately 9 am with approximately 240 mL of room temperature water. The actual date and time of each dose administered will be recorded in the source records and the eCRF.

Each dose of the trial drug will be administered under the supervision of the clinic staff and a visual mouth check will be performed after dose administration to verify that the participant has swallowed the drug. The oral capsules must be swallowed whole and not chewed.

6.1.2 Packaging and labeling

AEF0117 capsules will be supplied by Aelis Farma in dosage strengths of 1 mg. The AEF0117 trial drug is supplied in high-density polyethylene (HDPE) 30 mL bottles closed with a polypropylene (PP) cap. Each bottle contains 21 capsules.

The trial drug will be packaged and labeled in compliance with applicable federal regulations. The exact content of the actual label may be modified as long it complies with federal regulations.

The bottles with investigational products will bear at least the following information on the labels:

- Trial code
- Sponsor’s name
- Name and address of manufacturer & distributor
- Trial drug description and content
- Route of administration

- Dosage form
- Packaging number
- Storage conditions
- Phrase “New drug - limited by federal law to investigational use”

Additional details will be provided in the pharmacy manual.

6.2 Preparation, storage, and accountability

6.2.1 Preparation

The trial drug will be supplied in bottles to the site as described above and individual participant’s single oral dose will be dispensed by a designated investigational pharmacist at the research site or other authorized personnel with appropriate training delegated by the investigator. The process will be described in the trial pharmacy manual.

6.2.2 Product storage and stability

The AEF0117 formulation should be stored ambient at 20℃ (68°F), with excursions permitted from 15℃ to 25℃ (59°F to 77°F).

The AEF0117 formulation will be monitored for stability by the sponsor’s contract manufacturing designee.

6.2.3 Accountability

Responsibility for drug accountability at the trial site rests with the investigator; however, the investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and must be readily available for inspection by the trial monitor and are open to inspection at any time by any applicable regulatory authorities.

The investigator or designee will retain all used, unused, and partially used containers of trial drug until the end of the trial. The investigator or designee must maintain records that document:

- Investigational product delivery to the trial site.
- The inventory at the site.
- Use by each participant.

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the trial drug and trial participants.

The trial drug must be used only in accordance with the protocol. The investigator will also maintain records adequately documenting that the participants were administered the trial drug as specified.

Completed accountability records will be archived by the site and in the sponsor trial master file. At the completion of the trial, the remaining trial drug will be destructed as described in the pharmacy manual.

6.3 Participant identification and assignment to trial intervention

All participants will be assigned a unique trial participant number at the trial-specific screening.

A computer-generated randomization schedule will be prepared by a statistician. Eligible participants will be randomly assigned to 1 of the 2 groups. Randomization will be with a block size of 2 and stratified by sex.

The 2 groups will be divided into smaller cohorts of at least 2 participants for operational reasons (adjusted to in clinic facilities) and each cohort will include a similar number of participants from each group (fed or fasting).

6.4 Blinding and breaking the blind

Not applicable since the trial is not blinded.

6.5 Drug exposure and compliance

Each participant completing the trial will receive a single dose of 1 mg AEF0117.

Compliance will be recorded by the site staff administering the trial drug, see section 6.1.1 and 6.2.3.

6.6 Administration of meals

Standardized breakfast, lunch, dinner, and evening snack meals at applicable times will be served to participants during the trial.

At Day 1 in the morning prior to dosing, participants will, according to randomization to fed or fasted condition, either be given a high fat breakfast in which 50% of the calories are derived from fat (FDA breakfast) (see Appendix 4) or no breakfast. The high fat breakfast should be consumed within 30 minutes, and the dose will be administered 30 minutes after the start of the meal. In case of failure to complete ≥90% of the meal (as assessed by visual inspection) the participant must be excluded from trial and will not be administered the trial drug. The composition of the high fat meal should be recorded in the source document.

The dose will be administered with 240 mL of water. Additional water is not allowed from 1 hour prior to dosing until 2 hours after dosing but is allowed ad libitum thereafter. Food and fluids other than water is not allowed for 4 hours post dose.

A standardized lunch will be served approximately 4 hours after dosing on Day 1 (after completion of the 4-hour assessments, see section 8.1.3.2), and a standardized dinner will be served approximately 10 hours after dosing.

Noncaffeinated soft drinks and non-citrus and non-grapefruit juices will be offered with meals and ad libitum beginning 4 hours post dose. Snacks will be available and allowed from 4 hours after the dose.

The date and the exact time of administration of all meals during the confinement period should be recorded in the source documents and the eCRF.

6.7 Concomitant therapy

6.7.1 Previous and concomitant medication

All medications other than trial drug taken or received by the participant at any time during the trial from the first dose of trial drug through the follow-up visit or at early termination will be considered concomitant medications. All concomitant medications taken by a participant during the trial and the reason for its use must be recorded in the source documents and eCRF.

Any previous medication received within the last 30 days before dosing of the trial drug will also be recorded in the source documents and eCRF.

6.7.2 Restricted and/or prohibited previous and concomitant medication and foods

The use of concomitant medications or treatments, including prescription medications, over-the-counter medications, or supplements specified as prohibited is not allowed from 2 weeks prior to receiving the trial drug until the follow-up visit. For drugs with an elimination half-life greater than 10 days, this is extended to 60 days prior to dosing of the trial drug. Occasional use of paracetamol is allowed at the discretion of the investigator.

Any use of medication during the trial should be recorded in the eCRF as concomitant medication, and use of prohibited medication should in addition be recorded as a protocol deviation. If the participant uses any prohibited medication within the first 72 hours after dosing, the investigator should discuss the participant’s continued participation in the trial with the sponsor’s medical monitor.

6.7.3 Restricted and/or prohibited therapies and foods

Participants must refrain from foods that can affect the metabolism or absorption of some medications, including grapefruits, Seville oranges, tangelos (a cross between tangerines and grapefruit), and grapefruit juice are prohibited from 2 weeks prior to dosing and until the follow-up visit.

Participants are also requested to abstain from strenuous physical activity throughout the duration of the trial.

Consumption of alcohol and stimulating drinks (i.e., coffee, tea, chocolate, or cola like drinks) will not be allowed from 72 hours prior to admission on Day -1 until 72 hours after dosing.

Participants will be questioned about the above restrictions at each visit and the answer recorded in the source document and eCRF.

6.8 Rescue medication

It is anticipated that careful participant selection, dose selection and monitoring will obviate the need for emergency care. Emergency medical equipment is available in the research facility, which is in a hospital where a full medical emergency back-up team is constantly available.

In the event of an emergency, participants will be treated at the discretion of the investigator by appropriate measures.

7 PARAMETERS AND METHODS OF ASSESSMENT

Trial procedures and their timing are summarized in the schedule of activities in section 1.3. Protocol waivers or exemptions are not allowed.

Adherence to the trial design requirements, including those specified in the schedule of activities, is essential and required for trial conduct. However, unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow up of AEs, or for any other reason, as needed.

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.

In the event of a significant trial-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, and monitoring may be implemented by the sponsor or the investigator, as per local regulatory authority and IRB/EC requirements.

The maximum amount of blood collected from each participant over the duration of the trial, including any extra assessments that may be required, will not exceed 230 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

7.1 Screening and baseline procedures

The assessments performed at screening/baseline are described in the following and their timing are summarized in the schedule of activities in section 1.3.

7.1.1 Participant demography

Date of birth, sex, race, and ethnicity will be recorded for the participant demographics.

7.1.2 Body measurements

Height and weight will be measured on the days noted in the schedule of activities in section 1.3. and recorded on the eCRF. Height will be measured in cm and body weight will be measured in kg with 1 decimal. BMI will be calculated as body weight in kg / (height in meters)^2.

7.1.3 Medical history

Relevant previous and intercurrent diseases will be documented in the eCRF. The medical history will be obtained by interview with the participant and/or review of medical records.

7.2 PK parameters

7.2.1 Blood collection

Venous blood samples (6 mL each) to measure plasma concentrations of AEF0117 and potential metabolites will be collected at the times specified in the schedule of activities (section 1.3).

On Day -1, an indwelling catheter will be placed and may be used until the 14-hour blood sample; thereafter samples will be collected by individual venipuncture. The date and time of each blood sampling throughout the entire trial will be recorded in the eCRFs.

Detailed information regarding the procedures for PK blood sample collection, processing, storage, and shipment are described in Appendix 3.

7.2.2 Bioanalytical methodology

The plasma samples will be analyzed for AEF0117 by a validated assay method. The bioanalytical method for the metabolites will be developed.

The samples will be analyzed by: Biotrials Bioanalytical Services, Laval, Quebec, Canada.

7.2.3 PK analysis

For each evaluable participant, the PK parameters will be calculated from the plasma concentrations of AEF0117 using non-compartmental methods. The PK parameters are listed in Table 2. Additional details are described in section 9.6.

Table 2 Plasma PK parameters

PK parameter	Definition
C_{max}	maximum observed plasma concentration
$C_{min,24h}$	minimum observed (or trough) plasma concentration within 24 hours after dosing
C_{last}	last measurable plasma concentration
T_{max}	time to maximum plasma concentration
$T_{½}$	terminal elimination half-life
T_{lag}	the delay in achieving T_{max}
T_{last}	time to last measurable plasma concentration
AUC_{0-24}	area under the plasma concentration-time curve from time zero (pre-dose) to 24 hours
$AUC_{0\ t}$	area under the plasma concentration versus time curve from time 0 (pre-dose) to the last quantifiable concentration time point, calculated using the linear trapezoid rule
$AUC_{0-\infty}$	area under the plasma concentration versus time curve from time 0 (pre-dose) to infinity, calculated using the linear trapezoid rule
CL/F	apparent oral clearance, calculated as dose/$AUC_{0-\infty}$
$\%AUC_{extrap}$	percentage of $AUC_{0-\infty}$ due to extrapolation from T_{last} to infinity ($[AUC_{0-\infty} - AUC_{0-t}]$) / ($[AUC_{0-\infty}]$) × 100
Vd/F	apparent volume of distribution

7.3 Adverse events

7.3.1 Definition of adverse events and serious adverse events

Adverse event

An AE is defined as any untoward medical occurrence in a clinical trial participant which is temporally associated with the use of a trial intervention, and which does not necessarily have a causal relationship with the intervention. The definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the trial drug.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

An AE may therefore be:

- A new symptom/disease/condition.
- Worsening (increase in frequency or severity) of a pre-existing symptom/disease/condition.

Clinically significant laboratory abnormalities

Any laboratory abnormalities which are considered clinically significant by the investigator must be reported as AEs. A clinically significant abnormality is a confirmed abnormality (by 1 repeat test) resulting in the participant being symptomatic, requiring corrective treatment or additional examinations, or if the laboratory value leads to discontinuation of the participant from the trial, and/or fulfills a seriousness criterion. In the evaluation of whether laboratory abnormalities are

clinically significant, local laboratory reference values, relevant baseline parameters, medical history, concomitant medications, and concomitant symptoms reported as AEs should be considered.

Whenever possible, the etiology of the abnormal findings will be documented on the eCRF. Repeated additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

Other clinically significant safety assessments

Any changes from baseline in other safety assessments (e.g., vital signs measurements, ECGs, physical examinations), which are considered clinically significant in the judgment of the investigator should be reported as AEs.

Surgical procedures

Surgical procedures (e.g., appendectomy) are not AEs, but the condition for which the surgery is required may be an AE if it occurs or is detected during the trial period. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of the trial treatment. In the latter case, the condition should be reported as medical history.

Serious adverse event

An SAE is any medical occurrence that:

- Results in death.
- Is life-threatening at the time of the event as it occurred, i.e., the participant was at an immediate risk of death at the time of the SAE (not an event, which hypothetically might have caused death, if it was more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (involving at least an overnight stay for observation and/or treatment that would not have been appropriate in the physician’s office or in an outpatient setting). Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity defined as a substantial disruption of a person’s ability to conduct normal life functions. Events of relatively minor medical significance such as uncomplicated headache, vomiting, diarrhea, and accidental trauma such as a sprained ankle do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Is an important medical event that, when based upon appropriate medical judgment may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment at an emergency room or at home, blood dyscrasias, convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

7.3.2 Time period and frequency for collection of adverse event and serious adverse event

All AEs will be collected in this trial at each visit starting after the informed consent for trial participation has been signed and until the follow-up visit (Day 14).

Signs and symptoms present prior to dosing of the trial drug that would qualify as an AE if presented later, should be recorded as AEs in the eCRF with date/time of occurrence, to be able to evaluate any increase in severity during treatment, and will be designated pre-treatment-emergent AEs. AEs that are not present at baseline, or if present at baseline, have worsened in severity after dosing of AEF0117 on Day 1 will be considered treatment-emergent AEs (TEAEs).

The investigator is not obligated to actively seek information on AEs or SAEs after a participant has concluded trial participation. However, if the investigator detects an SAE in a trial participant after the end of the period of observation, and considers the event possibly related to prior trial treatment, he/she should promptly contact the sponsor to determine how the event should be documented and reported.

7.3.3 Method of detecting adverse events and serious adverse events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. AEs may be reported spontaneously by the participant, after a general non-leading question by the investigator (e.g., “How are you today”), or be observed by the investigator or designee (e.g., vomiting, or a clinically significant abnormal change from baseline in a laboratory parameter).

7.3.4 Assessment and recording of adverse events and serious adverse events

The investigator is responsible for ensuring that all AEs (as defined in section 7.3.1) are recorded in the participants’ source document and the eCRF.

The following information should be recorded for all AEs: diagnosis, start and stop date and time, severity and seriousness of the event, investigator’s opinion of causality, action taken regarding the trial drug, other action taken, treatment given for the AE, and resolution/outcome.

7.3.4.1 Nature of the adverse event

The AE should be reported in standard medical terminology. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. If a definitive diagnosis is not possible, the individual symptoms and signs should be recorded.

7.3.4.2 Intensity/severity of the adverse event

The severity of an AE will be graded according to the scale below. The severity of the AE is determined by the principal investigator, who may consult with the sponsor’s medical monitor, if needed.

- *Mild*: A sign or symptom that do not disrupt usual activity.
- *Moderate*: A sign or symptom with sufficient intensity to affect usual activity (disturbing).

- *Severe*: A sign or symptom resulting in considerable interference with the participant's daily activities (unacceptable).

When the intensity of an AE worsens over time for a reporting period (e.g., between visits, etc.), each increase in intensity will be reported as a new AE until the event resolves.

7.3.4.3 Duration of the adverse event

The duration of the AE will be described by the start and stop date and time.

7.3.4.4 Adverse event causality

The investigator must assess the relationship between the trial intervention and each occurrence of each AE using clinical judgment. The relationship or association of the AE to the trial drug will be characterized as related or not related by the investigator using the following classification:

- *Related*: The temporal relationship of the AE with the trial drug makes causality probable or possible and the AE cannot be due to another cause such as other drugs, a surgical intervention, or an underlying disease.
- *Not related*: The temporal relationship of the AE with the trial drug makes causality unlikely or certainly not related and/or the AE can be due to another cause such as other drugs, a surgical intervention, or an underlying disease.

7.3.4.5 Outcome of the adverse event

The outcome of all AEs will be described as:

- Recovered/resolved.
- Recovering /resolving.
- Not recovered/not resolved.
- Recovering with sequelae/resolved with sequelae.
- Fatal.
- Unknown.

7.3.5 Reporting of adverse events

All AEs must be recorded in the AE module in the eCRF, regardless of severity or apparent relatedness to dosing of the trial drug.

AEs classified as serious must be reported to the sponsor's designee immediately using the SAE form (see section 7.3.6).

Any clinically significant laboratory abnormalities that are either unexplained or considered treatment related should be discussed with the sponsor's medical monitor.

Additional non-protocol-specified laboratory tests performed if deemed necessary by the investigator or required by local regulations must be recorded on the eCRF.

7.3.6 Reporting of serious adverse events

Any SAE that occurs during the trial from the time of dosing, regardless of relationship to the trial drug, must be reported immediately and no later than 24 hours from the time the investigator or other trial staff becomes aware of the event. The SAE should be reported using the trial-specific SAE form provided by the sponsor. All SAEs should also be recorded as serious AEs in the eCRF.

The minimum information that should be included in the initial SAE report is the participant ID, reporter- and trial identifiers, the nature of the event, and assessment on seriousness and causality.

Any updated SAE information should be submitted to the sponsor within 24 hours of it being available. The investigator may change their opinion of the originally reported event based on follow-up information and include the updated information in the SAE follow-up report.

SAEs should be reported by email, telephone, or fax to Pharmalex using the contact details listed below and with copy to the site monitor. Initial notification via telephone does not replace the need for the investigator to complete and send the SAE form within the reporting timeline.

Report SAEs by fax or email to:	**Miriam Abril** Pharmalex, Coso, 103, 50001 Zaragoza, Spain Fax: +34 976 20 44 02 Tel: +34 976 20 44 00 Email: AelisSafety@pharmalex.com

If copies of medical records, special examinations, or pathology reports for certain cases are requested by PV, all participant identifiers, except for the participant trial ID number, must be redacted on the copies of the medical records before submission to PV.

The SAE report will be captured in the PV database, and Pharmalex will provide pharmacovigilance (case reporting, PV database maintenance).

A copy of the submitted SAE form must be retained on file by the investigator.

7.3.7 Suspected adverse reactions

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

The PV vendor will notify any Suspected Unexpected Serious Adverse Reaction (SUSAR) to the FDA. This notification will be made within a period of 15 calendar days since the sponsor has knowledge of the SUSAR and 7 days, if the SUSAR has caused death or was life-threatening.

7.3.8 Regulatory reporting requirements for serious adverse events

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of the trial intervention 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 intervention under clinical investigation. The sponsor will comply with all country-specific regulatory requirements relating to safety reporting to the regulatory authorities, IRBs/ECs, and investigators.

The investigator must report all SAEs promptly to the appropriate IRB/EC as required by the institution.

7.3.9 Follow up of adverse events and serious adverse events

After the initial AE/SAE report, the investigator is required to proactively follow up on the event at each subsequent visit.

All SAEs must be followed until resolution, even if this extends beyond the trial reporting period, or until the participant is lost to follow up. Resolution is defined as the return to baseline status, stabilization of the condition with the expectation that it will remain chronic, the event is otherwise explained, or the investigator considers it medically justifiable to terminate follow up. Should the AE result in death, a full pathologist's report should be supplied if, and when available.

All clinically significant laboratory abnormalities should be monitored until resolution.

If an AE remains unresolved at the follow-up visit, the participant will be followed, at the investigator's discretion, until resolution of the event.

New or updated information will be recorded in the originally submitted documents (i.e., eCRF and/or SAE form) while the trial is ongoing. Thereafter, new information will be submitted directly to the sponsor.

7.3.10 Reporting and follow up of pregnancies

Female participants participating in this trial must be of non-childbearing potential as defined in inclusion criterion 2. Serum and urine pregnancy tests will be performed on all females regardless of childbearing potential status as specified in the schedule of activities in section 1.3.

Pregnancy is not considered an SAE but if a pregnancy occurs in a participant or in the partner of a participant during the trial, the investigator must report it to the sponsor within 24 hours using the pregnancy notification form provided by the sponsor. For females who experience pregnancy during the trial, the female participant will be monitored for any adverse problems with the pregnancy and for the outcome of the pregnancy, if feasible. This implies that a female partner to a male participant will sign a specific ICF for collection of pregnancy information.

7.3.11 Events of special interest

Dosing error

For reporting purposes, the sponsor considers the occurrence of overdose (regardless of adverse outcome) as an event that must be reported as an important medical event (see definition in section 7.3.1).

Trial drug dosing errors made by the research facility staff must be documented as major protocol deviations and reported to the sponsor and the IRB/EC in accordance with the IRB/EC requirements.

7.4 Safety parameters

7.4.1 Clinical safety laboratory parameters

7.4.1.1 Clinical chemistry, hematology, hemostasis, and urinalysis

A local laboratory will perform the clinical safety laboratory tests. Samples for hematology, serum chemistry, coagulation profile, and urinalysis will be prepared using standard procedures. All participants will have samples of blood and urine collected on the days and times noted in the schedule of activities in section 1.3.

Blood must be collected under fasting conditions (no food or drink other than water for 6 hours prior to collection). A detailed listing of the serum chemistry, hematology, coagulation profile, and urinalysis tests is provided in Appendix 2.

The investigator must review the laboratory results, document the review of each laboratory safety report, and record any clinically significant changes occurring during the trial as an AE (see section 7.3.1). The laboratory results must be retained with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the trial or within 2 weeks after the dose of trial intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If clinically significant values do not return to normal/baseline within a period judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

Additional tests may be performed at any time during the trial as deemed necessary by the investigator or required by local regulations. If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in the management of the participant or are considered clinically significant by the investigator, then the results must be recorded.

7.4.1.2 Other safety laboratory tests

Urine drug screen and alcohol breath test will be performed at screening and at additional time points as indicated in the schedule of activities in section 1.3.

COVID-19 tests will be performed at screening and Day -1 according to the site's standard procedures. In addition, participants will be screened for COVID-19 symptoms on admission on Day -1 and on Day 1 which will be documented in the source document, and additional COVID-19 tests may be performed during the trial according to the standard procedures in place at the site at the time of the visits.

7.4.1.3 Pregnancy test

A serum ß-hCG will be performed for female participants at screening, and a urine pregnancy test will be performed at baseline (Day -1) and at the follow-up visit. A positive urine pregnancy test must be confirmed by a serum pregnancy test.

In case of a positive pregnancy test prior to dosing on Day 1, the participant will not be randomized and will be a screening failure. In case of a positive pregnancy test after dosing, the participant should continue following the trial procedures and the pregnancy should be reported as described in section 7.3.10.

7.4.2 Vital signs

Vital sign measurements (BP, HR, and oral temperature) will be performed on the days and at the times noted in the schedule of activities in section 1.3.

Vital signs will be measured using an automated device with the participant in a supine position after 5 minutes of rest and prior to blood sampling.

7.4.3 Physical examination

A comprehensive physical examination will be performed at screening. The comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities, and a brief neurological examination.

A brief physical examination will be performed at the times indicated in the schedule of trial activities in section 1.3 as directed by any signs or symptoms.

7.4.4 Electrocardiogram

A standard supine 12-lead ECGs will be obtained after 5 minutes of rest on the days and times noted in the schedule of activities in section 1.3. All ECGs should be collected prior to blood sampling.

Computerized 12-lead ECG recordings will be obtained. Each lead shall be recorded for at least 3 beats at a speed of 25 mm/s. Triplicate recordings will be made at the timepoints evaluated. The following parameters will be recorded in the eCRF: HR, PR interval, QRS duration, QT, and QTcF.

The ECGs will be assessed by the investigator and reported as normal or abnormal. Clinically notable ECG abnormalities that occur after dosing and are considered clinically significant in the judgment of the investigator should be reported as AEs.

The ECG report must be reviewed, signed, and dated by the investigator in a timely manner. The original ECG results will be kept on file at the site as source documentation.

7.4.5 Columbia-Suicide Severity Rating Scale

As this is a central nervous system active compound, the prospective assessment of suicidality is collected using the Columbia-Suicide Severity Rating Scale (C-SSRS) on the days and times noted in the schedule of activities in section 1.3. The C-SSRS is a comprehensive assessment that identifies whether someone is at risk for suicide, assesses the severity and immediacy of that risk, and gauges the level of support that the person needs [12]. The C-SSRS is designed to assess both suicidal behavior and suicidal ideation and consists of 2 questionnaires: one designed for the screening and baseline assessment (covers the participant's lifespan until the baseline visit) and one used during the trial ('Since last visit' questionnaire). A representative example of the C-SSRS that will be used in this trial is provided in Appendix 5.

8 TRIAL CONDUCT

8.1 Procedures by visit

8.1.1 Screening (Day -28 to Day -2)

Prior to any trial-specific procedures and evaluations, a written signed informed consent to participate in the trial must be obtained. The following screening procedures should be performed between Day -28 and Day -2. If some of the screening procedures have been completed as part of a general pre-screening procedure at the research facility within this period, those results can be transcribed to the eCRF for this trial, provided source documentation is available.

- COVID-19 test.
- Assessment of inclusion and exclusion criteria.
- Recording of demographics.
- Medical history, including intercurrent illness.
- Full physical examination of all major organ systems.
- Measurement of height and body weight, and calculation of BMI.
- Resting 12-lead ECG in a supine position prior to any blood sampling.
- Resting BP, HR, and oral temperature in a supine position prior to any blood sampling.
- Recording of signs and symptoms present that would qualify as an AE if presented later.
- Prior and concomitant medications.
- C-SSRS evaluation will be performed (Baseline/Screening version).
- Collection of blood samples for:
    - Fasting (at least 6 hours) safety laboratory parameters (chemistry, hematology, and coagulation profile).
    - Serum pregnancy test (female participants only).

- Collection of urine for:
  - Urinalysis.
  - Urine drug screen.
- Alcohol breath test.

8.1.2 Baseline (Day -1; confinement period)

The following procedures will be performed on Day −1 after check-in at the research facility:

- COVID-19 test.
- Questioning for COVID-19 symptoms.
- Confirmation of eligibility for the trial according to the inclusion and exclusion criteria.
- Update of medical history, including intercurrent illness.
- A brief physical examination will be performed.
- Body weight will be measured, and BMI calculated.
- Resting 12-lead ECG will be obtained in a supine position prior to any blood sampling.
- Resting BP, HR, and oral temperature will be measured in a supine position prior to any blood sampling.
- Recording of AEs.
- Update of prior and concomitant medications.
- C-SSRS evaluation (Screening/Baseline version) will be performed.
- Collection of blood samples for:
  - Fasting (at least 6 hours) safety laboratory parameters (chemistry, hematology, and coagulation profile).
- Collection of urine for:
  - Urinalysis.
  - Urine drug screen.
  - Urine pregnancy test (female participants only).
- Alcohol breath test.
- An evening snack will be consumed at approximately 21.30 pm.
- Participants will fast overnight beginning at approximately 23 pm.

8.1.3 Day 1 (confinement period)

8.1.3.1 Pre-dose assessments

The following evaluations and procedures will be performed before dosing on Day 1:

- Questioning for COVID-19 symptoms.
- Body weight will be measured (pre-breakfast, if applicable).
- Resting 12-lead ECG will be obtained in a supine position prior to any blood sampling.
- Resting BP and HR will be measured in a supine position prior to any blood sampling.
- Recording of AEs.
- Recording of any concomitant medications.
- Collection of blood samples for:
  - Determination of plasma AEF0117 concentration (6 mL) within 60 minutes prior to dosing.
  - Determination of concentration of potential metabolites (6 mL) within 60 minutes prior to dosing.
- Randomization.
- Only participants randomized to dose administration in fed state will receive a high fat breakfast that should be started 30 minutes prior to dosing and consumed within 30 minutes or less.

When all assessments have been performed, the trial drug (1 mg AEF0117) will be administered orally with approximately 240 mL of room temperature water at approximately 9 am.

8.1.3.2 Post dose assessments

- Resting 12-lead ECG will be obtained in a supine position at 1, 2, 4, 8, and 11 hours post dose and prior to blood sampling.
- Resting BP and HR will be measured in a supine position at 1, 2, 4, 8, and 11 hours post dose and prior to blood sampling.
- Blood samples (6 mL each) for determination of plasma AEF0117 concentration will be collected at 1, 1.5, 2, 3, 4, 5, 6, 8, 11, and 14 hours post dose.
- Blood samples (6 mL each) for determination of plasma concentration of potential metabolites will be collected at 2, 4, 6, 8 and 11 hours post dose.
- Recording of any concomitant medications.
- AE assessment throughout the day by querying with non-leading questions and observation.
- Water is allowed ad libitum from 2 hours after dosing. Snacks and noncaffeinated soft drinks and non-citrus and non-grapefruit juices will be offered with meals and ad libitum beginning at lunch.

- Lunch will be consumed by participants approximately 4 hours after dosing of trial drug, after completion of the 4-hour assessments.
- Dinner will be consumed by participants approximately 10 hours after dosing of trial drug.
- An evening snack will be offered to the participants at approximately 21.30 pm.

8.1.4 Day 2 (confinement period)

The following evaluations and procedures will be performed on Day 2:

- A brief physical examination will be performed.
- Pre-breakfast body weight will be measured.
- Resting 12-lead ECG will be obtained in a supine position at 24 hours post dose and prior to any blood sampling.
- Resting BP, HR, and oral temperature will be measured in a supine position at 24 hours post dose and prior to any blood sampling.
- AE assessment by querying with non-leading questions and observation.
- Recording of any concomitant medications.
- Collection of blood samples for:
  - Fasting (6 hours) safety laboratory parameters (chemistry, hematology, and coagulation profile) at 24 hours post dose.
  - Determination of plasma AEF0117 concentration (6 mL) at 24 hours post dose.
  - Determination of plasma concentration of potential metabolites (6 mL) at 24 hours post dose.
- Collection of urine for urinalysis.
- C-SSRS evaluation will be performed (Since Last Visit version).
- Breakfast will be consumed.

When all the above procedures have been performed, participants will be discharged from the research facility.

8.1.5 Days 3–11 (ambulatory visits)

On Days 3, 4, 5, 7, 9, and 11 after trial drug administration, the following evaluations will be performed during the participant's visits to the site:

- AE assessment by querying with non-leading questions and observation at each visit.
- Review of concomitant medications at each visit.

- Collection of blood samples for:
  - Determination of plasma AEF0117 concentration (6 mL) will be collected at Day 3 (48 hours), Day 4 (72 hours), Day 5 (96 hours), Day 7 (144 hours), Day 9 (192 hours), and Day 11 (240 hours) post dose.
  - Determination of plasma concentration of potential metabolites (6 mL) will be collected at Day 4 (72 hours) and Day 7 (144 hours) post dose.
- Resting 12-lead ECG will be obtained in a supine position at Day 11 prior to blood sampling.
- Resting BP and HR will be measured in a supine position at Day 11 prior to blood sampling.
- Urine drug screen and alcohol breath test will be performed 2–3 times during this period, randomly distributed.

8.1.6 Follow up or early termination (Day 14 ±1)

Volunteers will return to the research facility for a follow-up safety assessment on Day 14. The following procedures will be performed:

- A brief physical examination will be performed.
- Body weight will be measured.
- Resting 12-lead ECG will be obtained in a supine position prior to any blood sampling.
- Resting BP, HR, and oral temperature will be measured in a supine position prior to any blood sampling.
- AE assessment by querying with non-leading questions and observation.
- Review of concomitant medications.
- C-SSRS evaluation will be performed (Since Last Visit version).
- Collection of blood samples for:
  - Fasting (at least 6 hours) safety laboratory parameters (chemistry, hematology, and coagulation profile).
  - Determination of plasma AEF0117 concentration (6 mL).
- Collection of urine for:
  - Urinalysis.
  - Urine pregnancy test (females only).

9 STATISTICAL METHODS

9.1 Determination of sample size

The sample size has been chosen based on previous experience in phase 1 studies with AEF0117 where the CV was in the order of 0.3 for C_{max} and AUC after single doses. It is anticipated that food slightly increases the absorption of AEF0117 and a true ratio of 1.25 is assumed. To allow

for potential participants who dropout early, i.e., not allowing for estimation of C_{max} and/or AUC_{0-t}, 32 participants should be included. The power for showing that the upper bound of the 2-sided 90% CI is ≤1.75 is 90% with 14 participants per treatment group and 86% with 12 participants per group.

9.2 Trial participants

9.2.1 Disposition of participants

All randomized participants will be summarized, including participants dosed, completed, and discontinued. A participant is considered to have completed the trial if they complete the follow-up visit Day 14. All participants discontinued will be summarized by time of and reason for discontinuation.

A detailed listing of participants who failed screening for the trial will be provided. The number of participants screened but not found eligible will be stated in the CTR, together with a summary of reasons for screen failure.

The number of participants in the PK data population and the safety data population will be summarized with frequency and percentage in a patient disposition table.

9.2.2 Protocol deviations

The list of protocol deviations will be reviewed for evaluation of any importance for the analyses. The presence of deviations with major impact on the PK analyses might lead to exclusion of the participant from the PK data population. If the deviations are related to collection of other specific data, it may be considered only to exclude the data that have been invalidated by the deviation. Critical and major deviations will be described in the CTR.

9.2.3 Analysis populations

The populations to be analyzed include the following:

- PK data population: Participants randomized in the trial who took the assigned dose of trial drug and provided sufficient and valid plasma drug concentration data to allow the determination of PK parameters will be considered as potential PK-evaluable participants. In case a participant vomits within 3 hours after dosing, the participant will be excluded from the PK data set.
  During the data review meeting prior to database lock, participants or specific data from a participant that should be excluded from the analyses will be decided and documented.
- Safety data population: Participants randomized in the trial who were administered the trial drug.

9.3 General considerations

A statistical analysis plan, providing detailed discussion of the analyses outlined below, will be prepared, and finalized before the first dose. Deviations from the planned analyses will be described and justified in the final CTR.

All PK analyses will be based on the PK data population. All safety analyses will be based on the safety data population.

Numerical data will be presented in summary tables by number of participants, arithmetic mean, median, SD, geometric mean, CV%, minimum and maximum, as applicable for the specific data. Categorical data will be presented by the number and percentage of participants as well as the number of events (where applicable).

All data will be listed.

9.4 Demographics, baseline characteristics and concomitant medications

Descriptive statistics will be applied to demographics, baseline characteristics, concomitant medication, and medical history by group (fasted/fed) and total population.

Medical history will be coded according to the current version of MedDRA at the time of start of the trial, and concomitant medication will be coded with the WHO Drug Dictionary.

9.5 Treatment compliance

Dose and time of dosing will be listed by participant.

9.6 PK analyses

Pharmacokinetic parameters of AEF0117, including C_{max}, $C_{min,24h}$, C_{last}, T_{max}, T_{lag}, $t_{½}$, AUC_{0-t}, $AUC_{0-\infty}$, $\%AUC_{extrap}$, CL/F and Vd/F will be calculated using non-compartmental methods and summarized by graphic displays and descriptive statistics as data permit.

9.6.1 Primary endpoint

The primary analysis will be based on a comparison of the ratio between fed and fasting condition for the following parameters: the mean C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of each group. Descriptive statistics will be applied to T_{max} and T_{lag}.

PK analysis will consist of a non-compartmental evaluation of AEF0117 plasma concentration-time profiles to determinate PK parameters using a validated program. PK parameters will be tabulated and summarized using descriptive statistics (mean, median, SD, geometric mean, CV%, minimum, and maximum).

The relative bioavailability will be estimated by calculating the ratio of the geometric means between fed and fasted conditions, based on log-transformed data, for AUC_{0-t}, $AUC_{0-\infty}$ (when appropriate) and C_{max}. The 90% CI will be provided. The clinical relevance of any differences between fed and fasted conditions will be discussed, especially with respect to an assessment of the CI in relation to the limits.

An analysis of variance model will be applied, with sequence, period, and state (fed, fasting) as factors.

9.6.2 Secondary endpoints

Additional PK parameters of AEF0117, including $C_{min,24h}$, $t_{½}$, $\%AUC_{extrap}$, CL/F, and Vd/F will be calculated using non-compartmental methods and summarized by graphic displays and descriptive statistics as data permit. Individual and summary (means ± SD for each condition i.e., fed/fasting) plasma AEF0117 concentration-time plots will be displayed graphically.

9.7 Safety analyses

9.7.1 Drug exposure

Drug exposure (dosing) will be summarized descriptively for the safety data population.

9.7.2 Adverse events

An AE with onset after administration of trial drug is considered treatment emergent.

AEs will be summarized by MedDRA SOC and PT. AE summary tables will include the number of participants reporting an AE (n), the percentage of participants with an AE (%), and the number of events reported (E). AEs will be presented by group (fasted/fed) and the total population.

The incidence of treatment-related AEs and not related AEs will be tabulated. If the investigator does not specify the relationship of the AE to trial drug the AE will be considered treatment related. AEs will also be summarized by severity (mild, moderate, severe). If the severity is missing, the AE will be regarded as severe. An AE that increases in severity over time will for the purpose of analysis be considered as one AE with the maximum intensity recorded.

9.7.3 Other safety parameters

Clinical laboratory tests

Descriptive statistics and mean change from baseline to each post-baseline value will be provided for clinical laboratory tests (Day 2 - baseline, and follow up/ET - baseline).

Clinical laboratory values from fasting blood and urine samples will be reviewed for PCS values as assessed by the investigator. Participants with PCS laboratory values will be listed.

Vital signs

Descriptive statistics for each scheduled timepoint and for change from baseline to selected timepoints will be provided for vital signs (BP, HR, and oral temperature) and weight. Vital sign results will be reviewed for PCS abnormal values according to predefined criteria, and participants with PCS vital signs will be listed.

Electrocardiograms

Descriptive statistics for each scheduled timepoint and for change from baseline to each scheduled timepoint will be provided for each ECG parameter (HR, PR interval, QRS duration, QT, and QTcF). ECG results will be reviewed for PCS abnormal values according to predefined criteria. Participants with PCS ECG values will be listed.

Psychometric tests and C-SSRS test

Descriptive statistics for each scheduled time point and for change from baseline to each scheduled time point will be provided for each score or sub-score. Mean graphs may also be displayed.

9.8 Participant withdrawals and missing data

All data will be included and used as recorded. Specific participants and/or data may be excluded from the PK analysis as described in 9.2.3.

9.9 Interim analyses

Not applicable.

9.10 Other analyses

9.10.1 Subgroup analyses

Not applicable.

9.10.2 Exploratory analyses

If the data allow, a PK analysis will consist of a non-compartmental evaluation of the metabolite plasma concentration-time profiles to determine PK parameters using a validated program. PK parameters will be tabulated and plots of plasma concentration as a function of time provided for the 2 conditions (fed/fasting). The results of the explorative measures will be reported separately.

10 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Statement of compliance

The investigator is responsible for ensuring that the trial will be conducted in adherence with the clinical trial protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 50, 54, 56, 312 and Part 11 as well as ICH E6: Guideline for Good Clinical Practice (ICH GCP) [13] and applicable regulatory requirements (http://www.fda.gov/cder/guidance/index.htm).

The investigator is responsible for ensuring the accuracy and completeness of all research records, the accountability of the trial drug, and the conduct of clinical and laboratory evaluations as outlined in this protocol.

It is the responsibility of the investigator to assure that all aspects of the ethics and regulatory review are conducted in accordance with the Declaration of Helsinki as described in the ICH GCP, and/or local laws, whichever provides the greatest level of protection for the trial participants.

10.2 Institutional review board/ethics committee

The investigator must ensure that the protocol and any information provided to the participant such as written ICFs, written participant information, and participant recruitment procedures (e.g., advertisements) will be reviewed and approved by a qualified IRB/EC to initiation of the trial. In the event of amendments, approval of the updated documents must be obtained before they are implemented.

The investigator and sponsor or designee, will make all attempts to ensure that the IRB/EC is constituted and operates in accordance with ICH GCP, federal, and any local regulations.

All IRB/EC approvals must be dated and signed by the IRB/EC chairperson or designee and must identify the IRB/EC by name and address, the clinical protocol by title and/or protocol number, the date approval or favorable opinion was granted for the clinical trial, as well as the list of the committee members.

Prior to initiation of the trial, the sponsor must ensure that all ethical and legal requirements have been met and must receive documentation of the IRB/EC approval. No drug will be released to the site to dose a trial participant until written IRB/EC approval/favorable opinion has been received by the sponsor or designee.

Investigators must submit progress reports to the IRB/EC in accordance with the IRB/EC requirements. Continuing review and re-approval of the clinical trial must be performed at least annually or more often if specified by the IRB/EC. Copies of progress reports and re-approvals must be sent to the sponsor.

The sponsor and investigator will comply with all country-specific and local regulatory requirements relating to safety reporting to the regulatory authorities and IRBs/ECs.

The investigator, as part of the records retention requirements for the trial, must maintain documentation of all submissions, correspondence, and approvals to and from the IRB.

The investigator will notify the IRB when enrollment stops and when the analysis of data is completed.

10.3 Changes to the protocol

10.3.1 Protocol amendments

Any important changes to the protocol (i.e., changes that significantly affect participant safety or the scope or scientific quality of the trial), except those to remove an apparent immediate hazard to the trial participants, must be made in a substantial protocol amendment that must be reviewed and approved by the sponsor or designee, and the IRB/EC and regulatory authorities that approved the trial prior to participants being enrolled into the amended protocol.

Substantial amendments to the protocol must be reviewed and approved following the same requirements and conditions as for the original protocol. The investigator must send a copy of the approval letter from the IRB/EC to the sponsor and retain the original in the site trial regulatory file.

The sponsor may make administrative changes (i.e., changes that do not significantly affect participant safety or the scope or scientific quality of the trial) without any further approvals (non-substantial/administrative amendment).

All amendments will be distributed to all protocol recipients.

10.3.2 Protocol deviations

A protocol deviation is any noncompliance with the clinical trial protocol or with ICH GCP requirements. Deviations from the protocol should be avoided, except if necessary to remove an immediate hazard to the participants. Prospective approval of protocol deviations (also known as protocol waivers or exemptions) is not permitted.

All protocol deviations will be recorded and qualified as critical, major, or minor. Critical and major deviations will be summarized in the CTR.

Major and critical deviations must be reported to the sponsor and to the IRB/EC in accordance with the IRB/EC requirements. During the trial the trial monitor must notify the sponsor of subjects found not to have met eligibility criteria. The medical monitor in collaboration with the investigator will determine if the participant should be withdrawn from the trial.

The IRB/EC that granted original approval, or the IRB/EC currently responsible for overseeing the conduct of the trial, must be notified of all changes in and deviations from the protocol that may increase risk to the participants, and/or that may adversely affect the rights of the participant or the validity of the investigation.

10.4 Participant recruitment, consent, and participation

10.4.1 Recruitment strategies

Recruitment for this trial will occur primarily through advertisements in local newspapers and online, and by word of mouth. Interested individuals will respond to advertisements by calling the research facility for information about the trial.

Participants will be financially compensated for their time and traveling costs, subject to IRB/EC approval of conditions.

10.4.2 Written participant information and informed consent form

Preparation of the written participant information and ICF is the responsibility of the investigator and the sponsor or designee. The document must include all elements required by ICH GCP and applicable regulatory requirements, including 21 Code of Federal Regulations § 50, and must adhere to the ethical principles that have their origin in the Declaration of Helsinki [14].The document must be written in a language understandable to the participant and must specify who informed the participant.

The sponsor or designee must review and approve all changes to the trial-specific ICF. Any changes requested by the IRB/EC must also be approved by the sponsor or designee. The final IRB/EC-approved ICF must be provided to the sponsor or designee. Revisions to the ICF required

during the trial must be approved by the sponsor or designee, and a copy of the revised ICF provided to the sponsor or designee.

The ICF must include a statement that the sponsor or designee and regulatory authorities have direct access to participant records and that pseudonymized data will be securely transferred to the sponsor/third parties. Prior to the beginning of the trial, the investigator must obtain the IRB/ECs written approval/favorable opinion of the written ICF and any other information to be provided to the participants.

10.4.3 Informed consent process

The investigator will not undertake any measures specifically required only for the clinical trial until valid consent to participate in the trial has been obtained.

The participants must be informed about the nature, scope, and possible consequences of the trial in a form understandable to them. The written participant information that includes information about the trial and the ICF will be given to the participant.

Where required by local law, the person who informs the participant must be a physician. After the investigator or designee is assured that the participant understands the commitments of participating in the trial, the participant will be asked to sign and date the ICF.

A copy of the fully signed and dated consent documents must be given to the participant. The original signed consent documents will be retained by the investigator at the trial site. All active participants will sign an updated ICF if revisions are made to the ICF during the trial.

The investigator may inform the participant's primary physician about the participant's participation in the trial if the participant has a primary physician and if the participant agrees to the primary physician being informed.

10.4.4 Trial participation card

The subjects will be provided with a trial participation card including the following information:

- That he/she is participating in a clinical trial, including the trial code.
- That he/she is treated with an investigational drug.
- The name and phone number of the contact person at the site.

The participants will be asked to keep the trial participation card in their possession during the trial and to return it to the site at the follow-up visit.

10.5 Data protection and confidentiality

Participant confidentiality will be strictly maintained to the extent possible under the law.

Participants will be assigned a unique identifier by the sponsor when they are screened for the trial. If some of the screening procedures have been performed as part of a general pre-screening procedure at the research facility, the investigator must retain a list linking the pre-screening and the trial records for the participants, and in the general pre-screening ICF the participants must have consented to their results being used later for an investigational trial. Only the participant

number and birth date will be recorded in the eCRF, and if the participant's name appears on any other document (e.g., laboratory report), it must be erased on the copy of the document to be supplied to the sponsor. Participant names must not be disclosed.

The participants will be informed that clinical quality assurance auditors or other representatives of the sponsor, IRB/EC, or inspectors from regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for such audits or inspections will be handled in strictest confidence and in accordance with local data protection laws.

Trial findings stored on a computer will be stored in accordance with local data protection laws.

Applicable data privacy laws and regulations must be adhered to. The investigator and the sponsor are responsible for ensuring that sensitive information is handled in accordance with local requirements (e.g., Health Insurance Portability and Accountability Act [HIPAA]). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

All trial findings and documents will be regarded as confidential. The investigator and other trial personnel must not disclose such information without prior written approval from the sponsor.

10.6 Financial disclosure

Investigators and sub-investigators will provide financial disclosure information to the sponsor to permit the sponsor to fulfill its regulatory obligation. Investigators and sub-investigators must commit to promptly updating the information if any relevant changes occur during the trial and for a period of 1 year after the completion of the trial.

10.7 Liability and insurance

The sponsor will contract a liability insurance for this clinical trial.

10.8 Data quality assurance

10.8.1 Clinical monitoring

The investigator must permit periodic trial-related monitoring by qualified representatives of the sponsor or designee (trial monitors) at mutually convenient times during the trial. The trial monitor will visit the trial site to confirm that data in the eCRF are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

Relevant site staff should be available for discussions during monitoring visits and between monitoring visits (e.g., by telephone).

Monitoring details, including definition of critical trial data items and processes, the level of source data verification, methods, responsibilities, and requirements, including recording and escalation of noncompliance issues and monitoring techniques (e.g., central, remote, or on-site monitoring) will be provided in a trial-specific monitoring plan.

10.8.2 Audits and inspections

During the trial, individuals from the sponsor's Quality Assurance department and/or their authorized representative may visit the investigator's site to conduct an audit of the trial. The purpose of this visit will be to determine the investigator's adherence to the protocol, applicable regulations, and the sponsor's procedures, in addition to assessing the accuracy of the trial data. Prior to initiating this audit, the investigator will be contacted by the sponsor to arrange a convenient time for this visit.

At some point during the investigational product's development program, a regulatory authority may visit the investigator to conduct an inspection of the trial and the site. The investigator must immediately notify the sponsor when contacted by any regulatory authority for purpose of an inspection.

The investigator and staff are expected to cooperate with the auditors and inspectors and allow access to all source documents supporting the eCRFs and other trial-related documents.

10.8.3 Data collection and management

Data in this trial will be collected using electronic data capture. The trial site will be provided with access to eCRFs in which to record all the protocol-specified data for each participant in this trial. Data recorded in the eCRFs will be accessible by the trial staff, data management, and sponsor immediately after entry. The eCRF must be always maintained up to date.

Data collection in the eCRF is the responsibility of the investigator and delegated clinical trial staff. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported in the eCRF. Any correction(s) made by authorized site staff to the eCRF after original entries will be documented in the audit trail. The person making the change to the data, the date, time, and reason for the change will also be recorded in the audit trail. The investigator must sign and date the investigator's statement at the end of the eCRF to endorse the recorded data. This signature will be kept in the audit trail of the system and cannot be altered. Change to data that has been signed will require a new signature by the investigator.

Data management will be performed from eCRFs. Queries generated by the data management vendor will be sent to the trial site for resolution. The investigator is responsible for the review and approval of all responses to eCRF queries.

All eCRF data will be kept in a validated 21 CFR Part 11-compliant database. The system is password protected and includes internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate.

Laboratory PK data will be imported to the database electronically. C-SSRS tests will be entered into the eCRF by site staff.

All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of the sponsor or the data management vendor, as directed by the sponsor. The database will be authorized for lock once no data queries are outstanding, all trial data are considered clean, and all defined procedures completed.

10.8.4 Source documentation

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

The investigator must prepare and maintain accurate source documentation that supports all observations and other data pertinent to the trial for each trial participant.

Whenever possible and/or if demanded by the applicable local regulatory requirement, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable provided it is legible and is a verified copy of the original document.

Entries made in the eCRF must be verifiable against source documents. Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. In certain circumstances as defined by the sponsor, data may be directly entered into the eCRF; in such cases, the entry in the eCRF will be considered as the source data.

Definition of what constitutes source data, and its origin will be defined in the monitoring guidelines or source data acknowledgment.

10.8.5 Access to source data

The investigator must allow the trial monitors to periodically review, at mutually convenient times during the trial and after the trial has been completed, all eCRFs and office, hospital, and laboratory records supporting the participation of each participant in the trial. The eCRFs and other documentation supporting the trial must be kept up to date by the investigator and the research staff at the investigative site. These trial materials must be available for review by the trial monitor, and/or other qualified representatives of the sponsor, at each monitoring visit.

Additionally, competent authorities of certain countries, IRBs/ECs and/or the sponsor may wish to perform such source data checks and/or on-site audits or inspections. Direct access to source data will be required for these inspections and audits which will be performed with due consideration to data protection and participant confidentiality.

10.8.6 Archiving of trial records

The investigator must ensure that all records pertaining to the conduct of the clinical trial, ICFs, drug accountability records, source documents, and other trial documentation are adequately maintained and archived in compliance with ICH GCP. Essential documents should be retained for a period of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

The investigator must not destroy any records associated with the trial without receiving approval from the sponsor. The investigator must notify the sponsor in the event of accidental loss or destruction of any trial records. If the investigator leaves the institution where the trial was conducted, the sponsor must be contacted to arrange alternative record storage options. If the records are transferred to another location or party, the sponsor must be notified in writing.

The participant's medical records must be archived in accordance with local law. Patient identification codes will be retained strictly confidential for at least 15 years after the completion or discontinuation of the trial.

All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations.

The sponsor will retain the original eCRF data and audit trail.

10.9 Publication and public disclosure

10.9.1 Publication and data sharing policy

By signing the clinical trial protocol, the investigator and his or her institution agree that the results of the trial may be used by the sponsor, Aelis Farma, for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

A CTR will be prepared by the sponsor or designee and reviewed by the principal investigator. A summary of the CTR will be sent to the regulatory authorities and IRB/EC according to the relevant guidelines.

No data from the clinical trial may be published, presented, or communicated, except to regulatory authorities, prior to the release of the CTR, unless approved by the sponsor in writing.

Following completion of the trial, the data from this trial may be considered for reporting at a scientific meeting or for publication in a scientific journal. The sponsor will collaborate with the principal investigator on these activities and has the right to review and comment on any presentation of data or manuscript prior to submission. The collaboration may include development of the manuscript and selection of the scientific journal to which it will be submitted. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.9.2 Registration of clinical studies and disclosure of results

The sponsor will register this trial at clinicaltrials.gov in accordance with applicable law. Registration will be performed prior to enrollment of the first trial participant.

Trial results will be disclosed at clinicaltrials.gov by the sponsor, if required.

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12 APPENDIXES

12.1 Appendix 1: Key contacts for the trial

Sponsor contact	Stéphanie Monlezun Program Manager Aelis Farma Cell: +33 789 563 633 Tel: +33 557 573 670 Email: s.monlezun@aelisfarma.com
Sponsor trial manager	Ghislaine Campistron Project Manager Aelis Farma Cell: +33 557 573 772 Tel: +33 648 163 777 Email: g.campistron@aelisfarma.com
Principal investigator	Margaret Haney, PhD Columbia University Department of Psychiatry Tel: +1 646-774-6153 Email: mh235@cumc.columbia.edu
Qualified physician medically responsible for the trial	Dr. Jeanne Manubay Columbia University Department of Psychiatry Tel: +1 646-774-8016 Email: Jeanne.Manubay@nyspi.columbia.edu
Sponsor Medical Monitor	Lasse Steen Ravn, MD, PhD Aelis Farma Cell: +45 42 80 87 09 Email: l.steenravn@aelisfarma.com
Contract research organization responsible for project management, data management, and biostatistics	BIOCLEVER 2005 S.L.U. Rambla Catalunya 135, 08008 Barcelona, Spain Tel: + 34 934 086 388
Bioanalytical laboratory	Biotrials Bioanalytical Services Inc. 3885 Industriel Blvd. Laval (Quebec), Canada H7L 4S3 Tel.: +1 (450) 663-6724 ext. 6451 Fax: +1 (450) 669-2784
Serious adverse event reporting	Miriam Abril Pharmacovigilance Project Leader Pharmalex Fax: +34 976 20 44 02 Tel: +34 976 20 44 00 Email: AelisSafety@pharmalex.com

12.2 Appendix 2: Safety laboratory tests

Serum chemistry	**Hematology (complete blood count)**
Albumin	Hematocrit
Alkaline phosphatase (ALP)	Hemoglobin
Alanine aminotransferase (ALT)	Mean corpuscular hemoglobin (MCH)
Aspartate aminotransferase (AST)	Mean corpuscular volume (MCV)
CO_2	Platelet count
Blood urea nitrogen (BUN)	Red blood cell count
Calcium	White blood cell count
Chloride	White blood cell differential (% and absolute)
Cholesterol, total	Basophils
Creatinine	Eosinophils
Creatine phosphate kinase (CPK)	Lymphocytes
Glucose	Monocytes
HDL cholesterol	Neutrophils
LDL cholesterol	
Phosphorus	
Potassium	
Sodium	
Total bilirubin	**Coagulation profile**
Total protein	Prothrombin time / international normalized ratio (INR)
Triglycerides	Activated partial thromboplastin time (aPTT)
Uric acid	
Complete urinalysis (dipstick)	**Urine drug screen (dipstick)**
Color and appearance	Amphetamines
pH and specific gravity	Benzodiazepines
Glucose	Barbiturates
Protein	Cannabinoids
Occult blood	Cocaine (metabolite)
Leukocytes	Opiates
Ketones	Methamphetamine
Bilirubin	Methadone
Urobilinogen	
Nitrite	**Breath test**
Microscopic examination (if abnormal blood or protein)	Alcohol
COVID-19 test	**Pregnancy test**
According to the site's standard procedure	Female participants regardless of child-bearing potential status Serum test at Screening; urine test at other time points

12.3 Appendix 3: Pharmacokinetic sample collection and shipment

PK blood sample for determination of plasma AEF0117 concentration: Processing, storage, and shipment

1. Pre-cool the collection tubes in an ice bath.
2. Collect PK blood samples to analyze plasma concentrations of AEF0117 using 7-mL lavender-top (Lithium Heparin) Vacutainer® evacuated collection tubes at the time points indicated in schedule of activities in section 1.3.
3. If blood samples are to be collected via an indwelling venous catheter, only the undiluted blood (i.e., not diluted by heparin or saline in the catheter) will be collected.
4. After obtaining the PK blood sample, gently mix evacuated collection tube thoroughly by slowly inverting the collection tube several times to mix the blood with the anticoagulant.
5. Place as soon as possible the collection tube in an ice bath.
6. Within 20 minutes of sample collection, process collection tubes in a refrigerated centrifuge set at approximately 2000 x g for 15 minutes at approximately 4 ± 2°C.
7. Transfer plasma in 2 aliquots of approximately equal volume of at least 1.2 mL, using standard laboratory technique, into 2 appropriately labeled polypropylene cryogenic storage tubes.
8. Secure labels to each storage tube using a strip of tape wrapped completely around the tube. Labels will include the following information: protocol or trial number, participant number (e.g., 101); trial treatment (e.g., Day), time of sample collection (e.g., 4h post dose), aliquot number etc., as applicable.
9. Store both plasma aliquots in a freezer set to maintain a temperature of approximately −70°C.
10. At times specified by the sponsor, ship one aliquot of each PK sample for analysis of AEF0117 with a 2-day supply of dry ice (on Mondays, Tuesdays, or Wednesdays only) to:

    Name, Title
    Biotrial Bioanalytical Services Inc.
    3885 Industriel Blvd.
    Laval (Quebec), Canada H7L 4S3

11. On the day of shipment, the trial site's staff will notify by email the sponsor (s.monlezun@aelisfarma.com) and bioanalytical laboratory (nick.diakoumakos@biotrial.com) of the pending shipment, including tracking information. The second aliquot will be shipped after receipt of the first aliquot has been confirmed by Biotrial Bioanalytical Services Inc.

Additional details will be provided in the laboratory manual.

PK blood sample for determination of plasma concentration of potential metabolites: Processing, storage, and shipment

Collection, processing, storage, and shipment of PK samples for determination of the metabolites will be performed as described above for AEF0117.

12.4 Appendix 4: High fat breakfast

A high fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food-effect bioavailability (BA) and fed bioequivalence (BE) studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.

An example test meal would be 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk. Substitutions in this test meal can be made as long as the meal provides a similar number of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity.

The composition of the meal should be recorded in the source document.

12.5 Appendix 5: Columbia-Suicide Severity Rating Scale

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 6 Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. <u>Lifetime</u> - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation*** <u>Past 6 Months</u> ***- Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____

Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide stop you (2) Deterrents probably stopped you you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not (5) Deterrents definitely did not stop (0) Does not apply	____	____
INTENSITY OF IDEATION		
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on and to end/stop the pain living with the pain or how you were feeling) (0) Does not apply	____	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better,*** ***get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Post Dose

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____

Most Severe

Type # (1-5) ***Description of Ideation***

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

INTENSITY OF IDEATION	
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Post Dose
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐

Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____