CLINICAL STUDY PROTOCOL: INDV-2000-102

Protocol Title: A Phase I Double-Blind, Placebo-Controlled Randomized Study to Assess Repeated Doses of INDV-2000 (C4X_3256) up to 28 Days in Healthy Volunteers, and an Open-Label Study of INDV-2000 up to 11 Days in Treatment Seeking Individuals with Opioid Use Disorder

Protocol Number: INDV-2000-102

Original Protocol Date: 15 Apr 2021

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CLINICAL PROTOCOL SIGNATURE PAGE

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Protocol Number:	INDV-2000-102
Protocol Version Number:	v 5.0
Protocol Version Date:	09 May 2023

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) 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

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document History	
Document:	**Date:**
Amendment 4	09 May 2023
Amendment 3	28 July 2022
Amendment 2	15 July 2022
Amendment 1	18 May 2022
Original Protocol	15 Apr 2021

Amendment 4 (09 May 2023)

Section Number(s) and Name(s)	Description of Change	Brief Rationale
[redacted]		

A Phase I Double-Blind, Placebo-Controlled Randomized Study to Assess Repeated Doses of INDV-2000 (C4X_3256) up to 28 Days in Healthy Volunteers, and an Open-Label Study of INDV-2000 up to 11 Days in Treatment Seeking Individuals with Opioid Use Disorder.

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.

SYNOPSIS

Protocol Title:

A Phase I Double-Blind, Placebo-Controlled Randomized Study to Assess Repeated Doses of INDV-2000 (C4X_3256) up to 28 Days in Healthy Volunteers, and an Open-Label Study of INDV-2000 up to 11 Days in Treatment Seeking Individuals with Opioid Use Disorder

Protocol Number:

INDV-2000-102

Study Rationale:

[redacted]

Target Population:

Part I and Part II: Healthy male and female volunteers aged 18 to 55 years, body mass index (BMI) 18.0 to 32.0 kg/m².

Part III: Treatment seeking male and female subjects with a DSM-5 diagnosis of moderate or severe OUD aged 18 to 65 years, BMI 18.0 to 35.0 kg/m².

Number of Subjects:

Part I (2 cohorts) and Part II (2 cohorts): Each cohort will be composed of 12 healthy volunteers (9 receiving active and 3 placebo). A total of 48 healthy male and female volunteers total are planned to participate in both parts.

Part III: A single group of up to 16 treatment seeking subjects with OUD.

Duration of Study:

Part I: The study will be an INDV-2000 multiple ascending dose study. Total study duration per cohort inclusive of Screening through the End of Study (EOS) visit is approximately 42 days.

Part II: The study will be an INDV-2000 multiple ascending dose study. Total study duration per cohort inclusive of Screening through the EOS visit is approximately 63 days.

Part III: This study will be open-label dosing of INDV-2000. Total study duration inclusive of Screening through the EOS visit is approximately 56 days.

For study Parts I and II, male participants will complete a safety phone call 90 days after their last dosing day to assess any new pain, swelling or nodular lesions in scrotum.

Objectives:

The primary objectives for the study are:

Part I and Part II

- Assess safety and tolerability of INDV-2000 following repeated doses of INDV-2000 in healthy volunteers.

Part III

- Assess the safety and tolerability following repeated doses of INDV-2000 administered alone and with SUBOXONE sublingual (SL) film in an OUD treatment seeking population.

The secondary objectives for the study are:

Part I and Part II

- Characterize the pharmacokinetic (PK) profile following multiple doses of INDV-2000.

The exploratory objectives for the study are:

[redacted]

Study Design:

The study will be conducted in 3 parts:

Part I: Double-blind, placebo-controlled, randomized, multiple ascending dose study for 7 days of dosing with INDV-2000 in healthy volunteers. The screening period is up to 28 days. In each cohort, healthy volunteers will reside at the clinical unit from the evening of Day -1 to the morning of Day 8. In Cohort 1, doses will be administered once daily in the morning of Days 1-7. In Cohort 2, doses will be administered twice daily during Days 1-7. Healthy volunteers will be discharged on Day 8 except in the case the Investigator judges it appropriate to retain the healthy volunteer to address safety concerns until resolution. The EOS visit will be performed on Day 14 which is one week after the last dose. Male participants will complete a safety phone call 90 days after their last dosing day to assess any new pain, swelling or nodular lesions in the scrotum. Two cohorts are planned, where each cohort will utilize a different dose, and all healthy volunteers within the same cohort will receive the same dose. The dose escalation decision for Part I, Cohort 2 will be based on a blinded review of TEAEs, concomitant medications, vital signs, ECGs, clinical laboratory test results and PK data from Days 1-7 of the prior cohort.

Part II: Double-blind, placebo-controlled, randomized, multiple ascending dose study for 28 days of dosing with INDV-2000 in healthy volunteers. The screening period is up to 28 days. In each cohort, healthy volunteers will reside at the clinical unit from the evening of Day -1 to the morning of Day 8. Doses will be administered twice daily during Days 1-7. Healthy volunteers will be discharged after the morning dose administration on Day 8 except in case the Investigator judges it appropriate to retain the healthy volunteer to address safety concerns until resolution. Healthy volunteers will continue twice daily self-administration of INDV-2000 at home (except for in-clinic days) from Days 9 through 28. Healthy volunteers will return to the clinical unit for outpatient visits on Days 10, 15, 22 and 28 for safety assessments and PK samples. The EOS visit will be performed on the morning of Day 35 which is one week after the last dose. Male participants will complete a safety phone call 90 days after their last dosing day to assess any new pain, swelling or nodular lesions in the scrotum. This may be modified based on full evaluation of data from Part I in healthy volunteers. Two cohorts are planned, where each cohort will utilize a different dose, and all healthy volunteers within the same cohort will receive the same dose. Dose escalation decisions for Part II, Cohorts 1 and 2 will be based on a blinded review of TEAEs, concomitant medications, vital signs, ECGs, clinical laboratory test results and PK data from Days 1-7 of the prior cohort(s).

Part III: Part III dose determination will follow a blinded review of TEAEs, concomitant medications, vital signs, ECGs, clinical laboratory test results, and PK data from Part I, Cohorts 1 & 2, Part II, Cohort 1, and Part II, Cohort 2 Days 1-7. This part is an open-label study in OUD treatment seeking individuals. The screening period is up to 35 days. After screening, if check-in criteria are met, treatment seeking OUD subjects will enter the in-clinic portion of the study. First, subjects will initiate a run-in period with SUBOXONE SL film daily for 6 days. On Day -1 of the study, subjects must be stabilized on a SUBOXONE SL film dose between 8 mg/2 mg and 24 mg/6 mg of buprenorphine/naloxone. If run-in criteria are met, each subject will continue dosing with their stabilized dose of SUBOXONE SL film

after the run-in period for required in-clinic dosing. Qualifying subjects will continue to Day 1, where SUBOXONE SL film dosing alone continues for 2 more days. On Day 3, subjects will begin receiving doses of both SUBOXONE SL film and INDV-2000 for 7 days. Starting on Day 10, subjects will stop dosing with SUBOXONE SL film and dose with INDV-2000 alone for 4 more days and remain in clinic until completion of assessments on Day 14. Rescue medications to treat opioid withdrawal signs and symptoms will be allowed in the study based on Investigator's medical judgment. After assessments are completed on Day 14, subjects can begin a standard of care treatment for OUD. The EOS visit is scheduled for Day 21. If at any stage of the study a subject discontinues, they will be given options for their continued treatment for OUD by the clinical facility.

Primary Endpoint(s):

Part I and Part II: Safety and tolerability of multiple doses of INDV-2000 as determined by adverse event reporting (incidence, severity and relatedness of TEAEs; SAEs, events leading to discontinuation and deaths) in healthy volunteers.

Part III: Safety and tolerability following multiple doses of INDV-2000 administered alone and with SUBOXONE SL film as determined by adverse event reporting (incidence, severity and relatedness of TEAEs; SAEs, events leading to discontinuation and deaths) in an OUD treatment seeking population.

Secondary Endpoint(s):

Part I and Part II:

- Plasma PK parameters of INDV-2000 after multiple doses
  - Maximum plasma concentration (C_{max}), time of maximum plasma concentration (T_{max}), and area under the plasma concentration-time curve ($AUC_{0\text{-}24 \text{ or } 0\text{-}12}$) of INDV-2000 following dosing on Days 1 and 7 (Part I) and Days 1, 7 and 28 (Part II)

Exploratory Endpoints:

[redacted]

[redacted]

Safety Assessments

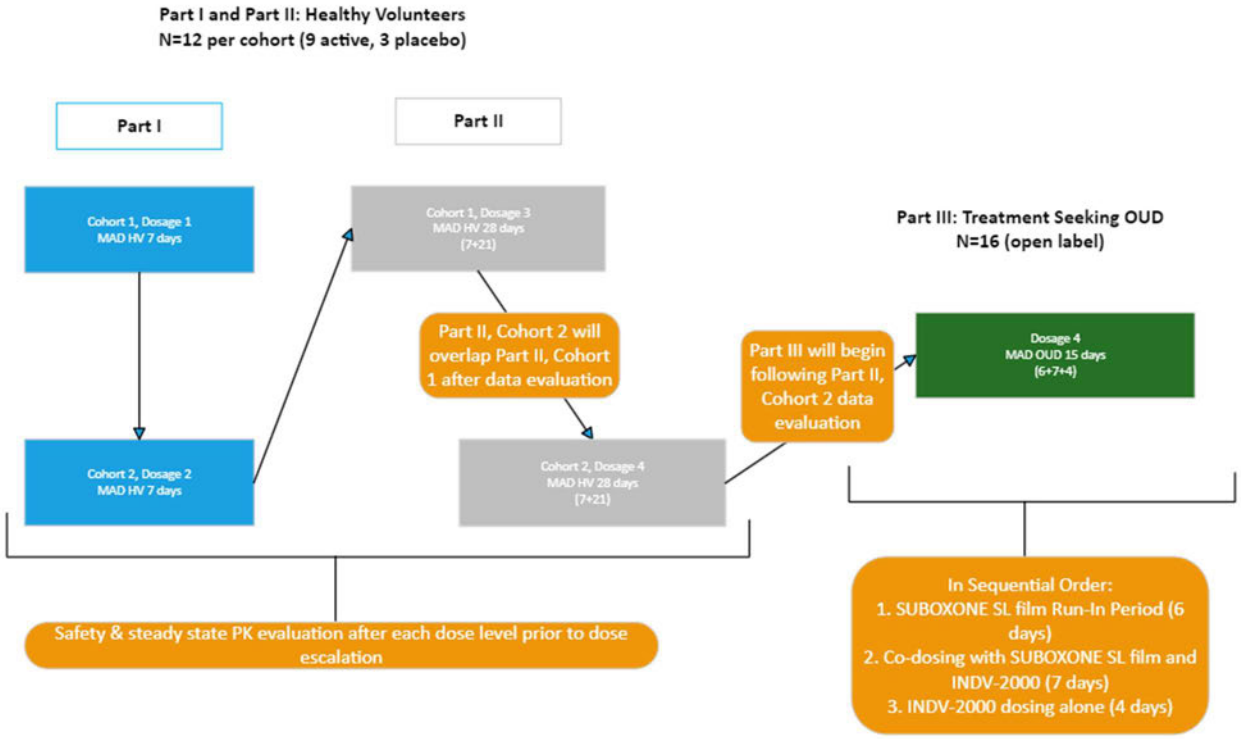
Part I, Part II and Part III:

The following clinical safety parameters will be assessed for means, trends and/or changes from baseline. Clinically significant findings for the following clinical safety assessments will be reported as adverse events:

- laboratory results
- electrocardiogram (ECG) findings
- vital sign measures
- physical examination
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- [redacted]

STUDY SCHEMATIC

Figure 1 Study Schematic



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List of Abbreviations

ADME	Absorption, distribution, metabolism and excretion
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the drug plasma concentration versus time curve
BID	Twice-daily
BMI	Body mass index
CDMS	Clinical Data Management System
cGMP	Current Good Manufacturing Practices
CHF	Congestive Heart Failure
C_{max}	Maximum plasma concentration
CNS	Central Nervous System
[redacted]	[redacted]
CPK	Creatine phosphokinase
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
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
FR	Fixed Ration
FSH	Follicle-stimulating Hormone
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
[redacted]	[redacted]
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)
PR	Progressive Ration
QA	Quality Assurance
QD	Once-daily
QTcF	QT interval corrected with Fridericia's formula
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard Deviation
SL	Sublingual
SOC	System Organ Class
SOP	Standard Operating Procedures
[redacted]	[redacted]
SUSAR	Suspected unexpected serious adverse reaction
[redacted]	[redacted]
T_{max}	Time to reach maximum (peak) plasma concentration
TEAE	Treatment-Emergent Adverse Events
TESAE	Treatment-Emergent Serious Adverse Events
UDS	Urine drug screen
ULN	Upper Limit of Normal
[redacted]	[redacted]

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 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 behaviours 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 behaviours 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

1.2.1 Dose Rationale

[redacted]

1.3 Nonclinical Pharmacology

[redacted]

1.4 Risk-Benefit Assessment

[redacted]

2 STUDY OBJECTIVES

2.1 Primary

The primary objectives for the study are:

Part I and II

- Assess safety and tolerability of INDV-2000 following repeated doses of INDV-2000 in healthy volunteers.

Part III

- Assess the safety and tolerability following repeated doses of INDV-2000 administered alone and with SUBOXONE sublingual (SL) film in an OUD treatment seeking population.

2.2 Secondary

The secondary objectives for the study are:

Part I and II

- Characterize the pharmacokinetic (PK) profile following multiple doses of INDV-2000.

2.3 Exploratory

3 STUDY ENDPOINTS

3.1 Primary

Part I and Part II: Safety and tolerability of multiple doses of INDV-2000 as determined by adverse event reporting (incidence, severity and relatedness of TEAEs; SAEs; events leading to discontinuation and death) in healthy volunteers.

Part III: Safety and tolerability following multiple doses of INDV-2000 administered alone and with SUBOXONE SL film as determined by adverse event reporting (incidence, severity and relatedness of TEAEs; SAEs; events leading to discontinuation and death) in an OUD treatment seeking population

3.2 Secondary

Part I and Part II:

- Plasma PK parameters of INDV-2000 after multiple doses
  - Maximum plasma concentration (C_{max}), time of maximum plasma concentration (T_{max}), and area under the plasma concentration-time curve ($AUC_{0\text{-}24 \text{ or } 0\text{-}12}$) of INDV-2000 following dosing on Days 1 and 7 (Part I) and Days 1, 7 and 28 (Part II)

3.3 Exploratory

[redacted]

3.3.1.1 Safety Assessments

Part I, Part II and Part III:

The following clinical safety parameters will be assessed for means, trends and/or changes from baseline. Clinically significant findings for the following clinical safety assessments will be reported as adverse events:

- laboratory results
- electrocardiogram (ECG) findings
- vital sign measures
- physical examination
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- [redacted]

4 STUDY PLAN

4.1 Study Design

The study will be conducted in 3 parts:

Part I: Double-blind, placebo-controlled, randomized, multiple ascending dose study for 7 days of dosing with INDV-2000 in healthy volunteers. The screening period is up to 28 days. In each cohort, healthy volunteers will reside at the clinical unit from the evening of Day -1 to the morning of Day 8. In Cohort 1, doses will be administered once daily in the morning of Days 1-7. In Cohort 2, doses will be administered twice daily during Days 1-7. Healthy volunteers will be discharged on Day 8 except in the case the Investigator judges it appropriate to retain the healthy volunteer to address safety concerns until resolution. The EOS visit will be performed on Day 14 which is one week after the last dose. Male participants will complete a safety phone call 90 days after their last dosing day to assess any new pain, swelling or nodular lesions in the scrotum. Two cohorts are planned, where each cohort will utilize a different dose, and all healthy volunteers within the same cohort will receive the same dose. The dose escalation decision for Part I, Cohort 2 will be based on a blinded review of TEAEs, concomitant medications, vital signs, ECGs, clinical laboratory test results and PK data from Days 1-7 of the prior cohort.

Part II: Double-blind, placebo-controlled, randomized, multiple ascending dose study for 28 days of dosing with INDV-2000 in healthy volunteers. The screening period is up to 28 days. In each cohort, healthy volunteers will reside at the clinical unit from the evening of Day -1 to the morning of Day 8. Doses will be administered twice daily during Days 1-7. Healthy volunteers will be discharged after the morning dose administration on Day 8 except in case the Investigator judges it appropriate to retain the healthy volunteer to address safety concerns until resolution. Healthy volunteers will continue twice daily self-administration of INDV-2000 at home (except for in-clinic days) from Days 9 through 28. Healthy volunteers will return to the clinical unit for outpatient visits on Days 10, 15, 22 and 28 for safety assessments and PK samples. The EOS visit will be performed on the morning of Day 35 which is one week after the last dose. Male participants will complete a safety phone call 90 days after their last dosing day to assess any new pain, swelling or nodular lesions in the scrotum. This may be modified based on full evaluation of data from Part I in healthy volunteers. Two cohorts are planned, where each cohort will utilize a different dose, and all healthy volunteers within the same cohort will receive the same dose. Dose escalation decisions for Part II, Cohorts 1 and 2 will be based on a blinded review of TEAEs, concomitant medications, vital signs, ECGs, clinical laboratory test results and PK data from Days 1-7 of the prior cohort(s).

Part III: Part III dose determination will follow a blinded review of TEAEs, concomitant medications, vital signs, ECGs, clinical laboratory test results, and PK data from Part I, Cohorts 1 & 2, Part II, Cohort 1, and Part II, Cohort 2 Days 1-7. This part is an open-label study in OUD treatment seeking individuals. The screening period is up to 35 days. After screening, if check-in criteria are met, treatment seeking OUD subjects will enter the in-clinic portion of the study. First, subjects will initiate a run-in period with SUBOXONE SL film daily for 6 days. On Day -1 of the study, subjects must be stabilized on a SUBOXONE SL film dose between 8 mg/2 mg and

24 mg/6 mg of buprenorphine/naloxone. If run-in criteria are met, each subject will continue dosing with their stabilized dose of SUBOXONE SL film after the run-in period for required in-clinic dosing. Qualifying subjects will continue to Day 1, where SUBOXONE SL film dosing alone continues for 2 more days. On Day 3, subjects will begin receiving doses of both SUBOXONE SL film and INDV-2000 for 7 days. Starting on Day 10, subjects will stop dosing with SUBOXONE SL film and dose with INDV-2000 alone for 4 more days and remain in clinic until completion of assessments on Day 14. Rescue medications to treat opioid withdrawal signs and symptoms will be allowed in the study based on Investigator's medical judgment. After assessments are completed on Day 14, subjects can begin a standard of care treatment for OUD. The EOS visit is scheduled for Day 21. If at any stage of the study a subject discontinues, they will be given options for their continued treatment for OUD by the clinical facility.

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, Section 22.2, Appendix 2 for Part II and Section 22.3, Appendix 3 for Part III of the study.

4.3 Duration of Study

Part I: The study will be an INDV-2000 multiple ascending dose study. Total study duration per cohort inclusive of Screening through the EOS visit is approximately 42 days.

Part II: The study will be an INDV-2000 multiple ascending dose study. Total study duration per cohort inclusive of Screening through the EOS visit is approximately 63 days.

Part III: This study will be open-label dosing of INDV-2000. Total study duration inclusive of Screening through the EOS visit is approximately 56 days.

For study Parts I and II, male participants will complete a safety phone call 90 days after their last dosing day to assess any new pain, swelling or nodular lesions in the scrotum.

5 STUDY POPULATION SELECTION

5.1 Number of Subjects

Part I (2 cohorts) and Part II (2 cohorts): Each cohort will be composed of 12 healthy volunteers (9 receiving active and 3 placebo). A total of 48 healthy male and female volunteers are planned to participate in both parts. Study subjects who are randomized but do not receive IMP will be replaced.

Part III: A single group of up to 16 treatment seeking subjects with OUD.

5.2 Inclusion Criteria

In order to participate in the study, subjects must meet the following criteria:

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

Part I and II only:

3. Male or female who is healthy as determined by a medical evaluation.
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).

Part III only:

6. Male or female seeking treatment for OUD with a diagnosis of moderate or severe OUD by DSM-5 criteria.
7. Between 18 and 65 years of age inclusive.
8. BMI within 18.0 to 35.0 kg/m^2, inclusive (minimum weight of at least 50.0 kg at Screening).

5.3 Exclusion Criteria

Subjects must <u>not</u> 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, haematology or urinalysis results as judged by an Investigator or medically responsible physician. (Refer to additional laboratory exclusion criteria for Part III subjects in Exclusion 28).
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 HIV-1/HIV-2 Antibodies, Hepatitis B surface Antigen (HBsAg) or Hepatitis C Antibody (HCVAb).
6. Serious cardiac illness or other cardiac assessments 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. QTcF >450 msec for males and >470 msec for females or history of prolonged QT syndrome.
7. Current active hepatic or biliary disease, including subjects with cholecystectomy <90 days prior to Screening.
8. Concurrent treatment or treatment with an investigational drug, or participation in any other clinical study within 30 days prior to the signing the informed consent form.
9. History of suicidal ideation within 30 days prior to providing written informed consent as evidenced by answering "yes' to questions 4 or 5 on the suicidal ideation portion of the C-SSRS completed at the Screening Visit or history of a suicide attempt (per the C-SSRS) in the 6 months prior to informed consent.
10. Pregnant or lactating females.
11. Any consumption of food or drink containing poppy seeds, grapefruit or Seville oranges within 7 days prior to the IMP administration.
12. Blood donation of greater than 500 mL within 56 days or plasma donation within 7 days of screening; clinically significant anaemia or low haemoglobin (<11 g/dL for females, <12 g/dL for males).
13. 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.
14. Known allergy or hypersensitivity to IMP or its excipients.
15. Any condition that, in the opinion of an Investigator or medically responsible physician, would interfere with evaluation of the IMP or interpretation of subject safety or study results.
16. 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.
17. Subjects who are unable, in the opinion of an Investigator or medically responsible physician, to comply fully with the study requirements.
18. Current incarceration or pending incarceration/legal action that could prevent participation or compliance in the study.

Part I and II only:

19. 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).
20. Positive test result for alcohol and/or any drugs of abuse at screening

21. Have a blood pressure reading outside of the following range: Systolic <86 or >149 mmHg; Diastolic <50 or >94 mmHg
22. 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.
23. Healthy volunteers who are taking, or have taken, any prescribed or over-the-counter drugs (other than 2 g per day acetaminophen, hormone replacement therapy [HRT]) 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.

Part III only:

24. Regular alcohol consumption in males >27 units per week and females >20 units per week (1 unit = ½ pint beer, 25 mL of 40% spirit or a 125 mL glass of wine).
25. Current substance use disorder, as defined by DSM-5 criteria, with any substances other than opioids, tobacco, cannabis, or alcohol, or dependence with any substance that would interfere with the completion of the study by judgment of the Investigator or medically responsible physician.
26. Current history of alcohol withdrawal within one year prior to screening.
27. Have a blood pressure reading outside of the following range: Systolic <86 or >159 mmHg; Diastolic <50 or >99 mmHg. Investigator should rule out acute changes resulting from opioid withdrawal.
28. Has total bilirubin ≥1.5 × upper limit of normal (ULN) (with direct bilirubin >1.3 mg/dL), alanine aminotransferase (ALT) ≥3 × ULN, aspartate aminotransferase (AST) ≥3 × ULN, serum creatinine >2 × ULN, or international normalized ratio (INR) >1.5 × ULN at Screening).
29. Received medication-assisted treatment for OUD (e.g., methadone, buprenorphine) in the 30 days prior to providing written informed consent.
30. Received any prior treatment with a buprenorphine implant or injection.
31. Treatment for OUD required by court order.

5.4 Check-In and Run-In Assessment Criteria

Upon passing screening and meeting inclusion and not meeting exclusion criteria, the subject will present to the clinic for admission.

For Part I and Part II, the following criteria must be met at Day -1 for the healthy volunteer to be checked into the clinic:

1. Females must have a negative urine pregnancy test.
2. Must not have a QTcF >450 msec for males and >470 msec for females.
3. Must have a negative result obtained from the urine drug screen (UDS) and the alcohol test (urine ethanol).
   a. Healthy volunteers 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.
4. Must have a negative polymerase chain reaction (PCR) test result for COVID-19.

If any of these criteria are not met, the subject will not be enrolled into the study.

For Part III, subjects must meet the following criteria in order to be checked into the clinic on Day -6:
1. Females must have a negative urine pregnancy test.
2. Must have a negative PCR test result for COVID-19.

For Part III, subjects must meet the following criteria in order to complete run-in, and proceed into the study on Day -1:
1. Tolerating daily dose of SUBOXONE SL film between 8mg/2mg – 24mg/6mg (inclusive).
2. COWS score of ≤ 12.

If any of these criteria are not met, the subject will not be enrolled.

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.

6 STUDY CONDUCT

6.1 Subject Enrolment

Study participation begins once written informed consent is obtained; a subject identification (ID) number is then assigned. The subject ID will be used to identify the subject during the screening process and throughout study participation. A subject is considered enrolled once randomized in Part I or Part II, and in Part III, if Day -1 run-in assessment criteria are met.

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 criteria or met one or more 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 Run-in Failure

In Part III only, a subject will be a run-in failure if written informed consent is obtained, the subject did meet inclusion criteria and did not meet exclusion criteria, however did not move past the run-in period of the study, and did not receive IMP (see Section 9 for the definition of "IMP"). Run-in failures will be documented on the Screening Log and the reason for run-in failure will be collected in the eCRF.

6.4 Subject Completion

For Parts I and II, a completed subject is one that completes the EOS visit. The end of the study is defined as the last subject's last visit.

For Part III, a completed subject is one who receives all scheduled doses of INDV-2000 and completes Day 14 safety assessments.

6.5 Dose Escalation and Stopping Criteria

The Data Review and Safety Committee (DRSC) will review blinded data from cohorts in Part I and Part II of the study and will determine if the dose can be escalated as planned, or alternatively, if any stopping criteria have been met. See Section 15.2

Dose escalation will be dependent upon observed safety, tolerability and PK, but the increase from one cohort to the next will not exceed 2-fold in dose. In no case will the maximum daily drug exposure exceed that observed at the NOAEL in the most sensitive toxicology species.

The DRSC will also review individual subjects as needed to determine if the individual's participation should be stopped based on emerging safety and PK data.

6.5.1.1 Part I and II - Individual Stopping Criteria

If the following criteria are met at any point during Parts I or II, the affected individual's dosing will be paused to allow unblinded review of affected individuals by the DRSC before continuing dosing. A healthy volunteer will be discontinued if any of the criteria listed below are confirmed:

AEs:

- The healthy volunteer experiences an SAE that is not clearly unrelated to the IMP.

Laboratory Abnormalities:

The healthy volunteer has an abnormality of one or both of the following parameters, whose temporal relationship to the IMP makes causality plausible, confirmed on repeat testing:

- Serum ALT or AST >3 times the ULN
- Total serum bilirubin >2 times the ULN (>35% direct bilirubin).

Vital Signs:

The healthy volunteer fulfils one or both of the following vital sign criteria based on the mean of triplicate measures (≥ 1 minute apart), that will be completed once the first blood pressure reading is outside the accepted range:

- Systolic blood pressure (SBP) <85 or >170 mmHg and/or change from Baseline >30 mmHg sustained for at least 1 hr (measures repeated every 15 min)
- Diastolic blood pressure (DBP) <45 or >105 mmHg and/or change from Baseline >30 mmHg sustained for at least 1 hr (measures repeated every 15 min)

ECG Criteria:

The healthy volunteer fulfils the following ECG criteria based on the mean of triplicate measures (≥ 1 minute apart), that will be completed once the first ECG demonstrates a prolonged interval:

- QTcF ≥500 msec or uncorrected QT interval of >600 msec.

Plasma INDV-2000 Concentrations

[redacted]

6.5.1.2 Part I and II – Cohort 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. The DRSC will conduct a review of unblinded data of the affected individuals to determine if any additional safety monitoring or changes to the protocol are required.

AEs:
- Three healthy volunteers experience a similar severe AE that is not clearly unrelated to the IMP, or
- Two healthy volunteers experience a similar SAE that is not clearly unrelated to the IMP.

Laboratory Abnormalities:

Two healthy volunteers with an abnormality of one or both of the following parameters, whose temporal relationship to the IMP makes causality plausible, confirmed on repeat testing:
- Serum ALT or AST >3 times the ULN.
- Total serum bilirubin >2 times the ULN (>35% direct bilirubin).

Vital Signs:

Two healthy volunteers fulfil one or both of the following vital sign criteria based on the mean of triplicate measures (≥1 minute apart), that will be completed once the first blood pressure reading is outside the accepted range:
- SBP <85 or >170 mmHg and/or change from Baseline >30 mmHg sustained for at least 1 hr (measures repeated every 15 min)
- DBP <45 or >105 mmHg and/or change from Baseline >30 mmHg sustained for at least 1 hr (measures repeated every 15 min)

ECG Criteria:

Two healthy volunteers fulfil the following ECG criteria based on the mean of triplicate measures (≥ 1 minute apart), that will be completed once the first ECG demonstrates a prolonged interval:
- QTcF ≥500 msec or uncorrected QT interval of >600 msec.

6.5.1.3 Part III - Individual Stopping Criteria

A subject will be discontinued if any of the criteria listed below are fulfilled:

AEs:
- The subject experiences an SAE that is not clearly unrelated to the IMP.

Laboratory Abnormalities:

The subject has an abnormality of one or both of the following parameters, whose temporal relationship to the IMP makes causality feasible, confirmed on repeat testing:

- Serum ALT or AST >5 times the ULN or 2-fold above baseline if baseline is ≥ 1.5 times ULN.
- Total serum bilirubin >2 times the ULN (>35% direct bilirubin).

ECG Criteria:

The subject fulfils the following ECG criteria based on the mean of triplicate measures (≥ 1 minute apart), completed once the first ECG demonstrates a prolonged interval:

- QTcF ≥500 msec or uncorrected QT interval of >600 msec.

If the preceding criteria are met, the DRSC will conduct a review of the affected individuals to determine if any additional safety monitoring or changes to the protocol are required.

6.5.1.4 Study Stopping Criteria (Parts I, II and III)

If the following criteria are met at any point during the study, the current cohort will be paused to allow review of the affected individuals by the DRSC before continuing dosing.

AEs:

- Four subjects experience a similar severe AE that is not clearly unrelated to the IMP, or
- Two subjects experience a similar SAE that is not clearly unrelated to the IMP.

Laboratory Abnormalities:

Two subjects with an abnormality of both of the following parameters, whose temporal relationship to the IMP makes causality feasible, confirmed on repeat testing:

- Serum ALT or AST >3 times the ULN or 2-fold above baseline if baseline is ≥ 1.5 times ULN.
- Total serum bilirubin >2 times the ULN (>35% direct bilirubin).

ECG Criteria:

Three subjects fulfil the following ECG criteria based on the mean of triplicate measures (≥ 1 minute apart), that will be completed once the first ECG demonstrates a prolonged interval:

- QTcF ≥500 msec or uncorrected QT interval of >600 msec.

6.5.2 Suicidal Ideation and Behaviour

Please refer to Section 8.8 for prospective assessment of suicidal ideation and behaviour. If a subject exhibits suicidal behaviour or active suicidal ideation with intent during the study, the Investigator should discontinue the subject and provide the appropriate treatment.

6.6 Subject Withdrawal from Study

A subject will be considered withdrawn from study if the subject has permanently discontinued study drug or study procedures. The primary reason for withdrawal from study must be entered

into the eCRF. All subjects that permanently discontinue the study must make every effort to complete the Early Termination Visit. The discontinuation date will be the date of the Early Termination Visit, last date of study drug or study assessment whichever is later.

For a subject who discontinues due to an AE, see Section 10.1.1 for follow-up procedures.

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

- Death
- AE
- Protocol non-compliance
- Pregnancy (See Section 12)
- 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

6.6.1 Subject Withdrawal of Consent

If a subject withdraws consent, the subject will not receive any additional doses of study drug (See Section 9 for a definition of "study drug"). However, the subject may be offered additional tests as needed to monitor their safety (e.g., EOS safety assessments or procedures).

6.6.2 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.

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 non-compliance. 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, Part II and Part III (Section 22.1, Appendix 1, Section 22.2, Appendix 2 and Section 22.3, Appendix 3). Further details on PK and safety assessments are provided in Section 14.8 and Section 14.9, respectively.

See Section 10 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, Baseline Characteristics and Medical History

The following demographic and baseline information will be captured: sex, race, age, 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 history of vasectomy in male participants should be recorded. 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 include a testicular/epididymal examination but will not include a breast, pelvic or rectal examination unless clinically indicated.

After the screening period, brief physical examinations will occur consisting of heart, lung and abdomen and targeted for any AEs. For men, a testicular/epididymal examination will be performed at the End of Study visit. If any clinically significant change from screening is noted, it will be reported as an AE.

Any clinically significant abnormalities, including changes from baseline, must be reported as AEs. Any findings from the testicular/epididymal examination, regardless of clinical significance, should be reported as an adverse event.

8.4 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 minutes according to the time schedule presented in the Schedule of Events tables (Section 22.1, Appendix 1, Section 22.2, Appendix 2 and Section 22.3, Appendix 3). Blood pressure will be measured 3 times (at least 1 minute apart) pre-dose and 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, a triplicate blood pressure measure will be taken at that timepoint, and the mean of the triplicate measures will be used for any subject discontinuation decisions. The abnormality will be followed to resolution if required. Additional measurements may be taken as deemed necessary by the Investigator (See Section 6.5.1.1).

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

Pending emerging data, any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment. The IRB will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5 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, Section **22.2**, Appendix 2 and Section 22.3, Appendix 3).

A triplicate ECG will be recorded for the determination of the baseline result at pre-dose on Day 1. For each numeric ECG parameter, 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, and the mean of the triplicate measures will be used for any subject discontinuation decisions. 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 (See Section 6.5.1.1).

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

8.6 26-Hour Holter Monitoring

8.7 Clinical Laboratory Tests

Clinical laboratory tests will be performed at the time points listed in Section 22.1, Section 22.2 and Section 22.3 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, Section 22.2, Appendix 2 and Section 22.3, Appendix 3.

Additionally, for Part III, fentanyl and oxycodone will be part of the UDS.

Table 1 List of Laboratory Tests

Haematology	**Serum Chemistry:**
Haematocrit	Albumin
Haemoglobin	Alkaline phosphatase
Mean corpuscular haemoglobin	Alanine aminotransferase (ALT)
Mean corpuscular haemoglobin 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
Urinalysis:	Creatinine
Appearance	Creatine kinase
Bilirubin	Gamma-glutamyl transferase
Colour	Glucose
Glucose	Lactate dehydrogenase
Ketones	Lipase
Leucocyte esterase	Magnesium
Microscopic examination of sediment[a]	Phosphorus
Nitrite	Potassium
Occult blood	Sodium
pH	Total bilirubin
Protein	Direct bilirubin
Specific gravity	Total cholesterol
Urobilinogen	Total protein
	Triglycerides
Pregnancy:	
Serum hCG	**Urine Drug Screen (UDS):**
Urine hCG	Opioids
	Cocaine
Molecular	Amphetamines
PCR for COVID-19	Cannabinoids
	Barbiturates
Screening Only:	Benzodiazepines
FSH (as needed in post-menopausal females only)	Methamphetamine
Haemoglobin A1c	Phencyclidine
Hepatitis B surface Antigen	Ethanol
Hepatitis C Antibody	**In addition to the above, for Part III:**
HIV-1 and -2 antibodies	Fentanyl
Prothombin Time with INR	Oxycodone
PTT	

Anti-HIV = human immunodeficiency virus antibodies; hCG = human chorionic gonadotropin; INR = international normalized ratio; 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).

8.7.1 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.

8.8 Columbia-Suicide Severity Rating Scale

For this drug with CNS activity, procedures follow recommendations of the FDA Guidance for Industry: Suicidal Ideation and Behaviour: Prospective Assessment of Occurrence in Clinical. Trials. (Accessed at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-suicidal-ideation-and-behavior-prospective-assessment-occurrence-clinical-trials on 05 May 2023)

The C-SSRS will be administered per the Schedule of Events in Section 22.1, Appendix 1, Section 22.2, Appendix 2 and Section 22.3, Appendix 3. The C-SSRS is a questionnaire designed for assessment of suicidal ideation and behaviour in adolescents and adults (Posner 2011). The questionnaire takes only a few minutes and must be administered by the PI or delegated to a suitably qualified individual by education and/or training. Clinical study versions of the questionnaire are available for study screening and follow-up visits.

If a subject exhibits suicidal behaviour or active suicidal ideation with intent during the study, the Investigator should discontinue the subject and provide the appropriate treatment.

8.9 Pharmacokinetic Assessments

8.9.1 Plasma Samples for Pharmacokinetic Analysis

[redacted]

8.9.2 Sample Bioanalysis

[redacted]

[redacted]

8.10 Pharmacodynamic Outcomes

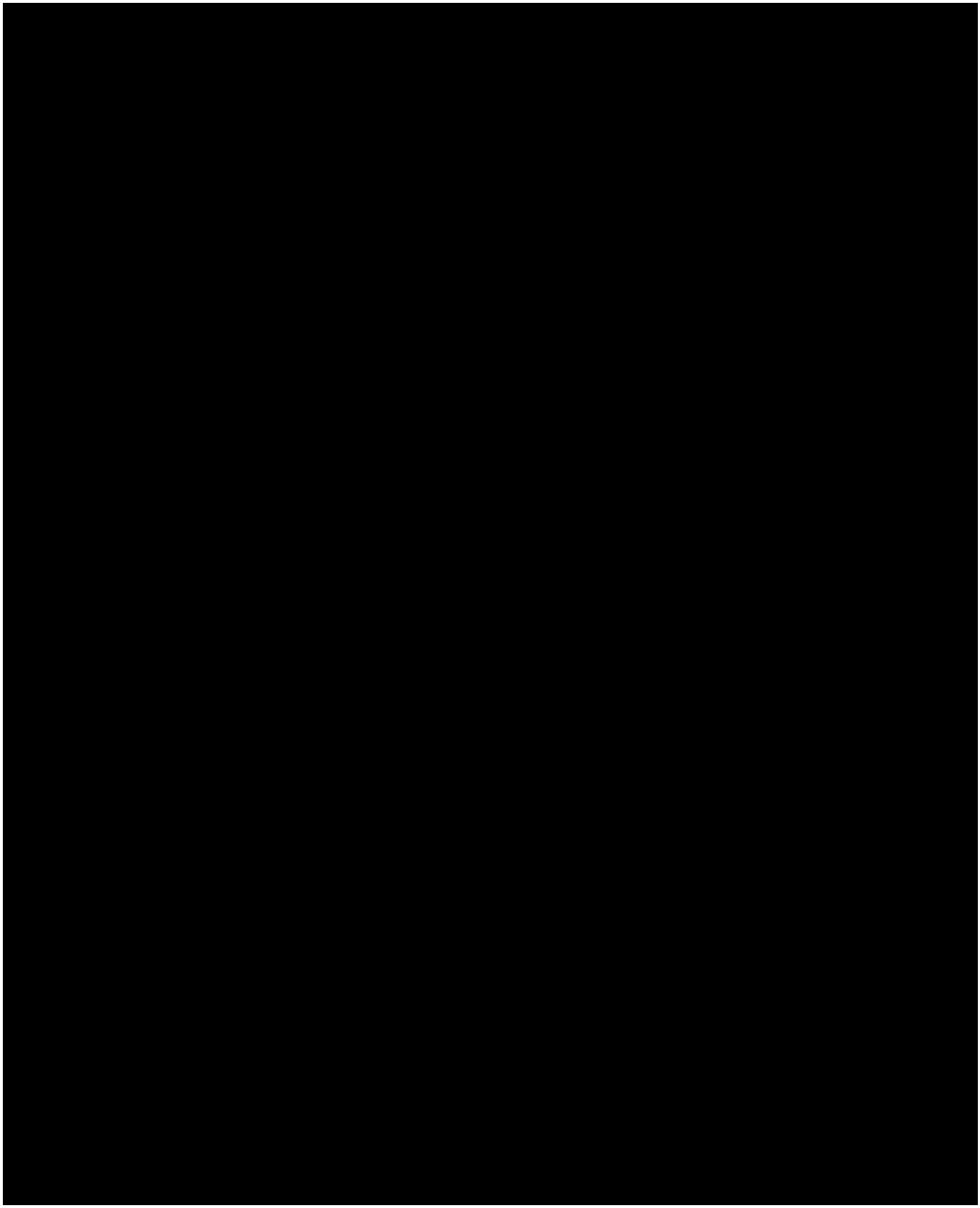
Pharmacodynamic outcomes will be performed as presented in the Schedule of Events tables (Section **22.1**. Appendix 1, Section **22.2**, Appendix 2 and Section 22.3, Appendix 3).

8.10.1 Part I, Part II and Part III

[redacted]

8.10.2 Part III Only

[redacted]



[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.

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 over time is standard for the evaluation of PK parameters.

8.12 Protocol Deviations

A protocol deviation is any non-compliance with the clinical study protocol or ICH/GCP requirements. The non-compliance 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, Section 22.2 Appendix 2 and Section 22.3, Appendix 3.

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

- [redacted] safety ECG tracings
- Vital signs
- Blood collection for plasma PK assessments and clinical safety laboratories
- PD assessments as applicable

9 STUDY DRUG MANAGEMENT

9.1 Description

The term “study drug” is used throughout the protocol to describe INDV-2000, placebo and/or the SUBOXONE SL film received by the subject as per the protocol design. The term “IMP” is used throughout the protocol to refer to INDV-2000 and its placebo.

9.1.1 Drug Manufacturer

9.1.2 Placebo

9.1.3 Blinding and Randomization

Part I and II of this study will be double-blinded to include the healthy volunteers, the Investigator and site staff. The clinical pharmacist and his/her designated team members responsible for IMP dispensation will be unblinded. The DRSC members will be blinded except for the Indivior PK scientist. The DRSC will review blinded clinical safety and laboratory data. Blinded PK data for dose escalation decisions may be presented, and if PK data cannot be presented in a blinded manner, the unblinded PK scientist will make blinded statements regarding those data to aid in dose escalation decisions. The Sponsor team may unblind after the dose escalation decision per cohort has been made (Section 15.2).

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 the study 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 Indivior unblinded statistician.

A copy of the randomization schedule will also be made available to the unblinded team at the clinical site, as well as the laboratory performing the bioanalysis to allow selective analysis of PK samples to measure drug concentrations.

Interim PK parameter calculations will be performed using bioanalytical data with dummy subject numbers and initials in order to maintain the study blind. Interim PK analyses will be performed using nominal time points.

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 date, time and reason for the unblinding must be captured in the source documentation. The Indivior Medical Monitor must be contacted as soon as possible when an unblinding has occurred, and not later than 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).

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 must not be forwarded or revealed to any other blinded team members.

Subjects who are unblinded due to an adverse event will be discontinued from the study and asked to complete an Early Termination Visit. In any instance of accidental subject unblinding, the Indivior Medical Monitor must be alerted as soon as possible and no later than 24 hours after awareness. The decision to continue/discontinue the subject will be made after consultation with the Indivior Medical Monitor.

The study blind will be broken after the completion of Part II of the study and the data have been locked.

9.1.4 Parts I and II

For Part I and Part II, there are 4 planned cohorts.

Part I, Cohort 1 (QD Dosing)

For in-clinic dosing, healthy volunteers will receive INDV-2000 following a fast of at least 2 hours. Healthy volunteers will be administered INDV-2000 with 240 mL (8 ounces) of water. No food will be allowed for at least 1-hour post-dose administration. Water is allowed as desired except for at least 1 hour before and at least 1 hour after drug administration.

Part I, Cohort 2 and Part II, Cohorts 1 and 2 (BID Dosing)

For in-clinic dosing, healthy volunteers will receive their first dose of INDV-2000 in the morning following a fast of at least 2 hours. Healthy volunteers will receive their second dose of INDV-2000 12 hours later, following a fast of a least 2 hours. Healthy volunteers will be administered INDV-2000 with 240 mL (8 ounces) of water. No food will be allowed for at least 1-hour post-dose each administration. Water is allowed as desired except for at least 1 hour before and at least 1 hour after each drug administration. For outpatient dosing, healthy volunteers will be instructed to administer their first dose of INDV-2000 in the morning following a fast of at least 2 hours, and their second dose 10-12 hours later, also following a fast of a least 2 hours. Healthy volunteers will be instructed to wait at least 1 hour before eating after each dose. On outpatient visit days, healthy volunteers will be instructed to not dose their morning dose prior to their clinic appointment and wait to dose until instructed by site staff.

See Table 2 for summary of projected dose per cohort.

Table 2 Part I and Part II Multiple Ascending Study Drug Dosing: Projected Doses

Cohort		Part I, Cohort 1	Part I, Cohort 2	Part II, Cohort 1	Part II, Cohort 2
Dose	Active N=9	INDV-2000 100 mg QD	INDV-2000 100mg BID	INDV-2000 200mg BID	INDV-2000 400mg BID
	Placebo N=3	INDV-2000 Placebo	INDV-2000 Placebo	INDV-2000 Placebo	INDV-2000 Placebo
[redacted]					

Safety and PK evaluation at each dose level.

9.2 Packaging, Labelling and Storage

9.2.1 Packaging and Labelling

[redacted]

9.2.2 Storage Conditions

[redacted]

9.2.3 Drug Shipment

[redacted]

9.3 Drug Administration

The study drug must 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.

9.3.1 Part III

Part III dosing of INDV-2000 will be open-label at projected doses determined after review of Part II, Cohort 2 data, and will not exceed the highest total daily dose leveraged in Part II, Cohort 2 of the study.[redacted]

Subjects will receive their first dose of INDV-2000 in the morning following a fast of at least 2 hours. For twice daily dosing, subjects will receive their second dose 12 hours later, also following a fast of a least 2 hours. No food will be allowed for at least 1 hour after each dose administration. Water is allowed as desired except for at least 1 hour before and at least 1 hour after each drug administration.

9.4 Accountability

The Investigator is responsible for ensuring that all 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 and after Indivior has approved the commencement of destruction, all unused study drug will be destroyed by the Investigator, as per local standard operating procedures (SOP). The IMP must be handled strictly in accordance with the protocol, handling guidelines and the label.

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

Used study drug bottles (for both INDV-2000 and placebo), used SUBOXONE SL film pouches, and unused study drug 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 study drug, and includes, but is not limited to, [redacted], labelling defects or packaging defects, study drug that is thought to be ineffective, or has an appearance, taste or odour that is outside of what is expected.

All product complaints must 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 are to 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 Prior and Concomitant Therapies

Therapies and medications will be collected from screening until the EOS visit or the ET visit, at the time points listed Section 22.1, Appendix 1, Section 22.2, Appendix 2 and Section 22.3, Appendix 3. 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 and medications during the study will be documented, including cessation of therapy and medication, initiation of therapy and medication and dose changes.

Prior therapies and medications are considered any medication ended prior to first dose of study drug. Therapies and medications are considered concomitant if taken after dosing with IMP.

For Part III, therapies and medications taken after study drug but prior to IMP are considered run-in therapies and medications.

Any changes to concomitant therapies and medications that are not listed as permitted concomitant therapies and medications must 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, dosing must be withheld for at least 2 hr before or 1 hr after administration of IMP. Additionally, in Part III of the study, non-opioid rescue medications to treat drug withdrawal signs and symptoms will be allowed in the study based on the Investigator's medical judgment. In Part III, if a subject screen fails, discontinues or completes the study, they will be given options for their continued treatment for OUD by the clinical facility.

9.6.2 Prohibited Concomitant Therapies

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

The following medications are CYP3A4 inhibitors or inducers and are expressly prohibited during study participation:

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.

Strong and moderate inducers of CYP3A4 include carbamazepine, phenytoin, rifampin, St John's wort, bosentan and phenobarbital.

Indivior or specified designee must be notified as soon as the site is aware that the subject received any of these medications during study participation to determine if they are to be discontinued.

9.6.3 Lifestyle Restrictions

9.6.3.1 Fluid and Food Intake (Parts I, II and III)

Dosages [redacted] should be swallowed whole. Healthy volunteers/subjects must avoid poppy seeds, grapefruit and grapefruit juice while on study drug.

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

9.6.3.2 Subject Activity Restrictions (Parts I, II and III)

Subjects will not be permitted to perform heavy exercise while housed in the clinical unit. For the outpatient portion of the study, subjects will be asked to refrain from heavy exercise that could result in muscle soreness starting 24 hours before IMP administration and before outpatient safety visits.

9.6.3.3 Caffeine, Alcohol and Tobacco Restrictions (Parts I and II, but Not Part III)

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

From 24 hours prior to the Day -1 check-in, through discharge from the in-clinic period, subjects will not be permitted to drink caffeine-containing beverages, eat caffeine-containing foods or use caffeine-containing products.

From 24 hours prior to the Day -1 check-in, through discharge from the in-clinic period, subjects will not be permitted to drink alcohol. Subjects must refrain from heavy alcohol use (>2 drinks/day for women and >3 drinks/day for men) from discharge through the EOS visit.

9.7 Compliance

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

In Part I and Part II, study drug will be dispensed by an unblinded member of the site staff, and it will be administered by designated qualified blinded study personnel at the clinical facility. Part III is open label and, as such, all parties are unblinded. The PI or sub-Investigator will be present during the in-clinic administration of study drug. The time and duration, the dose delivered and any in-clinic dosing observations will be recorded in source documentation. Study drug administration conducted by the subject on outpatient dosing days will be recorded in the subject's dosing diary. 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 a study drug regardless of the presence of a causal relationship to the study drug. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with a study drug, whether or not considered related to the study drug.

Events meeting the definition of an AE include:
- 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 of either study drug or a concomitant medication.
- Symptoms and/or the clinical sequelae of an overdose of study drug. Overdose per se will not be reported as an AE/SAE.
- Signs, symptoms or the clinical sequelae resulting from special interest conditions (e.g., study drug misuse, medication error, study drug withdrawal, etc.).
- 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 study drug 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 study drug-related or not.

10.1.1 Time Period for Collecting Adverse Events

Adverse event monitoring and reporting will begin after 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 study drug that may affect safety. Treatment-emergent AEs will be defined as events observed after starting administration of INDV-2000 or placebo. For Part III, run-in AEs will be defined as events observed after starting SUBOXONE SL film and before starting INDV-2000.

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 is to 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 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. If findings are noted in the 90 day post last dosing day safety follow up call for male participants, these will be recorded as Adverse Events and followed until completion of required assessments. The study site personnel will make every effort to contact the subject as outlined in Section 6.6.2, after which the outcome of the AE will be considered ongoing and 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.

An event existing prior to study drug administration and worsening in intensity post-study drug administration will be recorded as a new event. For events that occur after the first study drug administration, the maximum intensity, toxicity (Parts I and II only), and seriousness should be reflected in the event record.

Parts I and II only: For any applicable events appearing in the Toxicity Grading Scale considered by the Investigator to be an adverse event according to Section 10.1.4, the intensity 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). Any event not falling under one of the specific categories listed will be graded as above.

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 study drug.

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

- Not Related: Data are available to identify a clear alternative cause for the AE other than the study drug.

- Related: The cause of the AE is related to the study drug 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 study drug 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 study drug, 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 study drug 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 22.4, Appendix 4.

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, study drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though study drug-induced hepatitis can be fatal.

AEs requiring hospitalization will be considered SAEs. Hospitalizations for elective surgery or routine clinical procedures that are not the result of an 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 fulfils 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.

Additional PK samples may be collected for subjects who experience an SAE. Samples should be collected as soon as the Investigator is made aware of the SAE and additional blood samples may be collected after resolution of the SAE.

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). A paper SAE Reporting Form must be completed and submitted to Indivior Pharmacovigilance:

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 with concomitant medications or illicit drugs must be communicated as an SAE and fully documented. Any symptoms of overdose with study drug would be assessed according to criteria for treatment-emergent and SAEs outlined in sections above. Details of any signs or symptoms and their management should be recorded, including details of any antidote(s) administered.

12 PREGNANCY

In the case where a subject's routine pregnancy test as required per protocol is positive for pregnancy prior to dosing, the subject must not be dosed. If the subject has a positive urine pregnancy test, a confirmatory serum pregnancy test will be performed.

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

If a female subject suspects that she is pregnant (e.g., missed period, self-administered pregnancy test) during treatment or within 90 days of the last exposure to study drug, treatment will be immediately stopped, where applicable. The subject will be instructed to return to the clinical unit as soon as possible (preferably within 48 hours) to undergo a serum pregnancy test. If the result of the serum pregnancy test confirms the subject is pregnant, the subject will be discontinued from the study and will undergo all final study visit procedures (with the exception of any additional pregnancy testing).

In the case where a subject's routine pregnancy test as required per protocol is positive for pregnancy, treatment will be immediately stopped. If the subject has a positive urine pregnancy test, a confirmatory serum pregnancy test should be performed. The subject will be discontinued from the study and complete final study visit procedures (with the exception of any additional pregnancy testing). The Investigator should fully inform the female subject of the serious risk to the foetus as well as discuss the desirability of continuing the pregnancy.

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 pregnancy. The subject 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 foetal status (presence or absence of anomalies) or indication for procedure.

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

If the partner of a study subject becomes pregnant within 90 days of the last dose of study drug, 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 foetal status (presence or absence of anomalies) or indication for procedure.

13 DATA MANAGEMENT

13.1 Data Collection and Management

Data will be entered into subject eCRFs in a validated, access-controlled Clinical Data Management System (CDMS) and will be combined with other data captured centrally outside of the eCRF in a secure computing environment. Clinical data will be collected and managed in accordance with a study-specific data management plan to ensure that integrity of the data is maintained. Adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Completed eCRFs (including data queries and audit trail) will be retained by Indivior. Electronic copies of completed eCRFs 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.

13.1.1 Database Quality Assurance

Subject 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 programmatically and/or manually and addressed by the investigational site. Only authorized personnel will make corrections to the eCRFs, and all corrections will be documented in the CDMS audit trail.

13.1.2 Source Documents

The Investigator is responsible for the quality of the data recorded in the eCRFs. The data recorded must 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 eCRF will be considered the source document for individual eCRF elements such as study-specific scales if those data are collected directly onto an eCRF.

14 STATISTICS

14.1 General Procedures

This section describes the sample size, analysis populations and planned analyses for primary, secondary and exploratory endpoints and for safety assessments. 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, II and III of the study. For Parts I and II, data will be summarized by dosing cohort for active treatment and for placebo subjects combined over all dosing cohorts. 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 and the percentage of subjects in corresponding categories. Individual subject data will be presented in data listings. Data listings will include all data collected from enrolled subjects.

For change from baseline calculations, baseline will be defined as the last measurement taken prior to administration of IMP (INDV-2000 or placebo for Parts I and II, and INDV-2000 for Part III). For blood pressure and numeric ECG parameters, triplicate means will be used for baseline.

14.2 Sample Size

Part I (2 cohorts) and Part II (2 cohorts): Each cohort will be composed of 12 healthy volunteers (9 receiving active and 3 placebo). A total of 48 healthy male and female volunteers are planned to participate in both parts. Study subjects who are randomized but do not receive study drug will be replaced.

Part III: A single group of up to 16 treatment seeking subjects with OUD are planned to participate.

The sample sizes are not based on formal power calculations because the study is designed to provide preliminary descriptive assessments of the safety, tolerability and PK for INDV-2000. The sample sizes used are 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 Run-In Safety Population

The Run-In Safety Population is defined as subjects who received at least one dose of study drug during the Part III run-in period.

14.3.3 Pharmacokinetic Population

The PK analysis population is defined as subjects who received at least one dose of INDV-2000, have an adequate number of PK samples collected to derive any PK parameter, and have no protocol deviations that would significantly alter plasma concentration of INDV-2000.

14.4 Demographic and Baseline Characteristics

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

14.5 Extent of Exposure

Exposure will be summarized for the Safety Population. Exposure parameters will include total number of doses, dose duration, percentage of expected number of doses, and a binary variable for number of doses < 80% of expected. For Part II, percentage of expected doses and the binary variable will be summarized both overall and separately for in-patient vs. outpatient dosing. For Part III, exposure will be summarized for both INDV-2000 and buprenorphine.

14.6 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by WHO Drug Dictionary medication class and standardized name.

14.7 Study Endpoints

14.7.1 Primary Endpoints

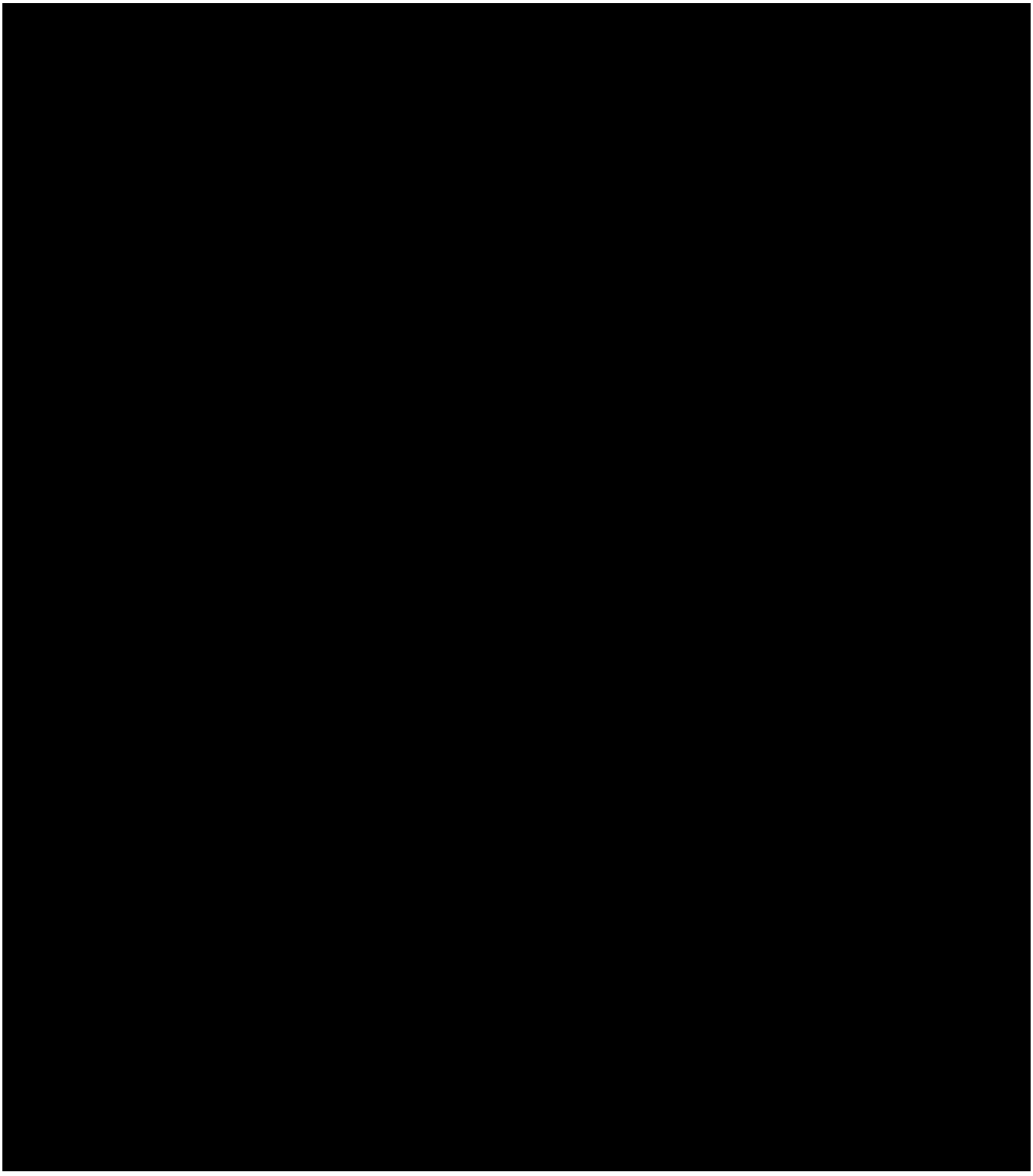
The primary endpoints for Parts I, II and III are the incidence, severity and relatedness of TEAEs; treatment-emergent SAEs (TESAEs); TEAEs leading to discontinuation; and fatal TEAEs. The primary endpoints will be assessed from first IMP dose through the final follow-up and will be summarized for the Safety Population as descriptive statistics only.

14.7.2 Secondary Endpoints

Secondary endpoints for Parts I and II will be PK parameters of INDV-2000 following dosing on Days 1 and 7, and Day 28 (Part II). PK parameters will be summarized as descriptive statistics for the PK Population and will comprise C_{max}, T_{max} and $AUC_{0\text{-}24 \text{ or } 0\text{-}12}$ for INDV-2000.

There are no secondary endpoints for Part III.

14.7.3 Exploratory Endpoints



[redacted]

14.8 Pharmacokinetic Analysis

[redacted]

14.9 Safety Assessments

Safety parameters will be summarized for the Safety Population and will comprise TEAEs, laboratory evaluations, vital signs, 12-lead ECG findings, physical examination findings and C-SSRS assessments.

14.9.1 Treatment-Emergent Adverse Events (TEAEs)

A TEAE is defined as an AE with start date/time at or after dosing with IMP. The number and percentage of subjects reporting TEAEs will be presented for each treatment by MedDRA system organ class (SOC) and preferred term (PT), each in descending order of frequency among all subjects in the given part of the study (then alphabetically in case of ties).

Incidence and number of study drug-related TEAEs, TESAEs, study drug-related TESAEs, TEAEs leading to death, TEAEs leading to IMP discontinuation, and TEAEs leading to IMP interruption will be presented both in an overall summary table and by SOC and PT. Included in the overall summary table will be incidence and number of severe TEAEs and TEAEs with grade 3 or higher toxicity grade (applicable for Parts I and II only). TEAE incidence will also be summarized by maximum severity within SOC and PT. Incidence of TEAEs will be summarized by PT only (not SOC) in descending order of incidence among all subjects (within study part).

In summaries by severity and relationship to study drug, 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/most related occurrence. Missing severity, toxicity, and relatedness will be queried until resolution.

Non-TEAEs and, for Part III, run-in AEs in the Run-In Safety Population will be summarized separately.

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

14.9.2 Laboratory Evaluations

Laboratory evaluations will be summarized as observed values and changes from baseline by analysis visit. Normal/abnormal shifts from baseline will also be summarized.

14.9.3 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, temperature) will be summarized as observed values and changes from baseline by analysis visit. For SBP and DBP, baseline will be defined as the mean of triplicate measurements.

14.9.4 12-Lead Electrocardiogram

Numeric 12-lead ECG parameters will be summarized as observed values and changes from baseline by analysis visit, with baseline defined as the mean of triplicate measurements. ECG interpretation will be summarized by visit as a categorical variable, with baseline interpretation defined as the majority of the triplicate assessments; if there is no majority, the Sponsor will be notified and will provide a baseline interpretation based on a review of the data.

14.9.5 Physical Examination

Clinically significant physical examination changes from screening will be reported as AEs; therefore, there will be no separate listings or summaries of physical examination findings.

14.9.6 Columbia-Suicide Severity Rating Scale

The composite endpoints Suicidal Ideation and Suicidal Behaviour will be derived from the following 10 binary C-SSRS questions, reordered from the actual scale to facilitate the derivation:

Question 1	Wish to be Dead
Question 2	Non-specific Active Suicidal Thoughts
Question 3	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Question 4	Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Question 5	Active Suicidal Ideation with Specific Plan and Intent
Question 6	Preparatory Acts or Behaviour
Question 7	Aborted Attempt
Question 8	Interrupted Attempt
Question 9	Actual Attempt (non-fatal)
Question 10	Completed Suicide

Suicidal Ideation is derived as “yes” if any of Question 1-5 has a “yes” response. Suicidal Behaviour is derived as “yes” if any of Question 6-10 has a “yes” response. If there are zero “yes” responses and at least one question has a missing response, the derived composite will be missing. Suicidal Ideation and Suicidal Behaviour will be summarized as a categorical variable by analysis visit.

14.10 Pharmacodynamic Outcomes

[redacted]

14.11 Interim Analysis

For Parts I and II there will be a blinded review of the safety and applicable PK data after completion of each cohort, before dose escalation. The safety data review will be conducted by the DRSC (Section 15.2) using stopping rules defined in Section 6.5.

14.12 Handling of Missing Data

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

15 ETHICS AND RESPONSIBILITIES

15.1 Good Clinical Practice

Prior to site activation, Indivior or a designated representative will obtain approval/favourable 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 members will be blinded except for the PK scientist. The DRSC will review blinded clinical safety and laboratory data. Blinded PK data for dose escalation decisions may be presented, and if PK data cannot be presented in a blinded manner, the unblinded PK scientist will make blinded statements regarding that data to aid in dose escalation decisions. Individual participant data may also be reviewed as needed (See Section 6.5). Based on the data presented, the DRSC may choose to unblind the data to the Sponsor only prior to making a dose escalation decision. Every effort will be maintained to keep the Investigator blinded. The proposed dose escalation scheme for Part I and Part II 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 favourable 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 centres, review of protocol procedures with the Investigators and associated personnel before the study, and periodic monitoring visits by Indivior (or designee's). Written instructions will be provided for IMP preparation and dosing, collection, preparation and shipment of blood, plasma and urine 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 centre. 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 centre without first redacting subject identifiers. In the case of the need for remote clinical monitoring, additional processes could be developed to allow for the secured electronic provision of unredacted source documentation to the clinical monitors. These will be defined within the Clinical Monitoring Plan.

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22 APPENDICES

22.1 APPENDIX 1 – Schedule of Events Part I

Evaluation	Screening Days -28 to -1	In clinical unit (Days)								Discharge	Outpatient	Follow-up
		-1	1	2	3	4	5	6	7	8	10 (± 2 days)	Day 14/EOS/ET[12] (± 3 days)
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Randomization		X										
Admission to Clinical Unit[1]		X										
COVID-19 PCR Test		X										
Discharge from Clinical Unit[2]										X[2]		
Demographics (Includes height, weight and BMI)	X											
Medical History	X											
Physical Examination[3]	X	X	X	X		X				X	X	X
Urine Drug Screen	X	X										
Alcohol test	X	X										
Serum Pregnancy Test	X											X
Urine Pregnancy Test		X										
Urinalysis	X	X								X	X	X
Clinical Laboratory Assessments (Chemistry and Haematology)	X	X	X[4]		X[4]		X[4]			X[4]	X	X
Serology (HIV, Hepatitis B and C)	X											
Coagulation Panel (PT/INR)	X											
FSH (post-menopausal females only)	X											
Vital Signs	X	X	X[5]	X[5]	X[5]	X[5]			X[5]	X[5]	X	X
12-Lead Electrocardiogram	X	X	X[6]	X[6]	X[6]	X[6]			X[6]		X	X
26-Hour Holter Monitoring[7]	[redacted]											
[redacted]												
PK Sampling[9]			X	X	X	X	X	X	X	X	X	
Drug Administration[10]			X	X	X	X	X	X	X			
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X

Evaluation	Screening Days -28 to -1	In clinical unit (Days)								Discharge	Outpatient	Follow-up
		-1	1	2	3	4	5	6	7	8	10 (± 2 days)	Day 14/EOS/ET[12] (± 3 days)
Prior or Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X
CSSR-S[11]	X	X				X			X	X	X	X

1: Check Day -1 Criteria prior to randomization

2: Discharge occurs after completion of assessments

3: A full physical examination will be completed at Screening. All other visits will be a brief physical examination consisting of heart, lung, abdomen and targeted for any AEs. Pre-dose exam can occur any time pre-AM dose on Day 1, 90 minutes post-Day 1 AM dose (±30 min), Day 2 24 hr post-Day 1 AM dose (±2 hr), and Day 4 72 hours post-Day 1 AM dose (±2 hr). To be performed also on Day 8 before discharge, and Day 10 72 hours post-Day 7 AM dose (±2 hr)

For male participants, a testicular exam will be performed at the Screening and End of Study visits.4: Clinical Laboratory Pre-AM dose (-1hr) on Day 1, Day 3 and Day 5 and on Day 8 before discharge.

5: **Part I, Cohort 1 (QD)**: On Day 1, Day 2 and Day 7: pre-dose (-60 min),1 hour post-dose (±30 min), 2 hours post-dose (±30 min), 4 hours post-dose (±30 min), and 6 hours post-dose (±30 min). On Day 3 and Day 4, vital signs are collected pre-dose (-60 min). On Day 8 vital signs are collected before discharge. Triplicate SBP and DBP assessments will be obtained at least 1 minute apart on pre-dose Day 1 and as needed to assess stopping criteria.
Part I Cohort 2 (BID): On Day 1, and Day 7 (relative to AM dose): pre-dose (-60 min), 1 hour post-dose (±30 min), 2 hours post-dose (±30 min), 4 hours post-dose (±30 min), 6 hours post-dose (±30 min), 8 hours post-dose (±30 min), 12 hours post-dose (±30 min), 14-16 hours post-dose (±30 min). On Day 2, Day 3, and Day 4 vital signs are collected pre-AM dose (-60 minutes). On Day 8 vital signs are collected before discharge. Triplicate SBP and DBP assessments will be obtained at least 1 minute apart on pre-AM dose Day 1 and as needed to assess stopping criteria.

6: On Day 1, Day 2 and Day 7: pre-AM dose (-60 min), 2 hrs post-AM dose (±30 min), and 6 hours post-AM dose (±30 min). On Day 3 and Day 4, ECGs are done pre-AM dose (-60 min). Triplicate tracings will be obtained at least 1 minute apart on pre-AM dose Day 1, and as needed to assess stopping criteria.

7: Holter Monitoring [redacted]

8: [redacted]

9: For PK collection timepoints, refer to Section 22.5, Appendix 5 – Plasma PK Sampling Windows.

10: **Part I, Cohort 1 (QD):** In house dosing is to occur 24 hr from the previous dose, ±30 min.
Part I, Cohort 2 (BID): In house dosing is to occur 12 hours apart, ±30 min.

11: Lifetime at Screening Visit, the rest of the assessments are the 'since last visit' assessment.

12: Male participants will complete a safety phone call 90 days (±10 days) after their last dosing day to assess any new pain, swelling, or nodular lesions in the scrotum. If findings are noted, these will be recorded as AEs and followed until completion of required assessments.

22.2 APPENDIX 2 – Schedule of Events Part II

Evaluation	Screening Days -28 to -1	In Clinical Unit (Days)								Discharge	Outpatient (Days)				Follow-up
		-1	1	2	3	4	5	6	7	8	10 (±2)	15 (±2)	22 (±2)	28 (±2)	Day 35/EOS/ET[12] (± 3 days)
Informed Consent	X														
Inclusion/Exclusion Criteria	X														
Randomization		X													
Admission to Clinical Unit[1]		X													
COVID-19 PCR Test		X													
Discharge from Clinical Unit[2]										X					
Demographics (Includes height, weight and BMI)	X														
Medical History	X														
Physical Examination[3]	X	X	X	X		X				X	X	X	X	X	X
Urine Drug Screen	X	X													
Alcohol test	X	X													
Serum Pregnancy Test	X														X
Urine Pregnancy Test		X										X		X	
Urinalysis	X	X							X			X		X	X
Clinical Laboratory Assessments (Chemistry and Haematology)	X	X	X[4]		X[4]		X[4]			X[4]	X[4]	X[4]	X[4]	X[4]	X
Serology (HIV, Hepatitis B and C)	X														
Coagulation Panel (PT/INR)	X														
FSH (post-menopausal females only)	X														
Vital Signs	X	X	X[5]	X[5]	X[5]	X[5]			X	X[5]	X[5]	X[5]	X[5]	X[5]	X

Evaluation	Screening Days -28 to -1	In Clinical Unit (Days)								Discharge	Outpatient (Days)				Follow-up
		-1	1	2	3	4	5	6	7	8	10 (±2)	15 (±2)	22 (±2)	28 (±2)	Day 35/EOS/ET[12] (± 3 days)
12-Lead Electrocardiogram	X	X	X[6]	X[6]	X[6]	X[6]			X[6]		X[6]	X[6]	X[6]	X[6]	X
26-Hour Holter Monitoring[7]	[redacted]														
PK Sampling[9]			X	X	X	X	X	X	X	X	X	X	X	X	
Drug Administration[10]			X	X	X	X	X	X	X	X	X	X	X	X	
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior or Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS[11]	X	X	X			X			X	X	X	X	X	X	X

1: Confirm Check-In Criteria (defined in Section 5.4) prior to admission to the unit
2: Discharge occurs after completion of assessments.
3: A full physical examination will be completed at Screening. All other visits will be a brief physical examination consisting of heart, lung, abdomen and targeted for any AEs. All timepoints are relative to the AM dose. Pre-dose exam can occur any time pre-dose on Day 1, 90 minutes post-Day 1 dose (±30 min), Day 2 24 hr post-Day 1 dose (±2 hr), and Day 4 72 hours post-Day 1 dose (±2 hr). To be performed also on Day 8 before discharge, and Day 10 at 72 hours post-Day 7 dose (±2 hr). On outpatient days, physical exam can occur any time prior to AM dosing.
For male participants, a testicular exam will be performed at the Screening and End of Study visits.
4: Clinical Laboratory Pre-AM dose (-1 hr) on Day 1, Day 3, Day 5 and Day 8 before discharge. On outpatient days obtain samples before AM dosing.
5: On Day 1, Day 2 and Day 7 (timepoints are relative to AM dose): pre-dose (-60 min), 1 hour post-dose (±30 min),2 hrs post-dose (±30 min), 4 hours post-dose (±30 min), 6 hours post-dose (±30 min), 8 hours post-dose (±30 min), 12 hours post-dose (±30 min), 14-16 hours post-dose (±30 min). On Day 3 and Day 4, vitals are done pre-dose (-60 min). Vital signs to be captured any time pre-dose and 90 minutes post-dose (±30 min) on Day 8 and each outpatient dosing day. Triplicate SBP and DBP assessments will be obtained at least 1 minute apart on pre-dose Day 1 and as needed to assess stopping criteria.
6: On Day 1, Day 2 and Day 7 (timepoints are relative to AM dose): pre-dose (-60 mins),2 hrs post-dose (±30 min), and 6 hours post-dose (±30 min). On Day 3 and Day 4, ECGs are done pre-dose (-60 min). ECG to be captured pre-dose (-1 hr), and 90 minutes post-dose (±30 min) on each outpatient dosing day. Triplicate tracings will be obtained at least 1 minute apart on pre-dose Day 1 and as needed to assess stopping criteria.
7: Holter monitoring [redacted]
9: For PK collection timepoints, refer to Section 22.5, Appendix 5 – Plasma PK Sampling Windows.

10: In house dosing on Days 1 through 8 inclusive is to occur every 12 hours, ±30 mins. Outpatient dosing will continue twice daily every 10-12 hours (±30 mins) until the final dose on Day 28. Subjects will only dose once on Day 28, in clinic. On days where the subject returns to the clinical unit, the subject will be instructed to take their first dose while in the clinic. On days when the subject is dosing at home, they will be instructed to capture each time and dose they took in their dosing diary.
11: Lifetime at Screening Visit, the rest of the assessments are the 'since last visit' assessment.
12: Male participants will complete a safety phone call 90 days (±10 days) after their last dosing day to assess any new pain, swelling, or nodular lesions in the scrotum. If findings are noted, these will be recorded as AEs and followed until completion of required assessments.

22.3 APPENDIX 3 – Schedule of Events Part III

22.3.1 Part III - Screening and SUBOXONE SL Film Run-In

Evaluation	Screening	SUBOXONE Sublingual Film (In clinical unit)					
		Induction (3 days)			Dose-Adjustment (3 days)		
	Days -35 to -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1[7]
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
COVID-19 PCR Test		X					
Admission to Clinical Unit[1]		X					
Demographics (Includes height, weight and BMI)	X						
Medical History	X						
Physical Examination[2]	X						
Urine Drug Screen	X	X					
Alcohol test	X	X					
Serum Pregnancy Test	X						
Urine Pregnancy Test		X					
Urinalysis	X						
Clinical Laboratory Assessments (Chemistry and Haematology)	X	X[3]					
Serology (HIV, Hepatitis B and C)	X						
Coagulation Panel (PT/INR)	X						
FSH (post-menopausal females only)	X						
Vital Signs	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
12-Lead Electrocardiogram	X						
[redacted]							
SUBOXONE SL film Administration[5]		X	X	X	X	X	X
AE Assessment		X	X	X	X	X	X

Evaluation	Screening	SUBOXONE Sublingual Film (In clinical unit)					
		Induction (3 days)			Dose-Adjustment (3 days)		
	Days -35 to -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1[7]
Concomitant Medication Assessment		X	X	X	X	X	X
C-SSRS[6]	X						

1: Confirm Check-In Criteria (defined in Section 5.4) prior to admission to the unit.
2: A full physical examination will be completed at Screening. For male participants, a testicular exam will be performed.
3: Clinical Laboratory Assessments are conducted pre-dose (-1 hr).
4: To be conducted pre-dose (-30 mins), and then at 2 hours (±30 mins)
5: Administer per the USPI.
6: Lifetime assessment to be completed during screening.
7: Day -1 procedures on this table are to be conducted prior to Run-In Assessment criteria on next table

22.3.2 Part III – Schedule of Events

Evaluation	In clinical unit (Days)															Follow-up EOS/ET (± 3 days)
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	21
Discharge from Clinical Unit															X[1]	
Run-In Assessment[2]	X															
SUBOXONE SL film[3] Administration		X	X	X	X	X	X	X	X	X						
INDV-2000 Administration				X	X	X	X	X	X	X	X	X	X	X		
PK Sampling[4]			X	X						X	X			X	X	
Physical Examination[5]	X		X			X				X		X			X	X
Urine Drug Screen	X							X							X	X
Alcohol test	X							X							X	
Urine Pregnancy Test	X														X	X
Urinalysis	X							X							X	X
Clinical Laboratory Assessments (Chemistry and Haematology)[6]	X			X		X				X		X			X	X
Vital Signs[7]	X	X	X	X		X		X		X		X		X		X
12-Lead Electrocardiogram[8]	X	X	X	X		X		X		X		X		X		X
[redacted]																
C-SSRS[13]	X		X		X		X		X		X		X		X	X
[redacted]																
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

1: Discharge occurs the morning of Day 14 and the clinical facility will provide the subject with options for their continued treatment for OUD.
2: Subjects must meet Run-In assessment criteria (defined in Section 5.4) on Day -1 prior to completing subsequent Day -1 procedures within this table.
3: Dose after INDV-2000 AM dose.
4: For PK collection timepoints, refer to Section 22.5, Appendix 5 – Plasma PK Sampling Windows.
5: A full physical examination will be completed at Screening; All other visits will be a brief physical examination consisting of heart, lung, abdomen and

targeted for any AEs. All timepoints are relative to the AM dose. Pre-dose exam can occur any time pre-dose on Day 2, 90 minutes post-dose (±30 min), Day 5, 9 and Day 11 pre-dose exam can occur any time pre-AM dose. For male participants, a testicular exam will be performed at the End of Study visit.

6: Chemistry and haematology to be collected pre-AM dose (-1hr) on Days 3, 9, and 14. Only liver function tests to be collected pre-AM dose on Days 5 and 11.

7: Vital signs will be completed on Day 1 any time pre-dose, 2 hrs post-dose (±30 min), and 4 hrs post-dose (±30 min) on Days 2, 3, 5, 7, 9, 11, 13. All timepoints are relative to the AM dose. Triplicate SBP and DBP assessments will be obtained at least 1 minute apart on pre-dose Day 1 and as needed to assess stopping criteria.

8:12-lead ECG tracing is to be obtained at admission, and on Days 2, 3, 5, 7, 9, 11 and 13 at pre-dose (-1 hr), 2 hrs post-dose (±30 min). All timepoints are relative to the AM dose. Triplicate tracings will be obtained at least 1 minute apart on pre-dose Day 1 and as needed to assess stopping criteria.

[redacted]

13: Baseline assessment to occur at Day -1, all remaining assessments will be ‘Since Last Visit’ CSSR-S.

[redacted]

22.4 APPENDIX 4 – Liver Safety

The following must occur if a subject meets any of the liver chemistry stopping criteria as outlined in Section 6.5 of the protocol:

- Subject must 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 must 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:

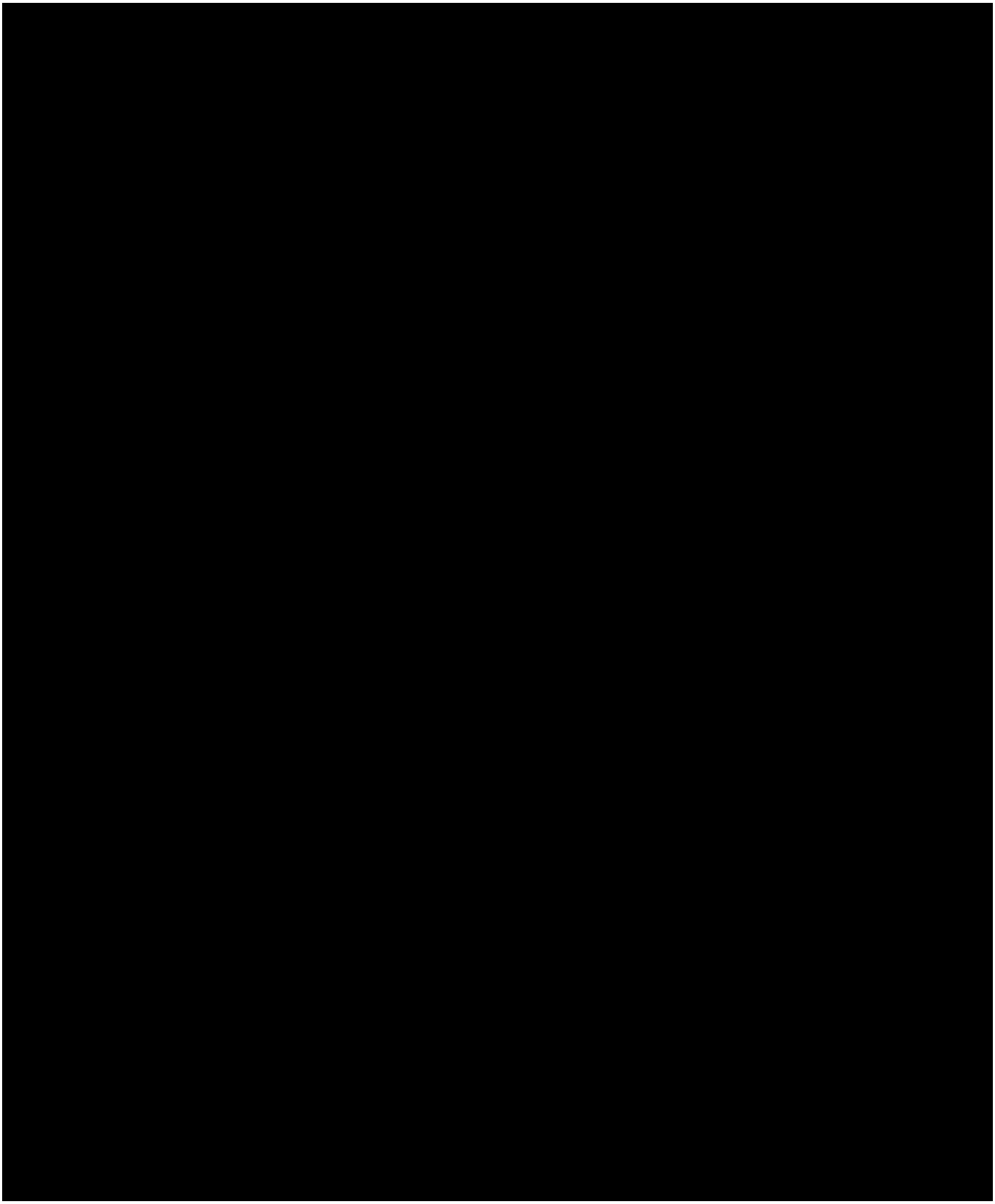
- Viral hepatitis serology including:
    - Hepatitis A Immunoglobulin M (IgM) antibody,
    - HBsAg and Hepatitis B Core Antibody (IgM),
    - Hepatitis C RNA,
    - Cytomegalovirus IgM antibody,
    - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or 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:

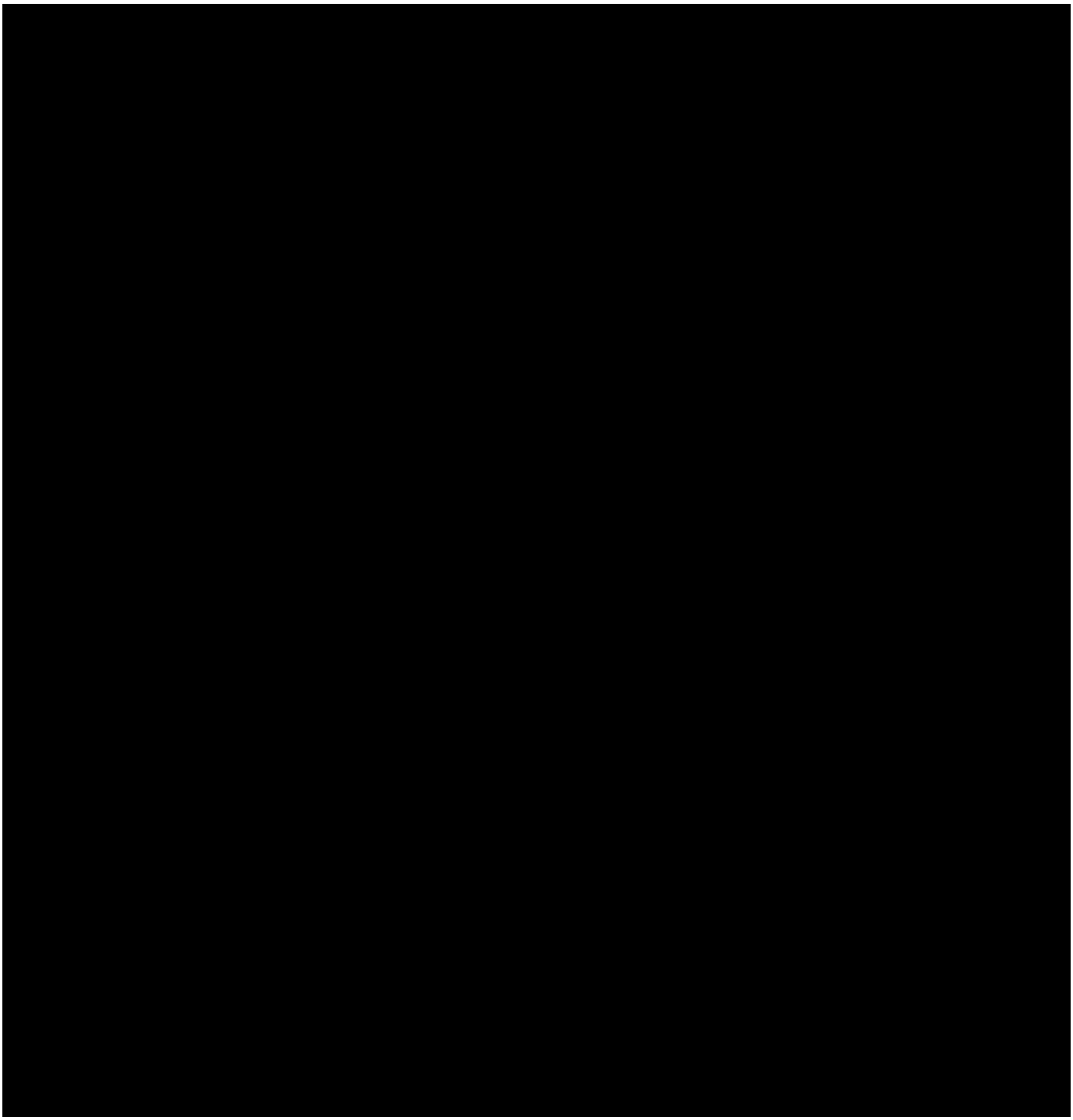
- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).

    - 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 must be entered into the eCRF, if these tests are performed.

22.5 APPENDIX 5 –Plasma PK Sampling Windows





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

Table of Contents

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 enrolment 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 volunteers.

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 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 judgment when characterizing bradycardia among some healthy volunteer 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
Diarrhoea	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 Illness	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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7. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory Reference Values. New England Journal of Medicine. 2004;351:1548-1563.