CLINICAL STUDY PROTOCOL: INDV-2000-101

Protocol Title: A Phase I, Double-blind, Placebo-controlled, Randomized, Single Ascending Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of INDV-2000 (C4X_3256) under Fasting and Fed Conditions in Healthy Volunteers

Protocol Number: INDV-2000-101

Original Protocol Date: 09 January 2020

Amendment Number/Date: Amendment 2/ 10 December 2020

NCT: NCT04413552

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Protocol Number:	INDV-2000-101
Product Name:	INDV-2000
Development Phase:	1
IND Number:	145881
Indivior Legal Registered Address:	Indivior 10710 Midlothian Turnpike, Suite 125 North Chesterfield, VA 23235 USA
Original Protocol Date:	09 January 2020
Amendment Number/Date:	Amendment 2 / 10 December 2020 Protocol Administrative Letter / 02 October 2020 Protocol Administrative Letter / 17 September 2020 Amendment 1 / 04 March 2020

CLINICAL PROTOCOL SIGNATURE PAGE

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Protocol Number:	INDV-2000-101
Protocol Version Number:	v 3.0
Protocol Version Date:	10 December 2020

This clinical study protocol was subject to critical review and has been approved by the appropriate protocol review committee of Indivior. The information contained in this protocol is consistent with:

The current risk-benefit evaluation of the investigational medicinal product.

The moral, ethical and scientific principles governing clinical research as set out in the principles of International Council on Harmonisation (ICH) E6 / Good Clinical Practice guidelines and according to applicable local laws and regulations.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational medicinal product.

[redacted]

STUDY PERSONNEL INFORMATION

INDV-2000-101: A Phase I, Double-blind, Placebo-controlled, Randomized, Single Ascending Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of INDV-2000 (C4X_3256) under Fasting and Fed Conditions in Healthy Volunteers

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to this investigational medicinal product (IMP) is the confidential and proprietary information of Indivior, and except as may be required by local laws or regulation, may not be disclosed to others without prior written permission of Indivior.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. My staff and/or I will conduct this study as outlined herein, in accordance with the regulations stated in the International Council on Harmonisation E6 / Good Clinical Practice guidelines and will make a reasonable effort to complete the study within the time designated.

I agree to ensure all associates, colleagues and employees delegated to assist with the conduct of the study are trained on this study protocol and amendments, other study-related materials and are qualified to perform their delegated tasks. I will provide all study personnel copies of the protocol and any amendments and grant access to all information provided by Indivior or specified designees. I will discuss the material with them to ensure that they are fully informed about the IMP and appropriate information throughout the study. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Signed:_____ Date:_____
DD-MMM-YYYY

Printed Name and Credentials:	
Title:	
Site Name:	
Telephone:	
Address:	

SYNOPSIS

Protocol Title:

A Phase I, Double-blind, Placebo-controlled, Randomized, Single Ascending Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of INDV-2000 (C4X_3256) under Fasting and Fed Conditions in Healthy Volunteers

Protocol Number:

INDV-2000-101

Rationale:

[redacted]

Pharmacological studies demonstrate that the orexin system has an important role in addiction, with a primary role for the OX1R. Literature evidence has shown that selectively antagonizing OX1R can successfully target a variety of substance use disorders, including opioid, cocaine, alcohol and nicotine (Mahler 2012).

[redacted]

Target Population:

Healthy male and non-childbearing potential female subjects aged 18 to 55 years, body mass index (BMI) 18.0 to 32.0 kg/m^2.

Number of Subjects:

Part I: Each of the up to 9 planned dosing cohorts will be composed of 8 subjects (6 receiving active drug and 2 placebo).

Additional cohorts may be included but predicted exposures will not exceed the maximum exposure limits defined.

Part II: 8 male subjects will receive INDV-2000 on 2 occasions separated by a 1-week washout period or at least 5 half-lives, whichever period is longer, once under fasting conditions and once after a standard high-fat breakfast.

If no clinically significant treatment-related toxicity is observed, and the study is completed as planned per protocol, the maximum number of completed subjects involved in the different study parts is: Part I: Total of up to 72 male and female subjects; Part II: 8 male subjects.

Duration of Treatment:

Part I: The study will be a single ascending dose (SAD) study with each dose administered in the morning of Day 1, followed by a residential period that concludes on Day 4 after assessments are completed, except in cases where the residence is extended due to safety concerns as determined by the Principal Investigator (PI) in consultation with the study Medical Monitor. An end-of-study (EOS) visit will be performed 7 days after discharge from the in-patient unit (Day 11). The time from Screening to the EOS Visit is 39 days per cohort in Part I, inclusive of the Screening window.

Part II: The study will be a cross-over, single-dose study with 2 treatment periods. Admission will occur on Day -1, followed by dosing (Day 1), and a washout period of at least 1 week or at least 5 half-lives between dosing. The duration of the washout period could be adapted based on the review of pharmacokinetic (PK) data of INDV-2000 collected in Part I. Subjects will be discharged on Day 2 unless tolerability from Part I indicates a longer stay is warranted. If that is the case, subjects will stay in the clinical unit until Day 4. If discharged on Day 2, subjects will return to the clinical unit on Day 3 and Day 4 for PK testing. Depending on PK results from Part I, the visit schedule may be modified. An EOS visit will be performed on Day 10 of the last Treatment Period (Period 2). The time from Screening to the EOS Visit is approximately 45 days, inclusive of the Screening window.

Objective(s):

The primary objective of this study is to:

- Determine the safety and tolerability of INDV-2000 over a proposed range of doses from 1mg up to a maximum exposure no greater [redacted]

The secondary objectives of this study are to:

- Determine the maximum tolerated single dose of INDV-2000
- Characterize pharmacokinetics for single doses of INDV-2000

- Determine potential effects of a high-fat meal on drug absorption and exposure.

Study Design:

The First-in-Human (FIH) SAD study will be conducted in 2 parts:

Part I: Double-blind, placebo-controlled, randomized, single ascending dose study with INDV-2000 in fasted condition.
The proposed doses will be: 1 mg, 5 mg, 20 mg, 50 mg and 120 mg with subsequent cohorts predicted to provide exposures no greater than the mean no observed adverse effect exposure (AUC) in the 28-day repeat dose toxicology study conducted in the most sensitive species (dog). At doses of 1 mg, 5 mg, 20 mg, 50 mg and 120 mg ,dose escalation factors will be dependent upon observed safety, tolerability and PK, [redacted]

A key goal for Part I is to identify the maximum tolerated (MTD) single dose. In each cohort, a sentinel group of 2 subjects will be randomized to active or placebo (1 active; 1 placebo) and will be dosed ahead of the rest of each cohort. A review of sentinel group safety data for 24 hours after dosing will be completed before dose administration will continue in the remaining 6 subjects (5 active; 1 placebo) of each cohort.

Dose escalation decisions between cohorts will be based on a review of safety data up to 72 hours post-dose, particularly Treatment-Emergent Adverse Events (TEAEs), vital signs, electrocardiography (ECGs), clinical laboratory test results and PK data.

Part II: Open, cross-over, food interaction, single-dose study with INDV-2000, which will be given once under fasting conditions and once at completion of a standard Food and Drug Administration (FDA) High-Fat Breakfast.

Part II will proceed based upon an acceptable safety evaluation of Part I. The dose studied will be a well-tolerated dose studied in Part I and not exceeding the second highest tolerated dose in Part I.

Primary Endpoint(s):

Safety and tolerability of single doses of INDV-2000 as determined by adverse event reporting.

Secondary Endpoint(s):

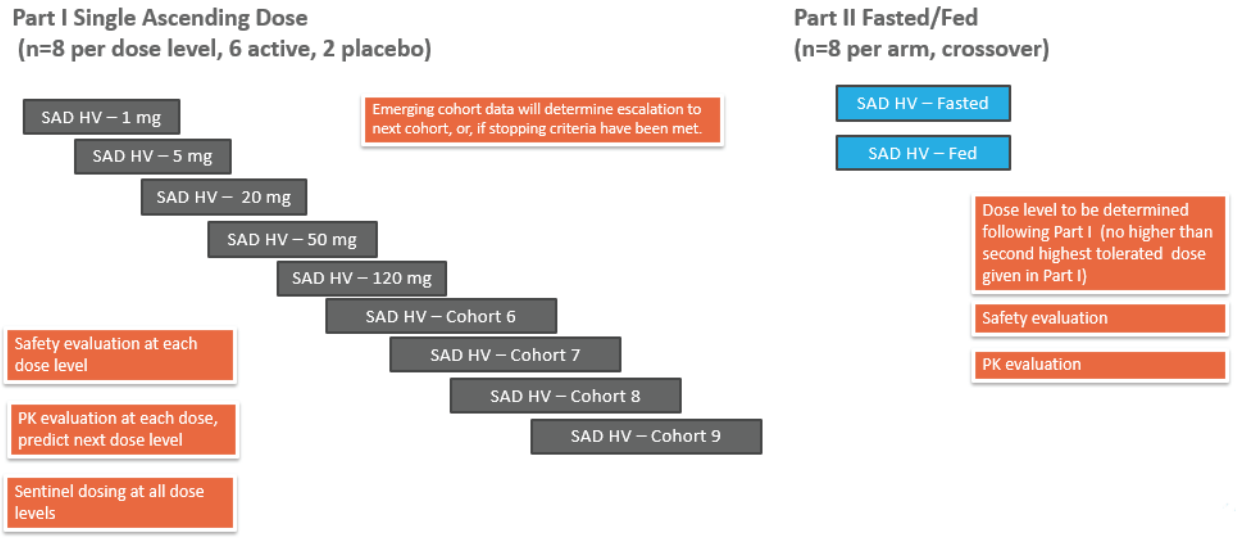
- Clinical safety assessments
  - laboratory results
  - electrocardiogram (ECG) findings
  - vital sign measures

- physical examination
- Plasma PK parameters of single doses of INDV-2000
  - C_{max} (Maximum concentration)
  - T_{max} (Time to reach maximum (peak) plasma concentration following drug administration)
  - AUC_{0-t}, $AUC_{0-\infty}$
  - CL/F
  - Plasma terminal half-life ($t_{1/2}$)

[redacted]

STUDY SCHEMATIC

Figure 1 Proposed Study Schematic- Part I and II



a=active, p=placebo, HV=healthy volunteers; SAD=Single ascending dose

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List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration versus time curve
BMI	Body mass index
C_{max}	Maximum concentration
CNS	Central Nervous System
CRF	Case Report Form
CSR	Clinical Study Report
CYP	Cytochrome P_{450}
DBP	Diastolic blood pressure
DRSC	Data Review and Safety Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
FIH	First-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface Antigen
hERG	Human Ether-a-Go-go Related Gene
HIV	Human immunosufficiency virus
IB	Investigator Brochure
IC_{50}	Half-maximal inhibitory concentration
ICF	Informed Consent
ICH	International Committee on Harmonisation
ID	Identification
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
LC	Locus coeruleus
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum well-tolerated
NOAEL	No Observed Adverse Effect Level
OUD	Opioid use disorder
OX1	Orexin-1
OX2	Orexin-2
OX1R	Orexin-1 receptor
OX2R	Orexin-2 receptor
PD	Pharmacodynamic(s)
PI	Principal Investigator
pIC_{50}	Negative log of IC_{50}

PK	Pharmacokinetic(s)
QA	Quality Assurance
QTcF	QT interval corrected with Fridericia's formula
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SOC	System Organ Class
SOP	Standary Operating Procedures
SUSAR	Suspected unexpected serious adverse reaction
$T_{½}$	Elimination half-life
T_{max}	Time to reach maximum (peak) plasma concentration following drug administration
TEAE	Treatment-Emergent Adverse Events
TESAE	Treatment-Emergent Serious Adverse Events
UDS	Urine drug screen
ULN	Upper Limit of Normal
VAS	Visual Analog Scale

1 INTRODUCTION AND RATIONALE

1.1 Background and Introduction

Orexin-A and Orexin-B are neuropeptides, also known as hypocretins, that regulate arousal, wakefulness, feeding and motivation (De Lecea 1998, Sakurai 1998). Orexin-A and Orexin-B are produced from a precursor polypeptide, prepro-orexin, by enzymatic cleavage. The orexin peptides are agonists of 2 G-protein coupled receptors (GPCRs): the Orexin-1 receptor (OX1R) and Orexin-2 receptor (OX2R). The OX1R has much higher affinity for Orexin-A compared to Orexin-B, whereas these 2 neuropeptides are equipotent at the OX2R (Sakurai 1998). Orexin-A is completely conserved across several mammalian species including human, rat and dog.

In humans, the OX1R is expressed predominantly in the brain (HCRTR1 2009) and in rat differential expression of the Orexin-1 and -2 receptors across brain regions has been demonstrated (Trivedi 1998, Marcus 2001). The OX1 and OX2 receptors are highly conserved across mammalian species with 94% identity at the amino acid level between humans and rats (Sakurai 1998). A limited number of coding and non-coding genetic variants of the OX1R have been identified but no clear functional impact or linkage to disease has been demonstrated (Thompson 2014). Both OX1R and OX2R are coupled to Gq/11 proteins that activate the Phospholipase C/Inositol Phosphate IP3 pathway, leading to a transient increase of intracellular calcium (Kukkonen 2013).

Studies in rats have shown that prepro-orexin is expressed exclusively in the lateral hypothalamic (LH) region and that orexin neurons project to multiple brain regions including the paraventricular nucleus of the hypothalamus (PVH), the amygdala, the locus coeruleus (LC), ventral tegmental area (VTA) and the nucleus accumbens (NAcc) (Peyron 1998). The orexin neurons in the lateral hypothalamus become activated by cues associated with the reward system such as drugs and food (Harris 2005). Stimulation of rat LC neurons with Orexin-A causes membrane depolarization and increased action potential firing, leading to increased neuronal excitability, an effect blocked by SB334867, an OX1R antagonist tool compound (Soffin 2002). The number of Orexin-A-producing neurons are increased in the brains of individuals with heroin dependence and in mice after long-term administration of morphine (Thannickal 2018). Antagonism of the OX1R inhibits addiction-related behaviors in rodent nonclinical models including self-administration, relapse to drug-seeking and withdrawal (Mahler 2012, Zarrabian 2018). Hence it is hypothesized that OX1R antagonists should show clinical benefit in the treatment of substance use disorders including opioid use disorder (OUD) by reducing craving, relapse and symptoms of withdrawal.

In addition to its role in addiction, Orexin-A has been shown to induce panic and anxiety-like behaviors in the rat which can be inhibited by OX1R antagonists (Johnson 2010, Bonaventure 2017). The OX1R may therefore play a role in anxiety.

1.2 Study Rationale

[redacted]

[redacted]

Literature evidence has shown that selectively antagonizing OXTR can successfully target a variety of substance use disorders, including opioid, cocaine, alcohol and nicotine (Mahler 2012).

[redacted]

This First-in-Human (FIH) study will be carried out in accordance with the protocol and with local legal and regulatory requirements, International Committee on Harmonisation (ICH)/GCP (Good Clinical Practice) and all applicable subject privacy requirements.

1.3 Dose Rationale

The planned starting dose in this FIH clinical study is 1 mg.

[redacted]

[redacted]

1.4 Pharmacokinetics (PK)

Pharmacokinetics of INDV-2000 in humans have not been characterized yet. This proposed FIH study will characterize PK of INDV-2000 in humans.

[redacted]

1.5 Nonclinical Pharmacology

[redacted]

[redacted]

Summaries of the nonclinical pharmacology with INDV-2000 are in the Investigator's Brochure (IB).

1.6 Risk-Benefit Assessment

Summaries of the nonclinical studies conducted with INDV-2000 are presented in the IB.

This FIH clinical study proposal contains risk mitigation features based on the nonclinical findings with INDV-2000.

[redacted]

The proposed FIH study contains extensive monitoring of cardiovascular events at all dose levels including vital signs and 12-lead ECG determinations at 8 timepoints over the 72 hours following dosing as well as at the end-of-study (EOS) visit, and 26 hour ECG Holter monitoring.

[redacted]

Standard laboratory, urinalysis, blood chemistry, hematology and serology tests will also be conducted throughout the course of the study.

1.7 Benefit Assessment

There is no expected benefit for the healthy subjects from taking part in this study. The development of a product to treat OUD will be of benefit to the wider community.

2 STUDY OBJECTIVES

2.1 Primary

The primary objective of this study is to:

- Determine the safety and tolerability of INDV-2000 over a proposed range of doses from 1 mg up to to a maximum exposure no greater [redacted]

2.2 Secondary

The secondary objectives of this study are to:

- Determine the maximum tolerated single dose of INDV-2000
- Characterize pharmacokinetics for single doses of INDV-2000
- Determine potential effects of a high-fat meal on drug absorption and exposure

3 STUDY ENDPOINTS

3.1 Primary

Safety and tolerability of single doses of INDV-2000 as determined by adverse event (AE) reporting.

3.2 Secondary

- Clinical safety assessments
  - laboratory results
  - electrocardiogram (ECG) findings
  - vital sign measures
  - physical examination
- Plasma PK parameters of single doses of INDV-2000
  - C_{max}
  - T_{max} (Time to reach maximum (peak) plasma concentration following drug administration)
  - AUC_{0-t}, $AUC_{0-\infty}$
  - CL/F
  - Plasma terminal half-life ($t_{1/2}$)

3.3 Exploratory Endpoints

[redacted]

4 STUDY PLAN

4.1 Study Design

This study will be conducted in 2 parts:

Part I: Double-blind, placebo-controlled, randomized, single ascending dose (SAD) study with INDV-2000 in fasted condition.

Healthy subjects who meet all eligibility criteria and provide informed consent will be randomized in cohorts of 8 subjects, with 6 subjects receiving active drug and 2 subjects receiving placebo. The proposed doses will be: 1 mg, 5 mg, 20 mg, 50 mg and 120 mg, with subsequent cohorts predicted to provide exposures no greater [redacted] At doses of 1 mg, 5 mg, 20 mg, 50 mg and 120 mg ,dose escalation factors will be dependent upon observed safety, tolerability and PK, but in no case will the incremental predicted exposure between doses be greater than the previous incremental factor or be in excess of the maximum exposure limits defined based on NOAEL exposures. [redacted] A key goal for Part I is to identify the maximum well-tolerated (MTD) single dose. A sentinel group of 2 subjects will be randomized to active or placebo (1 active; 1 placebo) and will be dosed ahead of the rest of each cohort. A review of sentinel group safety data for 24 hours after dosing will be completed before dose administration will continue in the remaining 6 subjects (5 active; 1 placebo) of each cohort (Section 15.2).

Dose escalation decisions between cohorts will be based on a review of available safety data up to 72 hours post-dose, particularly Treatment-Emergent Adverse Events (TEAEs), vital signs, ECGs, clinical laboratory test results and PK data.

Part II: Open, cross-over, food interaction, single-dose study with INDV-2000, which will be given once under fasting conditions and once at completion of a standard FDA High-Fat Breakfast.

Healthy males (n=8) who meet all eligibility criteria and provide informed consent will receive drug under fed and fasting conditions . Part II will proceed based upon an acceptable safety evaluation of Part I. The dose studied will be a well-tolerated dose studied in Part I and not exceeding the second highest tolerated dose in Part I.

A schematic depicting the study design is in Figure 1.

4.2 Schedule of Events

A complete list of procedures and assessments are located in the Schedule of Events tables in Section 22.1, Appendix 1 for Part I and Section 22.2, Appendix 2 for Part II of the study.

4.3 Duration of Treatment

Part I: The study will be a SAD study with subjects admitting to the clinic on Day -1, and dosing on Day 1, followed by a residential period that concludes on Day 4 after assessments are completed, except in cases where the residence is extended due to safety concerns determined by the Investigator in consultation with the study Medical Monitor. An EOS visit will be performed 7 days after discharge from the in-patient unit (Day 11). The time from Screening to the EOS Visit is 39 days per cohort in Part I, inclusive of the Screening window.

Part II: The study will be a cross-over, single-dose study with 2 treatment periods. Admission will occur on Day -1, followed by dosing (Day 1), and a washout period of at least 1 week or at least 5 half-lives between dosing, whichever period is longer. The duration of the washout period could be adapted based on the review of PK data of INDV-2000. Subjects will be discharged on Day 2 unless tolerability from Part I indicates a longer stay is warranted. If that is the case, subjects will stay in the clinical unit until Day 4. If discharged on Day 2, subjects will return to the clinical unit on the morning of Day 3 and Day 4 for PK testing. Depending on PK results from Part I, the visit schedule may be modified. An EOS visit will be performed on Day 10 of the last Treatment Period (Part II, Period 2). The time from Screening to the EOS Visit is approximately 45 days, inclusive of the Screening window.

5 STUDY POPULATION SELECTION

5.1 Number of Subjects

A sufficient number of subjects will be screened to enroll up to 80 subjects in Part I and Part II.

Part I: There will be up to 9 planned cohorts of male and non-childbearing potential female subjects. Each of the up to 9 planned cohorts will be composed of 8 subjects (6 receiving active and 2 placebo). Additional cohorts may be included but predicted exposures will not exceed the maximum exposure limits defined. Up to 72 male and female subjects will be enrolled in Part I.

Part II: Up to 8 male subjects will receive INDV-2000 on 2 occasions separated by a 1-week washout period or at least 5 half-lives whichever period is longer, once under fasting conditions and once after a standard high-fat breakfast.

5.2 Inclusion Criteria

In order to participate in Part I or Part II of the study, subjects must meet the following criteria:

1. Must be able to verbalize understanding of the consent form, able to provide written informed consent, and verbalize willingness to complete study procedures, be able to comply with protocol requirements, rules and regulations of study site, and be likely to complete all the study interventions.
2. Must be considered a healthy male or non-child-bearing female for Part I.

Women of non-childbearing potential are considered women who:
   a. Do not have a uterus, or
   b. Are surgically sterile (example: has undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation), or
   c. Have permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries, or
   d. Are post-menopausal as defined by 12 months or more of spontaneous amenorrhea as confirmed by an FSH >30 mIH/mL.

3. For Part II, must be considered a healthy male who did not participate in Part I who is willing to consume a high-fat meal.
4. Between 18 and 55 years of age inclusive,
5. Body mass index (BMI) within 18.0 to 32.0 kg/m^2, inclusive (minimum weight of at least 50.0 kg at Screening).
6. Male subjects who are sexually active with female partners of child-bearing potential must use, with their partner, a condom plus an approved method of effective contraception from the time of screening until 90 days after the last dose of Investigational Medicinal Product (IMP). Additionally, male subjects must agree to not donate sperm during the study and for at least 90 days from the last dose of IMP. Effective methods of contraception are:
   a. Combined (oestrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

i. oral
ii. intravaginal
iii. transdermal

b. Progestogen-only hormonal contraception:
i. oral
ii. injectable/implantable
iii. intrauterine hormone-releasing system (IUS)

c. Implantable intrauterine device (IUD)
d. Surgical sterilisation (for example, vasectomy or bilateral tubal ligation)
e. Male condom with spermicidal gel/foam or with female cap or diaphragm (double barrier)

5.3 Exclusion Criteria

In order to participate in Part I or Part II, subjects must not meet any of the following criteria:

1. Have a medical history of clinically significant neurological, cardiovascular, renal, hepatic, chronic respiratory or gastrointestinal disease, or psychiatric disorder as judged by an Investigator,
2. Have clinically significant abnormal biochemistry, hematology or urinalysis results as judged by an Investigator,
3. Have a history of narcolepsy or other significant sleep disorders
4. Have disorders that may interfere with drug absorption, distribution, metabolism and excretion (ADME) processes,
5. Positive test results for human immunosufficiency virus (HIV)-1/HIV-2 Antibodies, Hepatitis B surface Antigen (HBsAg) or Hepatitis C Antibody (HCVAb).
6. Serious cardiac illness or other medical condition including, but not limited to:
   a. Uncontrolled arrhythmias
   b. History of congestive heart failure (CHF)
   c. Myocardial infarction <6 months from receipt of first dose of IMP
   d. Uncontrolled symptomatic angina
   e. Corrected QT value (QTcF) >450 msec for males and >470 msec for females or history of prolonged QT syndrome.
   f. Have a blood pressure reading outside of the following range: Systolic <86 or >149 mmHg; Diastolic <50 or >94 mmHg
7. Current active hepatic or biliary disease. Subjects with cholecystectomy <90 days prior to screening.
8. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, 25 mL of 40% spirit or a 125 mL glass of wine).
9. Positive test result for alcohol and/or drugs of abuse at screening or prior to the first IMP administration.

10. Current smokers and those who have smoked within the last 90 days. Current users of e-cigarettes and nicotine replacement products, and those who have used these products within the last 90 days.
11. Concurrent treatment or treatment with an investigational drug within 30 days prior to the first dose.
12. Blood donation of approximately 500 mL within 56 days or plasma donation within 7 days of screening.
13. Subjects who are taking, or have taken, any prescribed or over-the-counter drugs (other than 2 g per day acetaminophen, hormone replacement therapy [HRT], hormonal contraception) or herbal remedies in the 14 days before IMP administration. Exceptions may apply on a case by case basis if considered not to interfere with the objectives of the study, as agreed by an Investigator and Sponsor's Medical Monitor.
14. Any consumption of food or drink containing poppy seeds, grapefruit or Seville oranges within 7 days prior to the IMP administration
15. Treatment with any known drugs that are moderate or strong inhibitors/inducers of cytochrome P450 (CYP) 3A4 within 30 days prior to first dose of IMP.
16. Known allergy or hypersensitivity to IMP or its excipients.
17. Any condition that, in the opinion of an Investigator, would interfere with evaluation of the IMP or interpretation of subject safety or study results.
18. Affiliated with, or a family member of, site staff directly involved in the study, or anyone with a financial interest in the outcome of the study.
19. Subjects who are unable, in the opinion of an Investigator, to comply fully with the study requirements.

5.4 Day -1 Check-In Criteria

Upon passing screening and meeting inclusion and not meeting exclusion criteria, the subject will present to the clinic on Day -1.

Part I and Part II (both periods, fasting and fed)

The following criteria must be met at Day -1 for the subject to be enrolled in the study.

1. Female subjects must have a negative urine pregnancy test.

2. Subjects must not have a Corrected QT value (QTcF) >450 msec for males and >470 msec for females.

3. Subjects must have a negative result obtained from the urine drug screen (UDS) and the alcohol test (urine ethanol).

    a. Subjects who have a positive result for alcohol will be asked to refrain from alcohol and return the next day for retest. This may only occur once.

If any of these criteria are not met, the subject will not be enrolled and randomized in Part 1, or will not be enrolled in Part II, Period 1 – Dosing Under Fasting Conditions, or will not be allowed to move forward into Part II – Dosing after High-Fat Content Meal.

5.5 Deviation from Inclusion/Exclusion Criteria

This study is intended to be conducted as described in this protocol. Waivers from inclusion and exclusion criteria are not allowed because they have the potential to jeopardize subject safety, the scientific integrity of the study or regulatory acceptability of the data. Indivior does not grant waivers to the protocol-defined inclusion and exclusion criteria, and strict adherence to these criteria as outlined in the protocol is essential. The Principal Investigator (PI), sub-Investigator or suitably qualified designee will be responsible for identifying, documenting and reporting all deviations, which are defined as isolated occurrences involving a procedure that did not follow the study protocol or study-specific procedure. In the event of a major deviation from the protocol due to an emergency, accident or mistake (e. g., eligibility or dosing errors), the PI, sub-Investigator or suitably qualified designee must contact the Indivior Medical Monitor at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the Investigator and the Sponsor. Deviations will be reported as required to the Institutional Review Board (IRB) per their reporting process and criteria, and in the final study report.

Protocol deviations will be identified and documented through programmatic checks of study data, as well as through review of selected subject data listings prior to database lock.

6 STUDY CONDUCT

6.1 Subject Enrollment

Study participation begins once written informed consent is obtained; a subject identification (ID) is then randomly assigned. The subject ID will be used to identify the subject during the screening process and throughout study participation, if applicable.

The Investigator is responsible for maintaining a master list (i.e., a subject ID list) of all consented subjects .This document will be reviewed by Indivior or designated representative for accuracy and completeness. Ineligible subjects, as defined by the protocol-specific inclusion and exclusion criteria, should not receive IMP and should be documented as screen failures.

6.2 Screen Failure

A subject will be considered a screen failure if written informed consent is obtained but the subject did not meet inclusion or exclusion criteria. The study site will keep a Screening Log documenting subjects who have signed an informed consent. Screen failure reasons will be documented on the Screening Log as well as collected in the electronic case report form (eCRF).

6.3 Subject Completion

A completed subject is one that has completed the EOS visit. The end of the study is defined as the last subject's last visit.

6.4 Dose Escalation and Stopping Criteria

6.4.1 Dose Escalation Criteria

Data Review and Safety Committee (DRSC, See Section 15.2) will review data from cohorts, and will determine if the dose can be escalated, or alternatively if any stopping criteria have been met.

[redacted]

Stopping Criteria

The study will be paused pending evaluation of all available data by the DRSC, if any of the criteria listed below are fulfilled for an individual dosing cohort:

AEs:

[redacted]

Laboratory Abnormalities:

[redacted]

Vital Signs:

[redacted]

ECG Criteria:

[redacted]

6.5 Subject Withdrawal from the Study

If the subject has permanently discontinued study treatment and is no longer being followed for study assessments and procedures (including follow-up procedures), he/she will be considered withdrawn from the study. The primary reason for withdrawing from the study must be entered into the eCRF (e.g., subject is lost to follow-up, Indivior terminates the study or Investigator discretion).

If a subject wishes to leave the study at any time, they will be permitted to do so. Every reasonable effort will be made to complete the Early Termination (ET) assessments and procedures. The primary reason for withdrawing from the study must be entered into the eCRF (e. g., subject is lost to follow-up, Indivior terminates the study or Investigator discretion). For any subject who withdraws from the study, every effort will be made to ensure the subject completes EOS/ET procedures.

For a subject who discontinues due to an AE, see Section 10.1.1 for follow-up procedures. Any subject withdrawn or discontinuing the study after being dosed will not be replaced.

Subjects can be withdrawn from the study for the following reasons:

- Pregnancy
- Termination of the study
- Upon the subject's request (withdrawal of consent)
- Significant deviation from the protocol
- Concurrent illness or requirement for prohibited medication
- At the discretion of the Investigator

6.5.1 Subject Withdrawal of Consent

If a subject withdraws consent, the subject will not receive any additional doses of study drug in Part II. However, the subject may be offered additional tests as needed to monitor their safety (e.g., EOS safety assessments or procedures).

6.5.2 Subjects Lost to Follow-up

In cases of a missed visit, the Investigator or designee must attempt to contact the subject and re-schedule as soon as possible. The Investigator or designee must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

In the event a subject is lost to follow-up, the Investigator or designee must make a reasonable effort to contact the subject. Two documented attempts (e. g., phone, email, etc.) to contact the subject followed by a certified mailed letter is considered reasonable.

For the purpose of documenting date of discontinuation for a subject confirmed to be lost to follow-up, the date of discontinuation should be the date of last contact with the subject.

In the case where a certified letter is sent but not confirmed as received by the subject, the date of discontinuation is the date the certified letter was sent.

In the case where a certified letter is sent and has been confirmed as received by the subject, the date of discontinuation is the date of the confirmed subject receipt.

In the event that neither of these above cases applies (which should be explained in the source documents), the date of discontinuation is the date of the subject's last study visit.

7 STUDY SUSPENSION OR TERMINATION

Indivior reserves the right to temporarily suspend and/or permanently discontinue the study at any time and for any reason, including safety or ethical concerns or severe noncompliance. If such action is taken, Indivior will discuss the rationale for the decision with the PI. In cases where a study is suspended or terminated for safety reasons, Indivior will promptly inform Investigators and the Regulatory Authorities of this action and the reason(s) for the suspension or termination.

If required by applicable regulations, the Investigator must inform the IRB promptly and provide the reason(s) for the suspension or termination. If the study is prematurely discontinued, all study data and drug substance remaining on-site will be returned to Indivior or its designated representative.

8 DESCRIPTION OF STUDY PROCEDURES

Study assessments and procedures, including the timing of assessments, are summarized in Schedule of Events tables for Part I and Part II (Section 22.1, Appendix 1 and Section 22.2, Appendix 2). Further details on safety and PK assessments are provided in Section 14.7 and Section 14.4, respectively.

See Section 0 for description of AE procedures.

8.1 Informed Consent

A signed written ICF (Informed Consent Form) must be obtained from the subject or a legal representative before any study assessments or procedures may be performed. The potential subject will be given the IRB-approved ICF to review and will have the opportunity to ask questions concerning the study until he or she is satisfied. The potential subject should be able to answer simple questions about the study after the ICF has been reviewed and explained. After this explanation, the potential subject will be asked to sign and date the written ICF. The PI or designee obtaining informed consent from the subject will also sign the ICF to confirm that consent has been obtained as required. A copy of the signed ICF will be given to the subject.

8.2 Demographics and Medical History

The following demographic information will be captured: sex, race, date of birth, ethnicity, height, weight and BMI.

A detailed medical history will be obtained during the screening period. This will include information regarding the subject's complete history of relevant medical conditions, diagnoses, procedures, treatments and any other noteworthy medical information. Any updates to medical history information made available during the course of the study will be captured.

8.3 Physical Examination

At Screening, a complete physical examination will include an assessment of general appearance, skin and extremities, head and neck, lymph nodes, eyes, ears, nose, throat, thyroid, neurological system, lungs, cardiovascular system, and abdomen (liver and spleen). The physical exam will not include a breast, pelvic or rectal examination unless clinically indicated.

After the screening period, brief physical examinations will occur [redacted]

Any clinically significant abnormalities, including changes from baseline, must be reported as AEs.

8.4 Body Weight

The subject's body weight will be measured as detailed in Section 22.1 Appendix 1 and Section 22.2 Appendix 2.

8.5 Vital Signs

Blood pressure, heart rate, respiratory rate and temperature will be measured by automated recorders after the subject has been in a semi-recumbent position for a minimum of 3 min according to the time schedule presented in the Schedule of Events tables (Section 22.1, Appendix 1 and Section 22.2, Appendix 2). The mean of the triplicate measures of blood pressure will define baseline SBP and DBP at the pre-dose timepoint.

If a subject shows an abnormal assessment at any stage, repeat measurements may be made, and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the Investigator.

Any clinically significant abnormalities, including changes from baseline, must be reported as AEs.

8.6 12-Lead Electrocardiograms

A 12-lead ECG will be recorded after the subject has been in the semi-recumbent position for a minimum of 5 minutes as presented in the Schedule of Events tables (Section 22.1. Appendix 1 and Section 22.2, Appendix 2).

A triplicate ECG will be recorded for the determination of the baseline result at pre-dose. The baseline value will be the mean of the 3 recordings. If a potentially clinically significant abnormality is noted during other ECG assessments, a triplicate ECG will be taken at that timepoint. All triplicate ECG recordings should occur at least 1 minute apart. If a subject shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution, if required. Additional measurements may be taken as deemed necessary by the Investigator.

Any clinically significant abnormalities, including changes from baseline, will be reported as AEs.

8.7 26 Hour Holter Monitoring

Continuous 12-lead ECG tracings will be recorded on Day 1 from at least 2 hours pre-dose until at least 24 hours post-dose. [redacted]

Subjects should be semi-recumbent for at least 10 minutes prior to the following time points: Part 1: At 3 time points prior to dosing, e.g., -45, -30 and -15 minutes, and then at 0.5, 1, 2, 3, 4, 6, 8, 12 hours post-dose; Day 2 (24 hours post-dose). Part II: At 3 time points prior to dosing,

e.g., -45, -30 and -15 minutes, and then at 0.5, 1, 2, 3, 4, 6, 8, 12 hours post-dose; Day 2 (24 hours post-dose). All extractions should occur within ± 15 minutes of the nominal PK timepoint. At time points with multiple activities, the preferred order of events is as follows: Holter extraction, safety ECG, vitals, PK collection. The PK collection takes precedence for being scheduled at the nominal time point.

[redacted]

8.9 Clinical Laboratory Tests

Clinical laboratory tests will be performed at the time points listed in Section 22.1 and Section 22.2 in a licensed clinical laboratory. A serum pregnancy test will be conducted at screening, while all remaining pregnancy tests will be urine pregnancy tests performed using a licensed test (dipstick). Subjects are to be in a seated or semi-recumbent position during blood collection.

The following clinical laboratory tests (Table 1) will be performed according to the Schedule of Events tables in Section 22.1, Appendix 1 and Section 22.2, Appendix 2:

Table 1 List of Laboratory Tests

Hematology	**Serum Chemistry:**
Hematocrit	Albumin
Hemoglobin	Alkaline phosphatase
Mean corpuscular hemoglobin	Alanine aminotransferase (ALT)
Mean corpuscular hemoglobin concentration	Amylase
Mean corpuscular volume	Aspartate aminotransferase (AST)
Platelet count	Blood urea nitrogen
Red blood cell count	Calcium
White blood cell count with differential (absolute count)	Carbon dioxide
	Chloride
	Creatinine
Urinalysis:	Creatine kinase
Appearance	Gamma-glutamyl transferase
Bilirubin	Glucose (non-fasting)
Color	Lactate dehydrogenase
Glucose	Lipase
Ketones	Magnesium
Leucocyte esterase	Phosphorus

Microscopic examination of sediment[a]	Potassium
Nitrite	Sodium
Occult blood	Total bilirubin
pH	Direct bilirubin
Protein	Total cholesterol
Specific gravity	Total protein
Urobilinogen	Triglycerides
Hormone Panel:	**Urine Drug Screen (UDS):**
Follicle Stimulating Hormone	Opioids
	Cocaine
Pregnancy:	Amphetamines
Serum hCG	Cannabinoids
	Barbiturates
Screening Only:	Benzodiazepines
Hemoglobin A1c	Methamphetamine
Hepatitis B surface Antigen	Phencyclidine
Hepatitis C Antibody	Ethanol
HIV-1 and -2 antibodies	
Prothombin Time (PT) with INR	
PTT	

Anti-HIV = human immunodeficiency virus antibodies; hCG = human chorionic gonadotropin; INR = international normalized ratio; PT = prothrombin time; and PTT = partial thromboplastin time.

[a] Microscopic examination of sediment will be performed only if the results of the urinalysis evaluation are positive (microscopic examination may include but is not limited to White Blood Cell count, Red Blood Cell count, casts and crystals).

8.9.1 Sample Collection, Storage and Shipping

Details for the collection, preparation, storage and shipment of centrally tested laboratory specimens will be outlined in the laboratory manual(s).

8.10 Pharmacokinetic Assessments

8.10.1 Plasma Samples for Pharmacokinetic Analysis

Blood samples for PK analysis of INDV-2000 [redacted] metabolite [redacted] will be collected at the time points listed in Section 22.4, Appendix 4. Depending on PK results from the first dose levels, up to 2 additional samples may be added or the schedule of samples may be modified. Approximately 14 blood samples of 6 mL per sample for PK in total will be taken from any subject, however, it could be more if the subject experiences an SAE, or requires their

sample(s) retaken. The actual date and time of each sample collection will be documented. Samples will be collected into appropriate tubes as specified by the bioanalytical laboratory. Details of sample tubes, processing, storage and shipping procedures are provided in the Laboratory Manual.

Additional PK samples may be collected for subjects who experience a SAE. Samples should be collected as soon as the Investigator is made aware of the SAE and additional blood samples may be collected, after a period of time, to confirm resolution of the SAE.

[redacted]

8.10.3 Sample Analysis

Concentrations of INDV-2000 and [redacted] in plasma [redacted] will be determined using the validated bioanalytical methodology.

[redacted]

8.11 Appropriateness of Measurements

The clinical data measures to be employed in this study are standard, generally accepted measures used for decision-making in clinical practice.

[redacted]

The conventional safety assessments that will be used in this study are suitable, standard and widely used measures for evaluating the safety of the study drug. Measurement of drug levels in plasma [redacted] over time is a standard evaluation of PK parameters.

8.12 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or ICH/GCP requirements. The noncompliance may be either on the part of the subject, the Investigator or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly and in accordance with ICH E6 Good Clinical Practice guidelines. It is the responsibility of the Investigator and study site staff to use continuous vigilance to identify and report deviations to Indivior or specified designee and the IRB per the IRB's reporting requirements. The Investigator and study site staff are responsible for knowing and adhering to

the IRB's requirements. Protocol deviations must be documented and will be included in the final study report.

8.13 Order of Procedures

Acceptable windows for assessment timepoints are located in the footnotes of the Schedule of Events tables, Section 22.1 Appendix 1 and Section 22.2 Appendix 2.

It is recommended that on days/times with multiple assessments, the assessments are completed in the following order, when applicable.

- ECG
- Vital signs
- Plasma PK
- PD assessments as applicable to Part I [redacted]

9 STUDY DRUG MANAGEMENT

9.1 Description

INDV-2000 is intended for oral administration and will be dosed as either a powder in solution [redacted] or a powder in capsule [redacted]

Indivior will provide drug substance to the clinic pharmacy and the required dosages and matching placebos will be prepared by the study site per site procedures in compliance with USP <795>, Pharmaceutical Compounding- Nonsterile Preparations and the Pharmacy Manual.

The term 'study drug' describes both drug product and placebo and is received by the subject as per the protocol design.

9.1.1 Drug Substance Manufacturer

Drug substance is manufactured in accordance with current Good Manufacturing Practices (GMP) at the following facility:

[redacted]

9.1.2 Placebo

Placebo formulations will be prepared by the study site to visually match each of the required study drug dosages.

[redacted]

9.1.3 Blinding and Randomization

Part I of this study will be double-blinded to include the subjects, the Investigator and the Sponsor [redacted]

Active drug assignment will not be known to the subjects, the clinical site staff who are involved in the clinical evaluation of the subjects and the analysis of data or the dosing team. The randomization schedule and disclosure envelopes will be generated by an unblinded statistician. The unblinded statistician will not be involved in any decisions relating to populations for analysis prior to unblinding. Prior to database lock and unblinding, all randomization materials, including the final signed and dated randomization schedule, will be held by the pharmacy department of the clinical site.

Interim PK parameter estimations will be performed using bioanalytical data applied with subject aliases in order to maintain the study blind. Interim PK analysis will be performed using nominal time points.

The unblinded pharmacist or designee at the clinical site will receive a copy of the final randomization schedule for preparation of the IMP and preparation of the treatment allocation list. A copy of the randomization schedule will also be made available to the laboratory performing the bioanalysis to allow selective analysis of PK samples to obtain drug concentrations.

One set of disclosure envelopes (i.e., sealed envelopes containing individual subject randomization details) will be provided. This set will be held in a secure and locked cabinet in a temporary drug room, having key fob controlled access, located just outside the pharmacy. Disclosure envelopes may be used by the Investigator in the event of an emergency, or if the Investigator deems it necessary to break the study blind in the interest of a subject's medical safety, or if warranted during scheduled safety reviews. Any request for information on the randomization schedule after initial issue must be made using a randomization disclosure form, except in the case of emergency unblinding. The Medical Monitor must be contacted within 24 hr following disclosure of IMP assignment.

Details of any disclosure of the randomization schedule will be documented and retained in the investigator site file (ISF). The Sponsor will be notified if the study blind is broken.

If any blinded study team member suspects that they have been unblinded, they are to immediately notify the Indivior unblinded contact. The suspected unblinded information should not be forwarded or revealed to any other blinded team members.

The study blind will be broken after the study database has been locked.

9.2 Packaging and Storage

[redacted]

9.2.2 Packaging

[redacted]

Study drug labels will be developed in accordance with cGMP and local regulatory requirements.

9.2.3 Storage Conditions

[redacted]

Temperature excursions outside of the defined ranges should be reported to the Sponsor, the product should be immediately quarantined and only used if/after Sponsor approval has been obtained. For further details please refer to the Pharmacy Manual.

9.2.4 Drug Substance Shipment

Drug substance will be shipped under monitored temperature conditions. Refer to the Pharmacy Manual for receipt instructions.

9.3 Drug Administration

The study drug should be dispensed under the supervision of the Investigator or a suitably qualified member of the study team. The Investigator or designee agrees to store and dispense the study drug per this protocol.

For Part I, there are up to 9 planned cohorts in this study. A sentinel group of 2 subjects will be randomized to active or placebo (1:1 active and placebo) and will be dosed ahead of remaining subjects of each cohort (Section 9.1.3).

For Part I, study drug will be administered under fasting condition [redacted] Subject will fast for at least 10 hrs prior to receiving study drug [redacted] Dosages provided in capsules should be swallowed whole. Subjects must avoid poppy seeds, grapefruit and grapefruit juice while on study drug. Subjects should be advised to avoid food and liquids other than water for at least 2 hours prior to dosing until at least 1 hour after dosing.

See Table 2 for summary of dose per cohort.

Table 2 Part 1 Single Ascending Dose IMP Dosing

Cohort		1	2	3	4	5
Dose	Active N=6	INDV-2000, 1 mg	INDV-2000, 5 mg	INDV-2000, 20 mg	INDV-2000, 50 mg	INDV-2000, 120 mg
	Placebo N=2	INDV-2000 Placebo,1 mg	INDV-2000 Placebo, 5 mg	INDV-2000 Placebo, 20 mg	INDV-2000 Placebo, 50 mg	INDV-2000 Placebo, 120mg
Dosage Form (Active; Placebo)	[redacted]					

Cohort		6	7	8	9
Dose	Active N=6	INDV-2000, Dose 6	INDV-2000, Dose 7	INDV-2000, Dose 8	INDV-2000, Dose 9
	Placebo N=2	Placebo, to match	Placebo, to match	Placebo, to match	Placebo, to match
Dosage Form (Active; Placebo)	[redacted]				

Safety and PK evaluation at each dose level.
Sentinel dosing at all dose levels.
[redacted]

Part II of the study is a cross-over, food interaction evaluation where INDV-2000 will be given once under fasting conditions and once at completion of a standard FDA High-Fat Breakfast.

There will be 2 treatment arms of 8 subjects each, fed and fasted, with the same treatment order randomly assigned within subject. The same INDV-2000 dose will be used for fed and fasted conditions. Dose level is to be determined following Part 1.

For the fasting condition of Part II, subjects will receive INDV-2000 following an overnight fast of at least 10 hrs. Subjects will be administered INDV-2000 with 240 mL (8 ounces) of water.

No food will be allowed for at least 4 hours post-dose administration. Water is allowed as desired except for at least 1 hour before and at least 1 hour after drug administration.

For the food effect evaluation of Part II, subjects will consume a high-fat meal within 30 minutes prior to INDV-2000 administration. The high-fat meal should provide approximately 800 to 1000 calories, and should derive approximately 150, 250 and 500 to 600 calories from protein, carbohydrate and fat, respectively. Examples of an appropriate high-fat meal are provided in Secition 22.5, Appendix 5. Subjects should consume the entire meal in 30 minutes or less; however, the dose must be administered 30 minutes after the start of the meal. If the subject cannot complete the meal, the approximate percentage of the meal consumed should be recorded in the eCRF and continue with the study. Additionally, the start and finish time of the meal will be recorded in the eCRF. INDV-2000 will be administered with 240 mL (8 ounces) of water. No food will be allowed for at least 4 hours post-dose administration. Water is allowed as desired except for at least 1 hour before and at least 1 hour after drug administration.

Lunch will be provided at least 4 hr post- INDV-2000 (or - placebo) dose for both parts.

9.4 Accountability

The Investigator is responsible for ensuring that all drug substance and study drug is inventoried, accounted for and documented in accurate accountability records. Upon completion of the study and/or as requested by Indivior, copies of study drug and drug substance accountability records will be provided to Indivior. After the monitor completes reconciliation, all unused study drug will be destroyed by the Investigator, as per local standard operating procedures (SOP), after Indivior has approved the commencement of destruction. All unused drug substance and requested retain samples will be maintained at appropriate storage conditions and shipped according to the details in the Pharmacy Manual. The IMP must be handled strictly in accordance with the protocol, handling guidelines and the label; it must be stored in a locked, limited-access area under appropriate environmental conditions.

Subject level dispensation of IMP must be documented on the appropriate subject level accountability form. All IMP dispensation will be performed by a pharmacist or designee, checked by a study site staff member and documented on a drug dispensation form.

Used IMP bottles (for both powder in solution and capsule), and unused IMP must be available for verification by the site monitor during monitoring visits.

9.5 Reporting Product Complaints

The Investigator and study site staff are responsible for prompt reporting of product quality complaints to Indivior. A product complaint is any concern pertaining to the preparation or quality of the drug substance or IMP, and includes, but is not limited to, broken capsules, labelling defects or packaging defects, IMP that is thought to be ineffective, or has an appearance, taste or odour that is outside of what is expected.

All product complaints should be reported to Indivior [redacted] in a timely manner and the following information provided:

- study number
- site contact/reported by
- subject number (if already assigned to a subject)
- description of issue
- picture, if available (photographs should be taken only if safe to do so/within site policy or practice to take photograph)

Retain the product and packaging in quarantine for further investigation, as required.

9.6 Concomitant Therapies

Concomitant therapies (medications) will be collected from screening until the EOS visit or the ET visit, and at the time points listed Section 22.1, Appendix 1 and Section 22.2, Appendix 2. Any concomitant medications (including herbal preparations) taken during the study will be recorded in the source documents and in the eCRF. Any changes in concomitant therapy during the study will be documented, including cessation of therapy, initiation of therapy and dose changes.

Any changes to concomitant therapies that are not listed as permitted concomitant therapies should be discussed with the study Medical Monitor.

9.6.1 Permitted Concomitant Therapies

The Investigator may prescribe concomitant medications or treatments for pain (acetaminophen up to 2000 mg per 24 hr, ibuprofen up to 600 mg per 24 hr administered orally) or nausea (promethazine 25 mg oral or suppository) as deemed necessary for the comfort of the subject. For oral therapies, please withhold dosing for at least 2 hr before or 1 hr after administration of IMP.

9.6.2 Prohibited Concomitant Therapies

Subjects should be instructed not to take any medications, including over-the-counter products, without first discussing with the Investigator.

The following medications are CYP3A4 inhibitors and are expressly prohibited during the study:

Strong inhibitors of CYP3A4 include clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir. Moderate inhibitors of CYP3A4 include amiodarone, erythromycin, fluconazole,

miconazole, diltiazem, verapamil, delavirdine, amprenavir, fosamprenavir, conivaptan. Cimetidine is an over-the-counter medication that is a weak CYP3A4 inhibitor.

Indivior or specified designee should be notified if a subject receives any of these medications during the study.

9.6.3 Lifestyle Restrictions

9.6.3.1 Fluid and Food Intake

Subjects are required to fast a minimum of 8 hours before blood sample collection at screening.

In accordance with the exclusion criteria, subjects will not be permitted to eat poppy seeds, grapefruit or Seville oranges or drink grapefruit juice or Seville orange juice within 7 days prior to study drug administration.

Restrictions for water and food intake related to study drug administration are discussed in Section 9.3.

9.6.3.2 Subject Activity Restrictions

While participating in the study, subjects will not be permitted to perform heavy exercise. Subjects are asked to refrain from heavy exercise starting 24 hours before IMP administration.

9.6.3.3 Caffeine, Alcohol and Tobacco Restrictions

Subjects will not be permitted to drink caffeine-containing beverages, eat caffeine-containing foods or use caffeine-containing products prior to check-in through the EOS visit.

In addition to 90 days prior to screening, subjects will refrain from smoking and from using e-cigarettes and nicotine-containing products through the EOS visit.

Subjects will refrain from drinking alcohol from prior to check-in throughthe EOS visit.

9.7 Compliance

The PI or sub-Investigator may terminate a subject based on the subject's ability to comply with the protocol requirements.

Study drug will be administered by designated qualified study personnel at the clinical facility. The PI or sub-Investigator will be present during the administration of study drug. The time and duration, the dose delivered and any dosing observations will be recorded in source documentation. The PI, sub-Investigator or designated individual will maintain a log of all study drugs dispensed and returned. Drug supplies will be inventoried and accounted for throughout the study. The clinical site will have access to the Indivior Medical Monitor for any safety events that occur.

10 ADVERSE EVENTS

The Investigator or designee is responsible for identifying, documenting and reporting events that meet the definition of an AE.

An AE is any untoward medical occurrence in a subject associated with the use of an IMP regardless of the presence of a causal relationship to the IMP. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with an IMP, whether or not considered related to the IMP.

- Events meeting the definition of an AE include:
- New condition detected after IMP administration even though the AE may have been present prior to receiving IMP.
- Exacerbation of a pre-existing condition (including intensification of a condition and/or an increase in frequency).
- Any abnormal laboratory test results or other safety assessments felt to be clinically significant in the opinion of the Investigator (including those that worsen from baseline).
- Symptoms and/or the clinical sequelae of a suspected interaction or an overdose of either IMP or a concomitant medication.
- Signs, symptoms or the clinical sequelae resulting from special interest conditions (e.g., IMP misuse, medication error, IMP withdrawal, etc.). Overdose per se will not be reported as an AE/SAE.
- Symptoms and/or clinical sequelae that resulted in intervention.

Events that do not meet the definition of an AE include:

- Medical or surgical procedures; the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, hospitalization for elective surgery, hospitalization for observation in the absence of an AE).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.1 Assessment of Adverse Events

The Investigator is ultimately responsible for assessing and reporting all AEs as outlined in the protocol. The assessment and reporting of AEs may be delegated to a medically qualified sub-Investigator, trained on this study protocol, who is listed on the delegation of authority log. All

AEs regardless of treatment group or suspected causal relationship to the IMP will be reported as described in this protocol.

Adverse events should be volunteered by the subject or solicited from the subject using a standard statement, obtained from examination of the subject at a site visit, or from observations of clinically significant laboratory values or special examination abnormal values. If an event assessed by one of the study scales requires intervention, or if in the opinion of the Investigator, it is clinically significant, then it will be reported as an AE.

All AEs are to be assessed and recorded in a timely manner and followed to resolution or until the Investigator determines that there is not an anticipated resolution. Each AE is to be documented with reference to severity, date of occurrence, duration, treatment and outcome. Furthermore, each AE is to be classified as being serious or non-serious. In addition, the Investigator must assess whether the AE is IMP-related or not.

10.1.1 Time Period for Collecting Adverse Events

Adverse event monitoring and reporting will begin after the subjects sign the ICF, continue throughout the study and include EOS/ET/Follow-up. Subjects will be monitored by the study site staff for untoward effects and will be released from the study after the last procedure is completed and confirmed that the subject has no residual untoward effects from the IMP that may affect safety. Treatment-emergent AEs will be defined events observed after starting administration of INDV-2000 or placebo.

Surgical procedures, planned before enrolment of the subject in the study, are not considered AEs if the condition was known before study inclusion. In this case the medical condition should be reported in the subject's medical history.

Any clinically significant symptoms will be reported as AEs. All AEs and corresponding treatment will be recorded in the eCRFs and a summary of all the safety data will be presented in the final Clinical Study Report (CSR). Any ongoing AEs will be appropriately followed up until resolution or 14 days after EOS/ET. The study site personnel will make every effort to contact the subject for a minimum of 2 attempts after which the outcome of the AE will be considered ongoingand the subject will be noted in source as lost to follow-up.

If a subject experiences the onset of an SAE within 5 days following study completion and in the opinion of the Investigator, that SAE is associated with the study drug, it will be followed and reported as described in Section 11.2.

If an SAE occurs that is deemed related to study drug, a PK sample will be taken as soon as possible after the event is reported. If possible, an additional sample should be collected when the SAE has been resolved.

10.1.2 Assessment of Intensity

The term “severe” is used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as “serious,” which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Intensity	Definition
Mild	Causes transient or mild discomfort; no limitation of usual activities; no medical intervention required.
Moderate	Causes mild to moderate limitation in activity; some limitation of usual activities; no or minimal medical intervention or therapy is required.
Severe	Causes marked limitation in activity; some assistance is usually required; medical intervention or therapy is required; hospitalization is probable.

For vital sign assessments and clinical laboraty abnormalities considered by the Investigator to be an Adverse Event according to Section 10.1.4, the intensitiy of adverse events will be graded in accordance with the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Section 22.6, Appendix 6).

Adverse events with changes in severity should be documented as separate events.

10.1.3 Assessment of Causality

The Investigator or a medically qualified sub-Investigator, trained on this study protocol and listed on the delegation of authority log is responsible for determining the AE relationship to the IMP.

The following categories will be used to define the relationship of an AE to the administration of the IMP:

Not Related:	Data are available to identify a clear alternative cause for the AE other than the IMP.
Related:	The cause of the AE is related to the IMP and cannot be reasonably explained by other factors (e.g., the subject’s clinical state, concomitant therapy and/or other interventions).

A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the IMP will be considered and investigated. The Investigator will also consult the

IB in the determination of his/her assessment. For each AE/SAE the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to Indivior or designated representative. However, it is imperative that the Investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to Indivior or designated representative. The Investigator may change his/her opinion of causality in light of follow-up information and amend the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.1.4 Clinical Laboratory Changes

Changes in laboratory values, vital signs or other safety parameters (e. g. , neurological and clinical symptom assessments) as noted in the protocol are a subset of AEs and are reportable only if the lab test result is associated with accompanying symptoms, and/ or requires additional diagnostic testing or intervention (medical, surgical), and/or requires additional significant treatment, and/or requires temporal or permanent discontinuation of IMP, or a change to dosing other than as permitted by protocol, or if considered to be clinically significant by Investigator or medically qualified designee.

Screening laboratory assessments, if determined to be clinically significant by the Investigator, are not AEs.

11 SERIOUS ADVERSE EVENTS

The Investigator or designee is responsible for identifying, documenting and reporting events that meet the definition of an SAE.

An SAE is any event that meets any of the following criteria:

- Death
- Life-threatening
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received INDV-2000
- Other: Important medical events that may not result in death, be life-threatening or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:

Intensive treatment in an emergency room or at home for allergic bronchospasm

Blood dyscrasias or convulsions that do not result in in-patient hospitalization

Development of IMP abuse or diversion

- Potential Hy's Law cases indicative of medication-induced hepatocellular injury, defined as:
    - ALT ≥3x ULN and total bilirubin of ≥2x ULN (or INR >1. 5 if measured)
    - ALT or AST >3x ULN with systemic symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [>5%])
- Potential Hy's Law cases should be managed as described in Section 22.3, Appendix 3.

An AE is considered "life-threatening" if the subject was at immediate risk of death from the event as it occurred; i.e. , it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, IMP-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though IMP-induced hepatitis can be fatal.

AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e. g. , elective surgery for a pre-existing condition that has not worsened) should not be considered AEs or SAEs. If anything untoward is

reported during the procedure, that occurrence must be reported as an AE (either 'serious' or 'non-serious') according to the usual criteria.

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

An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

11.1 Documenting Serious Adverse Events

When an SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostic reports) pertaining to the event. The Investigator will then record all relevant information regarding the SAE on the appropriate electronic or paper form(s).

It is not acceptable for the Investigator to send photocopies of the subject’s medical records to Indivior in lieu of completion of the SAE Reporting Form. However, there may be cases where copies of medical records are requested by Indivior or designated representative. In this instance, all subject identifiers, with the exception of subject number, will be redacted on the copies of the medical records prior to submission to Indivior.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis will be documented as an AE or SAE and not the individual signs/symptoms.

11.2 Reporting Serious Adverse Events

11.2.1 Investigator Reporting of Serious Adverse Events

Once the Investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to Indivior (or designated representative) by the Investigator (or designee) **within 24 hours** from first being aware of the event using the form provided by Indivior or designated representative. Any follow-up information on a previously reported SAE will also be reported to Indivior within 24 hours.

Where additional information is needed or expected, the Investigator will not wait to receive all information before reporting the event to Indivior. The Investigator must provide an assessment of causality at the time of the initial report as described in Section 10.1.3.

In the event of an SAE, the Investigator or designee will notify both the Indivior Medical Monitor at the phone number and/or email address listed under Study Personnel Information and

Indivior Pharmacovigilance by completing the appropriate form(s) in a paper SAE Reporting Form should be completed and submitted to Indivior Pharmacovigilance:

[redacted]

11.2.2 Regulatory Reporting Requirements for Serious Adverse Events

Prompt receipt of notifications of SAEs to Indivior or designated representative from Investigators is essential in ensuring that legal obligations and ethical responsibilities regarding the safety of subjects are met.

Indivior has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the IMP. Indivior or designated representative will comply with country-specific regulatory requirements pertaining to safety reporting to Regulatory Authorities, IRBs and Investigators.

A suspected unexpected serious adverse reaction (SUSAR) is an SAE related to the IMP administered in any dose and that, in its nature or severity, is inconsistent with the IB. Indivior Pharmacovigilance will determine if an SAE meets the definition of a SUSAR and distribute SUSAR reports according to local regulatory requirements and Indivior policy. An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e g., summary or line listing of SAEs, Dear Investigator Letter) will file it with the IB and will notify the IRB, if required according to local requirements.

11.2.3 Overdose

Any instance of overdose (whether or not it involved IMP) must be communicated as an SAE and fully documented. Details of any signs or symptoms and their management should be recorded, including details of any antidote(s) administered.

12 PREGNANCY

Participants will include women of non-childbearing potential and men who agree to use highly effective means of contraception. Pregnancy is not anticipated during the conduct of this study. In the case where a subject's routine pregnancy test as required per protocol is positive for pregnancy prior to dosing, the subject should not be dosed. If the subject has a positive urine pregnancy test, a confirmatory serum pregnancy test should be performed.

12.1 Action to be Taken if Pregnancy Occurs in a Female Partner

If the partner of a study subject becomes pregnant, the pregnancy will be reported to the clinical unit within 48 hours of the subject's knowledge of the pregnancy. The Investigator will attempt to collect pregnancy information on any female partner of a randomized male study subject who becomes pregnant while participating in this study.

After obtaining the necessary signed informed consent from the female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to Indivior or designated representative within 24 hours of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy and information on the status of the mother and child will be forwarded to Indivior or designated representative. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

13 DATA MANAGEMENT

13.1 Data Collection and Management

Data will be entered into the eCRF and will be combined with other data captured centrally outside of the eCRF into a validated system. Clinical data will be managed in accordance with the data management plan to ensure that the integrity of the data is maintained. Adverse events, medical history and indication for concomitant medications will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The eCRFs (including queries and audit trails) will be retained by Indivior. An electronic copy of the eCRF will be sent to the Investigator for their records. Subject identifiers will not be collected or transmitted to Indivior according to Indivior standards and procedures. Data collection will be completed according to the study plans.

13.1.1 Database Quality Assurance

The eCRFs will be reviewed and checked for omissions, apparent errors and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the investigational site. Only authorized personnel will make corrections to the eCRFs, and all corrections will be documented in an audit trail.

13.1.2 Source Documents

The Investigator is responsible for the quality of the data recorded in the eCRFs. The data recorded should be a complete and accurate account of the subject's record collected during the study.

Study data are not to be gathered directly onto the eCRF, but must be gathered onto primary source documents at the clinical site. Completion of source documents will precede the completion of the eCRF. Source documents may be electronic, hard copy, or a combination of both and are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, screening logs and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the Investigator and made available for direct inspection by the authorized study personnel outlined in the ICF. The CRF will be considered the source document for individual CRF elements such as study-specific scales if those data are collected directly onto a CRF.

14 STATISTICS

14.1 General Procedures

This section describes the sample size, analysis populations and planned analyses for PK and safety endpoints. A comprehensive statistical analysis plan (SAP) will be developed to detail the statistical methodology for all aspects of the planned analyses. The SAP will be approved after the protocol is finalized and before the database is locked. Any deviations from the analyses described below will be identified in the SAP (and subsequently the CSR). Any unplanned analyses not described in the SAP will be identified in the CSR.

Data will be listed and summarized separately for Parts I and II of the study. For Part I, data will be summarized by dosing cohort for active treatment and for all placebo subjects combined. For Part II, data will be summarized by treatment group (fed or fasted) where applicable. Continuous variables will be summarized using descriptive statistics such as means, standard deviations (SD), medians, minimums and maximums. Categorical variables will be reported as frequency counts (including number missing) and the percentage of subjects in corresponding categories. Individual subject data will be presented by subject in data listings. Data listings will include all data collected from screened subjects (i.e., subjects who sign informed consent).

For change from baseline calculations, baseline will be defined as the last measurement taken prior to dosing.

14.2 Sample Size

The sample size is not based on formal power calculations because the study is only designed to provide initial assessment of the safety, tolerability and PK for INDV-2000. The sample size used is typical for studies of this nature and should be adequate to assess the parameters described.

14.3 Analysis Populations

14.3.1 Safety Population

The Safety Population is defined as subjects who received at least one dose of IMP.

14.3.2 Pharmacokinetic Population

The PK analysis population is defined as subjects who received at least one dose of INDV-2000 and have an adequate number of PK samples collected to derive PK parameters.

14.3.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics (e.g., sex, race, age, weight, height, BMI) will be summarized for the Safety Population and separately for screen failures.

14.4 Key End Point Analyses

14.4.1 Primary Endpoint

The primary endpoint for the study is the incidence, seriousness, severity, and relationship to IMP of TEAEs in the Safety Population.

For Part I of the study, a TEAE is defined as an AE with start date/time at or after IMP dosing. For Part II of the study (a cross-over design), a Period 1 (Fasted) TEAE is defined as an AE with start date/time at or after IMP dosing in Period 1 and no later than IMP dosing in Period 2, and a Period 2 (Fed) TEAE is defined as an AE with start date/time at or after IMP dosing in Period 2 and within the period of time equal to the interval from Period 1 dosing to Period 2 dosing.

The number and percentage of subjects reporting TEAEs will be presented overall, by MedDRA system organ class (SOC) and preferred term (PT), each in descending order of frequency (then alphabetically in case of ties).

IMP-related TEAEs, treatment-emergent SAEs (TESAEs), IMP-related TESAEs, TEAEs leading to death, TEAEs leading to IMP discontinuation, and TEAEs leading to IMP interruption will be presented both overall and by SOC and PT. TEAEs will also be summarized by intensity within SOC and PT. In addition, TEAEs leading to death and IMP-related TEAEs leading to death will be summarized separately by PT.

In summaries by severity and relationship to IMP, if more than one TEAE is coded to the same PT for the same subject, the subject will be counted only once for that PT using the most severe and most related occurrence. Missing severity will be summarized as "severe" and missing relatedness will be summarized as "related."

Separate listings will be presented for TEAEs, TESAEs, TEAEs leading to IMP discontinuation and TEAEs leading to death.

14.4.2 Pharmacokinetic Analysis

Plasma samples will be analyzed for INDV-2000 and its metabolite, [redacted] See Section 22.4, Appendix 4 for more details about blood sample collection timepoints.

PK data will be listed, summarized and analyzed using the PK population.

Concentrations for INDV-2000 and M12 at each blood sample collection time [redacted] will be summarized descriptively [number, mean, standard deviation, median, minimum, maximum, and coefficient of variance (CV)] by dose level. In addition, [redacted] plasma [redacted] PK parameters will be summarized descriptively by dose level.

Individual and mean plasma concentration versus time plots will be presented on linear and semi-logarithmic scales, by treatment, for INDV-2000 and [redacted] as appropriate.

Pharmacokinetic parameters based on the actual sample collection will be derived for INDV-2000 and [redacted] using standard non-compartmental methods.

The following plasma PK parameters to be assessed include, but are not necessarily limited to, the following:

C_{max}	Maximum observed plasma concentration
t_{max}	Time of maximum observed plasma concentration
$AUC_{0\text{-}last}$	Area under the plasma concentration-time curve from time zero to the last quantifiable time point
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity
$AUC_{(t1\text{-}t2)}$	Area under the plasma concentration-time curve from t1 to t2
t1/2	Plasma terminal half-life
CL/F	Plasma clearance

A more complete description of the PK analyses will be provided in the SAP.

[redacted]

14.5 Interim Analysis

No formal interim analysis is planned. In Part I, there will be a review of safety data for the sentinel group in each cohort before proceeding to the next subject in the cohort. There will also be a review of the safety and PK data for each cohort before dose escalation. The safety data review will be conducted by the DRSC (Section 15.2) using stopping rules defined in Section 6.4.

14.6 Handling of Missing Data

In general, missing data (caused by premature discontinuation or otherwise) will not be imputed.

14.7 Other Safety Analyses

Other safety endpoints will be listed and summarized using the Safety Population. Other safety endpoints include changes from baseline in clinical laboratory evaluations, vital signs, ECG parameters and physical examinations.

14.8 Extent of Exposure

Frequency and percentage of subjects dosed in each cohort for Part I and dosed in each Fed/Fasted group separately for Part II will be provided.

14.8.1 Laboratory Data

Observed values and changes from baseline in laboratory parameters will be summarized by analysis visit.

Clinically abnormal laboratory results will also be summarized by frequency and percentages for each category.

14.8.2 Vital Signs

Observed values and changes from baseline in vital signs (SBP and DBP, respiratory rate, heart rate and temperature) will be summarized by analysis visit.

14.8.3 Physical Examination

Clinically significant physical examination findings will be summarized by analysis visit.

14.8.4 Electrocardiogram

Results from 12-lead ECG will be categorized as normal, abnormal not clinically significant, or abnormal clinically significant and will be summarized by analysis visit using frequencies and percentages for each category. Observed values and changes from baseline in ECG interval measurements will also be summarized by analysis visit.

[redacted]

15 ETHICS AND RESPONSIBILITIES

15.1 Good Clinical Practice

Prior to site activation, Indivior or designated representative will obtain approval/favorable opinion from the relevant regulatory agency(ies) to conduct the study in accordance with ICH/GCP and any applicable country-specific regulatory requirements.

The study will be carried out in accordance with the protocol and with local legal and regulatory requirements, ICH/GCP and all applicable subject privacy requirements.

15.2 Data Review and Safety Committee

The DRSC will include the Investigator, Sponsor Medical Monitor and PK scientist. Other members will be added as necessary. The DRSC will be blinded and will review clinical safety, laboratory data and PK data. Based on the data presented, the DRSC may choose to unblind the data to the Sponsor only. Every effort will be maintained to keep the Investigator blinded. The proposed dose escalation scheme for Part I is described in the study design section, however, a more conservative dose escalation may be explored based on PK, safety and/or clinical observations. Dose escalation factors will be dependent upon observed safety, tolerability and PK.

[redacted]

15.3 Institutional Review Board

The protocol, ICF(s) and any other written information and/or materials to be provided to subjects will be reviewed by an independent and appropriately constituted IRB. If required by local regulations, the protocol should be re-approved by the IRB annually. The IRB must be constituted and operate in accordance with the principles and requirements of ICH/GCP.

Investigational medicinal product can only be released to the Investigator after documentation that all ethical and legal requirements for starting the study has been received by Indivior or designated representative.

15.4 Informed Consent

The Investigator or a person designated by the Investigator (if allowed by local regulations) is to obtain written informed consent from each subject prior to entering the study. All written

informed consent documents are required to have been reviewed and received a favorable opinion/approval from an IRB prior to presenting them to a potential subject.

Any changes to the ICF must be reviewed by Indivior before submission to the IRB.

The written informed consent process will include the review of oral and written information regarding the purpose, methods, anticipated duration and risks involved in study participation. The Investigator is to ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided. The Investigator or a person designated by the Investigator must also explain to each subject that participation is voluntary, and that consent can be withdrawn at any time and without reason. Subjects will receive a signed and dated copy of the signed ICF before any study-specific procedures are conducted.

In the event that new safety information emerges that represents a significant change in the risk/benefit assessment, the signed ICF should be updated accordingly. All subjects should be informed of the new information, provide their consent to continue in the study, and be provided with a signed and dated copy of the revised signed ICF.

15.5 Records Management

The Investigator must maintain all study-related records (except for those required by local regulation to be maintained elsewhere) in a safe and secure location throughout the conduct and following the closure of the study. The records must be accessible upon request (e. g. , for an IRB, Indivior or regulatory inspection) along with the facility, study personnel and supporting systems/hardware. All documents pertaining to the study, including all versions of the approved study protocol, copy of the ICF and other documents as required per local laws and regulations (e. g. , Health Insurance Portability and Accountability Act [HIPAA] documents), completed CRFs, source records (subject records, subject diaries, hospital records, laboratory records, drug accountability records, etc.), and other study-related materials will be retained in the permanent archives of the study site.

Where permitted by local laws and regulations, records may be maintained in a format other than hard copy (e. g. , electronically in an electronic medical records system). The Investigator must ensure that all reproductions are an accurate legible copy of the original and that they meet necessary accessibility and retrieval standards. The Investigator must also ensure that a quality control process is in place for making reproductions and that the process has an acceptable back-up of any reproductions.

The minimum retention time for retaining study records will be in accordance with the strictest standard applicable for the study site as determined by local laws, regulations or institutional requirements. At a minimum, records will be maintained for 25 years. If the Investigator withdraws from the study (e. g. , relocation, retirement) all study-related records should be transferred, in a written agreement with Indivior, to a mutually agreed upon designee within Indivior-specified timeframe.

16 AUDITING AND MONITORING

The purpose of an audit or regulatory inspection is to verify the accuracy and reliability of clinical study data submitted to a regulatory authority in support of research or marketing applications, and to assess compliance with statutory requirements regulations governing the conduct of clinical studies.

In accordance with applicable regulations, GCP and Indivior procedures, the clinical monitor(s) will periodically contact the site, including conducting on-site visits at intervals agreed by the Investigator and documented in the Clinical Monitoring Plan and the Site Initiation Visit Report.

The clinical monitor(s) will contact the site prior to the start of the study to discuss the protocol and data collection procedures with site personnel. In accordance with applicable regulations and GCP guidelines, the Investigator shall make available for direct access all study-related records upon request by Indivior, Indivior's agents, clinical monitor(s), auditors and/or IRB. The monitors will visit the site during the study in addition to maintaining frequent telephone and written communication. The extent, nature, and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity and enrolment rate.

The Investigator must allow the clinical monitor(s) direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the clinical monitor(s) to discuss findings and any relevant issues.

Upon completion of the study, study closeout activities must be conducted by Indivior or its designee in conjunction with the PI, as appropriate.

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigators and associated personnel before the study, periodic monitoring visits by Indivior, and direct transmission of clinical laboratory data from a central laboratory into Indivior's (or designee's) database. Written instructions will be provided for IMP preparation and dosing, collection, preparation and shipment of blood, plasma [redacted] samples. Guidelines for CRF completion will be provided and reviewed with study personnel before the start of the study. Indivior (or designee) will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to Indivior (or designee). Any discrepancies will be resolved with the Investigator or suitably qualified designee, as appropriate.

This study will be organized, performed and reported in compliance with the protocol, SOPs, working practice documents and applicable regulations and guidelines.

In accordance with the standards defined in Indivior SOPs and applicable regulatory requirements, clinical studies sponsored by Indivior are subject to Indivior Quality Assurance (QA) Investigator Site Audits that may be delegated to a Contract Research Organization or Indivior contract auditors. Investigator Site Audits will include review of, but are not limited to, drug supply, presence of required documents, the informed consent process and comparison of

CRFs with source documents. The Investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner. Full consultation with the Investigator will be made prior to and during such an audit, which will be conducted according to Indivior's or a Contract Research Organization's QA SOPs. In addition, this study is subject to inspections by Regulatory Authorities. If such a regulatory inspection occurs, the Investigator agrees to allow the regulatory inspector direct access to all relevant study documents. The Investigator must contact Indivior immediately if this occurs and must fully cooperate with the inspection conducted at a reasonable time in a reasonable manner.

17 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Indivior. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB and the Investigator must await approval before implementing the changes. Indivior or designated representative will submit protocol amendments to the appropriate Regulatory Authorities for approval.

If in the judgment of the IRB, the Investigator and/or Indivior, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study subject, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation, based on IRB determination.

18 STUDY REPORTS AND PUBLICATIONS

A CSR will be prepared following completion of the study. An Investigator signatory may be identified for the approval of the report if required by applicable regulatory requirements.

The study data will be owned by Indivior. Publication of any and all data will be at the discretion of Indivior. The Investigator will not disseminate, present or publish any of the study data without the prior written approval from Indivior to do so.

19 STUDY TERMINATION

Both Indivior and the Investigator reserve the right to terminate the study at the Investigator's site at any time. Should this be necessary, Indivior, or a specified designee will inform the appropriate Regulatory Authorities of the termination of the study and the reasons for its termination, and the Investigator will inform the IRB of the same. In terminating the study, Indivior and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

20 CONFIDENTIALITY

All subject-identifying documentation generated in this study is confidential and may not be disclosed to any persons not directly concerned with the study without written permission from the subject. However, authorized regulatory officials and Indivior personnel (or their representatives) will be allowed full access to inspect and copy the records. All subject bodily fluids and/or other materials collected shall be used solely in accordance with this protocol and the ICF signed by the subject, unless otherwise agreed to in writing by Indivior.

Each subject will be identified by an assigned subject number when reporting study information to any entity outside of the study center. During the blinded portion of the study, if use of the subject number could be unblinding, false or 'dummy' subject identifiers may be used. Data containing subject identification will not be removed from the study center without first redacting subject identifiers.

21 REFERENCES

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22 APPENDICES

22.1 APPENDIX 1 – Schedule of Events Part I

Evaluation	Screening Days -28 to -1	In clinical unit					Follow-up
		Day -1[12]	Day 1	Day 2	Day 3	Day 4	Day 11/EOS[10]/ET
Informed Consent	X						
Inclusion/Exclusion Criteria	X	X					
Randomization		X					
Demographics (Includes height, weight and BMI)	X						
Medical History	X						
Physical Examination[1]	X	X		X		X	X
Urine Drug Screen	X	X					
Alcohol test	X	X[13]					
Serum Pregnancy Test	X						
Urine Pregnancy Test		X					X
Urinalysis	X	X		X			
FSH test (for post-menopausal women only)	X						
Clinical Laboratory Assessments (Chemistry and Hematology)	X	X		X		X	X
Serology (HIV, Hepatitis B and C)	X						
Coagulation Panel (PT/INR)	X						
Vital Signs[2]	X	X	X[2]	X		X	X
12-Lead Electrocardiogram[3,4]	X[3]	X	X[4]	X		X	X
26 Hour Holter Monitoring[5]			X				

Evaluation	Screening Days -28 to -1	In clinical unit					Follow-up
		Day -1[12]	Day 1	Day 2	Day 3	Day 4	Day 11/EOS[10]/ET
PK Sampling[7]			X[7]	X	X	X	
[redacted]							
Drug Administration[11]			X				
AE Assessment		X	X	X	X	X	X
Concomitant Medication Assessment	X	X	X	X	X	X	X
Admission to Clinical Unit		X					
Discharge from Clinical Unit						X	
[redacted]							

22.2 APPENDIX 2 – Schedule of Events Part II

Evaluation	Screening Days -28 to -1	Period 1 - Dosing Under Fasting Condition					Period 2 - Dosing after High-Fat Content Meal					Follow-up
		In clinical unit			Outpatient visits		In clinical unit			Outpatient visits		
		Day -1[11]	Day 1	Day 2	Day 3	Day 4	Day -1[11]	Day 1	Day 2	Day 3	Day 4	Day 10/EOS/ET[9]
Informed Consent	X											
Inclusion/Exclusion Criteria	X	X										
Demographics (Includes height, weight and BMI)	X											
Medical History	X											
Physical Examination[1]	X	X		X			X		X			X
Urine Drug Screen	X	X					X					
Alcohol test	X	X[12]					X[12]					
Urinalysis	X	X		X			X		X			
Clinical Laboratory Assessments (Chemistry and Hematology)	X	X		X		X	X		X		X	X
Serology (HIV, Hepatitis B and C)	X											
Coagulation Panel (PT/INR)	X											
Vital Signs[2]	X	X	X[2]	X		X	X	X	X		X	X
12-Lead Electrocardiogram[3,4]	X[3]	X	X[4]	X			X	X[4]	X			X
26 Hour Holter Monitoring[5]			X					X				
PK Sampling[6]			X[6]	X	X	X		X[6]	X	X	X	

Evaluation	Screening Days -28 to -1	Period 1 - Dosing Under Fasting Condition					Period 2 - Dosing after High-Fat Content Meal					Follow-up
		In clinical unit			Outpatient visits		In clinical unit			Outpatient visits		
		Day -1[11]	Day 1	Day 2	Day 3	Day 4	Day -1[11]	Day 1	Day 2	Day 3	Day 4	Day 10/EOS/ET[9]
Standard High-Fat Breakfast[10]								X				
Drug Administration			X					X[8]				
AE Assessment		X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X
Admission to Clinical Unit		X					X					
Discharge from Clinical Unit				X[7]					X[7]			

[redacted]

[redacted]

[redacted]

22.3 APPENDIX 3 – Liver Safety

The following should occur if a subject meets any of the liver chemistry stopping criteria as outlined in Section 6.4 of the protocol:

- Subject should immediately be withdrawn from treatment. Do not re-challenge with study treatment.
- Notify the Indivior Medical Monitor or specified designee within 24 hours of learning of the abnormality.
- Completed the "Safety Follow-up Procedures" listed below.
- Upon completion of the safety follow-up, the subject must be withdrawn from the study unless further follow-up is required.

Subjects with ALT ≥3x ULN and bilirubin ≥2x ULN (>35% direct); or ALT ≥3x ULN and INR >1. 5:

This event is an SAE and should be reported using the SAE Reporting Form (Section 11). Serum bilirubin fractionation should be performed, if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).

Make every reasonable attempt to have the subject return to the clinic within 24 hours for repeat liver chemistries, additional testing and close monitoring (with specialist or hepatology consultation recommended).

Monitor the subject twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Subjects with ALT ≥5x ULN or ALT ≥3x ULN who have hepatitis symptoms or rash, cannot be monitored for 4 weeks or have elevations that persist ≥4 weeks:

- Make every reasonable attempt to have the subject return to the clinic within 24-72 hours for repeat liver chemistries and additional testing.
- Monitor subject weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Subjects with ALT ≥3x ULN and <5x ULN and bilirubin <2x ULN, who do not exhibit hepatitis symptoms or rash:

- Contact the Indivior Medical Monitor within 24 hours of learning of the abnormality to discuss subject safety.

- Subject may continue study treatment, if liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) can be monitored weekly for up to 4 weeks.

- If the subject later meets the liver chemistry stopping criteria (outlined in Section 6.5 of the protocol), immediately withdraw study treatment, perform additional testing and continue safety follow-up until liver chemistries resolve, stabilize or return to baseline values.

- After 4 weeks of monitoring, if ALT <3x ULN and bilirubin <2x ULN, subject must be monitored twice monthly until liver chemistries normalize or return to within baseline values.

Additional follow-up procedures for subjects who meet any of the stopping criteria:

- Viral hepatitis serology including:

    - Hepatitis A Immunoglobulin M (IgM) antibody,

    - HBsAg and Hepatitis B Core Antibody (IgM),

    - Hepatitis C RNA,

    - Cytomegalovirus IgM antibody,

    - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing), and

    - Hepatitis E IgM antibody.

    - Blood sample for PK analysis, obtained within 48 hours of last dose.

    - Serum creatine phosphokinase and lactate dehydrogenase.

    - Fractionate bilirubin, if total bilirubin ≥2x ULN.

    - Assess eosinophilia.

    - Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) as relevant on the AE eCRF.

    - Record use of concomitant medications, acetaminophen, herbal remedies, other over-the-counter medications or putative hepatotoxins on the Concomitant Medications eCRF.

- Record alcohol use in the eCRF.
- **In addition, the following are required for subjects with ALT ≥3x ULN and bilirubin ≥2x ULN (<35% direct) but optional for other abnormal liver chemistries**:
    - Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).
    - Serum acetaminophen adduct High-Performance Liquid Chromatography (HPLC) assay (quantifies potential acetaminophen contribution to livery injury in subjects with definite or likely acetaminophen use in the preceding week [
    - James 2009]).
    - Liver imaging (ultrasound, MRI, or CT) to evaluate liver disease. Data should be entered into the eCRF, if these tests are performed.

22.4 APPENDIX 4 –Pharmacokinetic Sampling Windows

Part I

Day	Timepoint	Assessment	Window
Day 1	pre-dose	[redacted]	[redacted]
[redacted]			
Day 1	0.5 hr post-dose		
Day 1	1 hr post-dose		
Day 1	2 hr post-dose		
Day 1	3 hr post-dose		
Day 1	4 hr post-dose		
Day 1	6 hr post-dose		
Day 1	8 hr post-dose		
Day 1	12 hr post-dose		
[redacted]			
Day 2	24 hr post-dose		
[redacted]			
Day 3	48 hr post-dose		
[redacted]			
Day 4	72 hr post-dose		
[redacted]			

Part II

Period	Day	Timepoint (hours)	Assessment	Window
Period 1 - Fasted	Day 1	Pre-dose	[redacted]	
Period 1 - Fasted	Day 1	0.5 hr post-dose		
Period 1 - Fasted	Day 1	1 hr post-dose		
Period 1 - Fasted	Day 1	2 hr post-dose		
Period 1 - Fasted	Day 1	3 hr post-dose		
Period 1 - Fasted	Day 1	4 hr post-dose		
Period 1 - Fasted	Day 1	6 hr post-dose		
Period 1 - Fasted	Day 1	8 hr post-dose		
Period 1 - Fasted	Day 1	12 hr post-dose		
Period 1 - Fasted	Day 2	24 hr post-dose		
Period 1 - Fasted	Day 3	48 hr post-dose		
Period 1 - Fasted	Day 4	72 hr post-dose		
Period 2 - Fed	Day 1	Pre-dose		
Period 2 - Fed	Day 1	0.5 hr post-dose		
Period 2 - Fed	Day 1	1 hr post-dose		
Period 2 - Fed	Day 1	2 hr post-dose		
Period 2 - Fed	Day 1	3 hr post-dose		
Period 2 - Fed	Day 1	4 hr post-dose		
Period 2 - Fed	Day 1	6 hr post-dose		
Period 2 - Fed	Day 1	8 hr post-dose		
Period 2 - Fed	Day 1	12 hr post-dose		
Period 2 - Fed	Day 2	24 hr post-dose		
Period 2 - Fed	Day 3	48 hr post-dose		
Period 2 - Fed	Day 4	72 hr post-dose		

22.5 APPENDIX 5- Example of High-Fat Meal

The following is an example of an appropriate high-fat meal to be consumed within 30 minutes of INDV-2000 administration in Part II, Period 2 on Day 1 for subjects participating in the food effect evaluation.

Food item [a]	**Calories (kcal)**	**Fat (g)**	**Carbohydrates (g)**	**Protein (g)**
2 eggs, fried	185	14. 1	1. 3	12. 5
2 strips bacon, fried	84	6. 4	0. 2	6. 0
2 slices of white bread, toasted	129	1. 8	24. 0	4. 0
4 ounces of hash brown potatoes	207			
8 fluid ounces of whole milk	146			
1 tablespoon butter	102			
Total grams (g)	-			
Total Calories (kcal)	853			
% of Total Calories	100			

[a] Substitutions can be made as long as the meal provides a similar amount of calories from protein, carbohydrate and fat and has comparable meal volume and viscosity.

22.6 APPENDIX 6- Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852- 1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review at 301-827-3070.

U.S. Department of Health and Human Services
Food and Drug
Administration Center for
Biologics Evaluation and
Research
September 2007

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Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

Preventive vaccines are usually developed to prevent disease in a healthy population. The Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, regulates preventive vaccines under authority of section 351 of the Public Health Service Act (42 U.S.C.262), as well as specific sections of the Federal Food, Drug, and Cosmetic Act, and reviews investigational new drug applications (INDs) and biologics license applications (BLAs). (See, for example, Title 21 Code of Federal Regulations (CFR) Parts 312, 600, and 601). Most of the clinical trials of preventive vaccines conducted to support INDs and BLAs enroll healthy volunteers in all phases of vaccine testing. The enrollment of healthy volunteers warrants a very low tolerance for risk in those clinical trials.

This guidance provides you, sponsors, monitors, and investigators of vaccine trials, with recommendations on assessing the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials. The grading system described in the table can also be useful in defining a particular study's stopping rules (e.g., a certain number of adverse events, as defined in the table, may call for stopping the study). Less extreme observations (e.g., mild) may not require discontinuing the study vaccine but can still contribute to evaluating safety by identifying parameters to focus upon in subsequent product development. Uniform criteria for categorizing toxicities in healthy volunteers can improve comparisons of safety data among groups within the same study and also between different studies. We, FDA, recommend using toxicity grading scale tables, provided below, as a guideline for selecting the assessment criteria to be used in a clinical trial of a preventive vaccine. We recommend incorporation of such appropriate, uniform, criteria into the investigational plan, case report forms, and study reports and correspondence with FDA, sponsors, monitors, investigators, and IRBs.

This guidance finalizes the draft guidance of the same title dated April 2005 (70 FR 22664, May 2, 2005).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Standardized toxicity assessment scales have been widely used to evaluate products treating specific diseases. For example, the National Cancer Institute's Common Toxicity Criteria Scale and the Division of AIDS' Toxicity Grading Scale standardize the evaluation of adverse events among patients with cancer and HIV/AIDS, respectively (Refs. 1, 2). The defined toxicity parameters in those scales are designed for patients who may already experience mild, moderate, or severe adverse clinical or laboratory events due to the disease process, and may not be appropriate for healthy volunteers.

In the development of the toxicity grading scales for healthy volunteers, we chose parameter limit values based on published information, when such values were available (Refs. 1-6). For example, the Brighton Collaboration has developed case definitions and guidelines to evaluate some adverse events associated with administering vaccines (Ref. 3). In some cases, parameter limit values were based on clinical experience and experience reviewing vaccine clinical trials that enroll normal healthy subjects.

Toxicity grading scales for laboratory abnormalities should consider the local laboratory reference values when the parameter limit values are defined. The characterization of laboratory parameters among some populations of healthy adults and adolescents may require the exercise of clinical judgment, for example, consideration of the potential for ethnic differences in white blood cell (WBC) counts or gender differences in creatine phosphokinase (CPK) values.

III. TOXICITY GRADING SCALE TABLES

Adverse events in a clinical trial of an investigational vaccine must be recorded and monitored and, when appropriate, reported to FDA and others involved in an investigation (sponsors, IRBs, and investigators). (See, for example, 21 CFR 312.32, 312.33, 312.50, 312.55, 312.56, 312.60, 312.62, 312.64, 312.66). Although the use of a toxicity grading scale for adverse events would not replace these regulatory requirements, using a scale to categorize adverse events observed during a clinical trial may assist you in monitoring safety and making required reports.

Nonetheless, we believe that categorization or grading of data as outlined in this document is supplementary to and should not replace full and complete data analysis.

These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers. The parameters in the tables below are not necessarily applicable to every clinical trial of healthy volunteers. The parameters monitored should be appropriate for the specific study vaccine. For some preventive vaccines under development, it may be appropriate

to include additional parameters to be monitored during a clinical trial or to alter the choice of values in the toxicity table. For example, additional parameters might be added based on one or more of the following: safety signals observed in pre-clinical toxicology studies, the biological plausibility of the occurrence of certain adverse events, or previous experience with a similar licensed product.

As discussed above, the tables do not represent a recommendation to monitor all the listed parameters in all clinical trials of healthy volunteers, nor do the tables represent all possible parameters to be monitored. In addition, these tables do not represent study inclusion or exclusion criteria. We recommend that the parameters monitored be appropriate for the study vaccine administered to healthy volunteers participating in the clinical trial.

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non- narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non- narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illnes	**Mild (Grade 1)**	**(Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** "ULN" is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

IV. REFERENCES

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