Title: A Phase 1 Study to Assess Absolute Bioavailability of TAK-935 (OV935) and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [14C]TAK-935 (OV935) in Healthy Adult Male Participants

NCT Number: NCT04992442

Protocol Approve Date: 04 June 2020

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- Named persons or organizations associated with the study.
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PROTOCOL TAK-935-20-001 (OV935)

A Phase 1 Study to Assess Absolute Bioavailability of TAK-935 (OV935) and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [^{14}C]TAK-935 (OV935) in Healthy Adult Male Participants

Sponsor:

Sponsor Contact:

Medical Monitor:

IND Number: 121,234

Date of Final Protocol: 04 June 2020

SPONSOR SIGNATURE PAGE

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PROTOCOL NUMBER: TAK-935-20-001 (OV935)

PPD

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure (IB) (IB, Ed.5) for TAK-935-20-001 (OV935). I have read the TAK-935-20-001 (OV935) study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the International Council for Harmonisation (ICH) E6 Guidelines for Good Clinical Practice (GCP), and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

I will permit study related monitoring, audits, institutional review board (IRB)/independent ethics committee (IEC) review and regulatory inspection, providing direct access to source data/documents.

PPD

Signature of Investigator

Date

PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

Study Role	Name	Address and Telephone Number
Clinical Project Leader	PPD	
Clinical Project Leader		
Medical Monitor		
Drug Safety Physician		
24-Hour Emergency Contact		
Clinical Operations Leader		

Key Study Participants

Study Role	Name	Address and Telephone Number
Clinical Project Leader	PPD	
Clinical Project Leader		
Medical Monitor		
Drug Safety Physician		
Statistician		
Certified Clinical Laboratory		
Total Radioactivity Determination		

1. SYNOPSIS

Name of Sponsor/Company: Ovid Therapeutics Inc.	
Name of Investigational Product: TAK-935 (soticlestat [OV935])	
Name of Active Ingredient: Soticlestat TAK-935 (OV935)	
Title of Study: A Phase 1 Study to Assess Absolute Bioavailability of TAK-935 (OV935) and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [^{14}C]TAK-935 (OV935) in Healthy Adult Male Participants	
Study Center(s): Single site in the USA	
Length of Study: Approximately 65 days from the start of Screening Period until Follow-up Estimated date first participant enrolled: 07/2020 Estimated date last participant completed: 10/2020	**Phase of Development:** Phase 1
Planned Duration of Treatment: Approximately 65 days including the Screening Period. Screening period: 28 days Treatment Period 1: at least 6 days (up to 8 days) Washout period: at least 7 days (from last dosing in Period 1 to dosing in Period 2) Treatment Period 2: at least 6 days (up to 11 days) Follow-up period: 30 days (from dosing in Period 2)	
Objectives and Endpoints: **Study Primary Objectives:** <u>Period 1 (Absolute Bioavailability [ABA])</u> • To determine ABA of TAK-935 following a single microdose intravenous (IV) administration of 50 µg (approximately [~] 1 microcurie [µCi]) [^{14}C]TAK-935 and a single oral administration of 300 mg TAK-935. <u>Period 2 (absorption, distribution, metabolism, and elimination [ADME])</u> • To assess the mass balance (ie, cumulative excretion of total radioactivity in urine and feces) following a single oral administration of 300 mg (~100 µCi) [^{14}C]TAK-935.	

- To characterize the pharmacokinetics (PK) of TAK-935 and its metabolite (M-I) in plasma and urine, and total radioactivity concentration equivalents in plasma and whole blood following a single oral administration of 300 mg (~100 µCi) [^{14}C]TAK-935.

Study Secondary Objectives:

Period 1 (ABA):

- To determine the PK of [^{14}C]TAK-935 following a single IV administration of 50 µg (~1 µCi) [^{14}C]TAK935 and the PK of TAK-935 and M-I following a single oral administration of 300 mg TAK-935.
- To determine fecal and urinary excretion of the parent [^{14}C]TAK-935 following a single IV administration of 50 µg (1 µCi) [^{14}C]TAK-935.

Period 2 (ADME):

- To assess the metabolic profile of TAK-935 in plasma, urine, and feces following a single oral administration of 300 mg (~100 µCi) [^{14}C]TAK-935.

Periods 1 (ABA) and 2 (ADME):

- To assess the safety of TAK-935 during the ABA and ADME study periods.

Study Primary Endpoints

Period 1 (ABA):

- Absolute bioavailability (F) as percent F (%F) for TAK-935.

Period 2 (ADME):

- Percent of total radioactivity excreted in urine (Cum%Dose[u]) and feces (Cum%Dose[f]) relative to the administered radioactive dose (Combined Cum%Dose).
- Amount of total radioactive excreted in urine (Ae[u]) and feces (Ae[f]) and the percent of administered radioactive dose excreted in urine and feces within a given collection interval urine (%Dose[u]) and feces (%Dose[f]).
- PK parameters C_{max}, t_{max}, $t_{1/2z}$, AUC_{∞}, AUC_t, and AUC_{last} for TAK-935 in plasma.
- PK parameters C_{max}, t_{max}, $t_{1/2z}$, AUC_{∞}, AUC_t, and AUC_{last} for total radioactivity concentration equivalents in plasma and whole blood.
- PK parameters for renal clearance (CL_R) for TAK-935 in urine.
- PK parameters for amount excreted in each collection interval (Ae_{t1-t2}) for TAK-935 in urine.
- The change over time in percentage of [^{14}C] radioactivity in whole blood relative to plasma (ie, whole blood:plasma partitioning ratio).

Study Secondary Endpoints

Period 1 (ABA):

- PK parameters C_{eoi} (IV infusion), C_{max} (oral), t_{max} (oral), AUC_{∞}, AUC_t, AUC_{last}, and $t_{1/2z}$ for TAK-935, and [^{14}C]TAK-935 in plasma.
- Total radioactivity excreted and percentage of dose excreted in the feces (Ae[f] and %Dose[f]) and urine (Ae[u] and %Dose[u]) as total radioactivity following IV dosing.

Period 2 (ADME):

- Metabolic profile of TAK-935 in plasma, urine, and feces following a single oral administration of 300 mg (~100 µCi) [^{14}C]TAK-935.

Periods 1 (ABA) and 2 (ADME):

- Tabulated treatment-emergent adverse events (TEAEs) and summary statistics for clinically relevant 12-lead electrocardiograms (ECGs), vital signs, and clinical laboratory test results.

Study Design and Methodology:

This is an open-label, 2-period, fixed-sequence, single-dose study in 6 healthy adult male participants.

On Day 1 of Period 1 (ABA Study Period), participants will receive a single unlabeled oral 300 mg dose of TAK-935 in tablet form (three 100 mg tablets). At 0.17 hours (10 minutes) post oral dosing (ie, 15 minutes prior to the median t_{max} for the oral unlabeled dose [~ 0.42 hours or 25 minutes]), participants will receive a 15-minute IV infusion of a microdose of 50 µg (approximately equivalent to ~1 µCi) [^{14}C]TAK-935. Serial blood sampling will be performed up to 48 hours (Day 3) to determine the PK of TAK-935 and M-I metabolite (and others, if applicable) in plasma for the oral dose and [^{14}C]-total radioactivity and PK of [^{14}C]TAK-935 in the plasma for the IV dose. Urine and fecal output will also be collected up to 120 hours post dose to determine [^{14}C]-total radioactivity. Collection of urine and fecal samples will continue until one of the release criteria (participants remain in the clinical research unit [CRU]) is met (ie, 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to Day 8, but no less than Day 6, for [^{14}C]-total radioactivity excretion in urine and feces. Participants who meet release criteria before Day 8 will remain confined in the CRU until Day -1 of Period 2 and throughout Period 2 (until Period 2 discharge criteria are met).

There will be a washout period of at least 7 days between the last dose in Period 1 and the dose in Period 2.

On Day 1 of Period 2 (ADME Study Period), participants will receive a single oral dose of 300 mg (~100 µCi) [^{14}C]TAK-935 in solution. Serial blood sampling will be performed and urine and feces will be collected to determine the PK of TAK-935 and M-I metabolite (and others, if applicable) in plasma and urine, and total radioactivity in plasma, whole blood, urine, and feces, and to characterize the metabolite profiles of TAK--935 in plasma, urine, and feces. Complete urinary and fecal output will be collected during the confinement period until discharge criteria are met (anticipated to be 10 days post dose or less).

In Period 2, participants will be confined to the CRU for at least 5 days post dose (ie, 120 hours) and until 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples. If less than 90% of the total dose of radioactivity administered is recovered in urine and fecal samples the participant will continue to stay at the CRU until a discharge criterion is met (ie, 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity per 24 hour interval for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to Day 11 (ie, 240 hours).

Since up to an approximate 24-hour time lag is anticipated for radioactivity counting of samples, actual participant release from the CRU may occur 1 day after discharge criteria are met.

In both periods, any participant who experiences emesis within 1 hour post oral dosing will be excluded in the PK data analysis and may be replaced with a new participant. For a participant who drops out in Period 2, the replacement participant will be required to complete Period 2 only. If a participant experiences emesis after dosing in Period 2, vomitus will be collected throughout the study and assayed for total radioactivity.

The clinic will contact all participants (including participants who terminate the study early) 30 ± 2 days after the last study drug administration to determine if any adverse events (AEs) have occurred since the last study visit.

Main Criteria for Inclusion:

In order to be eligible for study participation, participants must:

1. Healthy adult male, ≥19 and ≤55 years of age at the time of the first dose of study drug.
2. Weighs at least 50 kg and body mass index (BMI) ≥18.0 and <32.0 kg/m^2 at screening.
3. Continuous nonsmoker who has not used nicotine -containing products (including vaping) for at least 3 months prior to the first dosing and throughout the study, based on participant self -reporting.
4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the Investigator or designee.

Main Criteria for Exclusion:

The participant must be excluded from participating in the study if the participant:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the Screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History or presence of cataracts or other clinically significant vision disturbances.
4. Abnormal clinical laboratory test results at the Screening visit that suggest a clinically significant underlying disease that would compromise the well-being of the participant (if the participant has alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST] >2.5 × the upper limit of normal [ULN], the Medical Monitor should be consulted)
5. Abnormal and clinically significant ECG abnormality at Screening visit:
    a. QT interval with Fridericia's correction method (QTcF) >450 ms confirmed with one repeat testing.
6. History or presence of gastritis, gastrointestinal tract, gastric bypass surgery, or hepatic disorder or other clinical condition which, in the opinion of the Investigator or designee, may affect the absorption, distribution, metabolism, or elimination of study drug.
7. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the participant by their participation in the study.
8. History or presence of alcohol or drug abuse within the past 2 years prior to Screening visit.
9. History or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
10. Has a risk of suicide according to the Investigator's clinical judgment (eg, per Columbia -Suicide Severity Rating Scale [C-SSRS]), or has made a suicide attempt in the previous year prior to Screening visit.
11. Has infrequent bowel movements (less than approximately once per day) within 30 days prior to first dosing.
12. Recent history of abnormal bowel movements, such as diarrhea, loose stools, or constipation, within 2 weeks prior to first dosing.
13. Has received radiolabeled substances or has been exposed to radiation sources within 12 months of first dosing or is likely to receive radiation exposure or radioisotopes within 12 months of first dosing such that participation in this study would increase their

total exposure beyond the recommended levels considered safe (ie, weighted annual limit recommended by the International Commission of Radiological Protection [ICRP] of 3000 mrem).

14. Unable to refrain from or anticipates the use of:
    - Any drug, including prescription and nonprescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing and throughout the study, including the follow-up period. Thyroid hormone replacement medication may be permitted if the participant has been on the same stable dose for the immediate 3 months prior to first study drug administration. After the first dose of study drug, ibuprofen (up to 1.2 g per 24 hours) may be administered at the discretion of the Investigator or designee. Milk of Magnesia (ie, magnesium hydroxide) (≤60 mL per day) may be administered to ensure defecation, at discretion of the Investigator or designee.
    - Any drugs known to be significant inducers of Cytochrome P450 (CYP) 3A4, CYP2C19, or uridine diphosphate glucuronosyltransferase (UGT), including St. John's Wort, within 28 days prior to the first dosing and throughout the study, including the follow-up period. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamic interaction with study drug.
    - Alcohol, as defined in Table 3.

Investigational Product, Dosage, and Mode of Administration:

TAK-935 in Period 1 will be provided as 100 mg tablets;

[^{14}C]TAK-935 in Period 1 will be provided as an IV solution

[^{14}C]TAK-935 in Period 2 will be provided as an oral solution

Treatments in each period are described as follows:

Period 1: 300 mg TAK-935 (3 x 100mg tablets) administered orally at Hour 0 on Day 1 followed by 50 µg (~1 µCi) [^{14}C]TAK-935 IV solution administered at Hour 0.17 (10 minutes post oral dosing) for 15 minutes.

Period 2: 300 mg (~100 µCi) [^{14}C]TAK-935 administered as an oral solution at Hour 0 on Day 1 of Period 2.

Reference Therapy, Dosage, and Mode of Administration:

Not Applicable

Statistical methods:

PK Analysis:

Descriptive statistics will be provided for the total radioactivity (whole blood, plasma, urine, feces, and if applicable, emesis), plasma and urine TAK-935 concentrations and PK parameters, and [^{14}C]TAK935 plasma, urine, and feces radioactivity concentration equivalent, using appropriate summary statistics to be fully specified in the statistical analysis plan (SAP).

ABA of TAK-935 will be estimated using a ninety percent (90%) confidence interval (CI) constructed for the difference in least squares mean (LSM) on the log scale for dose normalized AUC_∞ between a single oral dose and the IV microdose. Exponentiating the log-scale 90% CI will provide a 90% CI for the dose-normalized AUC_∞ geometric mean ratio (TAK-935 administered as oral dose / [^{14}C]TAK-935 administered as IV microdose). AUC_{last} will be analyzed in a similar fashion if AUC_∞ cannot be calculated.

Mass balance will be calculated as a sum of the percent of the total radioactivity recovered in urine and feces plus any radioactivity dose due to emesis (if any occurred) relative to the administered radioactivity dose.

Safety:

Safety will be monitored through AEs, 12-lead ECGs, vital sign measurements, C-SSRS, clinical laboratory tests, and physical examinations. AEs will be tabulated and summary statistics for the 12-lead ECGs, vital signs, and clinical laboratory tests may be computed and provided, as deemed clinically appropriate.

Sample Size Justification: The sample size of 6 healthy adult male participants was selected without statistical considerations and is deemed adequate to meet the study objectives. In addition, this sample size is limited based on clinical considerations for this type of study and in order to limit exposure to radioactivity.

Interim Analysis: Not Applicable

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
24HC	24*S*-hydroxycholesterol
~	Approximately
%	Percent
%Dose(f)	Percent of administered radioactive dose excreted in feces within a given collection interval
%Dose(u)	Percent of administered radioactive dose excreted in urine within a given collection interval
%F	Percent absolute oral bioavailability
[^{14}C]	Carbon-14; radiocarbon
ABA	Absolute bioavailability
ADME	Absorption, distribution, metabolism, and elimination
AE	Adverse event
$Ae_{t1\text{-}t2}$	Amount of drug excreted in the urine from time 1 to time 2
Ae(f)	Amount of total radioactivity excreted in feces within a given collection interval
Ae(u)	Amount of total radioactivity excreted in urine within a given collection interval
AGP	α-1-acid glycoprotein
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{extrap}%	Area under the curve from the last quantifiable concentration to infinity calculate dosing the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞}
AUC_{last}	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_t	Area under the concentration-time curve from time 0 to time t
AUC_{∞}	Area under the concentration-time curve from time 0 to infinity
BCRP	Breast cancer resistance protein

Abbreviation	Definition
BMI	Body mass index
Bpm	Beats per minute
C-SSRS	Columbia-suicide severity rating scale
C_{eoi}	Concentration at end of infusion
CH24H	Cholesterol 24*S* hydroxylase
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL_R	Renal clearance
cm	Centimeter
C_{max}	Maximum observed concentration
CRF	Case report form
CRU	Clinical research unit
COVID-19	Novel coronavirus 2019
Cum%dose	Combined cumulative percent of administered radioactive dose recovered in feces and urine
Cum%dose(f)	Cumulative percent of administered radioactive dose recovered in feces
Cum%dose(u)	Cumulative percent of administered radioactive dose recovered in urine
CYP	Cytochrome P450
ECG	Electrocardiogram
F	Bioavailability
FDA	Food and Drug Administration
G	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus

Abbreviation	Definition
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
ICRP	International Commission on Radiological Protection
ID	Identification number
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
λ_z	Terminal disposition phase rate constant
LFT	Liver Function Test
LSM	Least-squares mean
µCi	Microcurie
µg	Microgram
µmol	Micromolar
m^2	Meters squared
MBq	Megabecquerel
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
mmHg	Millimeter of mercury
mrem	Millirem
msec	Millisecond

Abbreviation	Definition
mSv	Millisievert
oz	Ounce
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
QD	Once daily
QTcF	QT interval with Fridericia's correction method
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSARs	Suspected unexpected serious adverse reactions
$t_{1/2z}$	Terminal disposition phase half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time of first occurrence of C_{max}
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
US	United States
USA	United States of America

4. INTRODUCTION

4.1. Background

TAK-935 is a potent and selective cholesterol 24*S* hydroxylase (CH24H) inhibitor currently in development for adjunct treatment of developmental and epileptic encephalopathies (DEEs).

In the brain, cholesterol is metabolized by CH24H, which is specifically and constitutively expressed in neurons, to 24*S*-hydroxycholesterol (24HC). This cholesterol metabolite, 24HC, leaves the brain via lipoproteins and is excreted in bile. Aberrant cholesterol metabolism is implicated in epilepsy disorders and syndromes.

TAK-935 is a first-in-class therapeutic candidate that has the potential to control seizures in treatment-resistant participants with epilepsy by reducing over-activated glutamate signaling.

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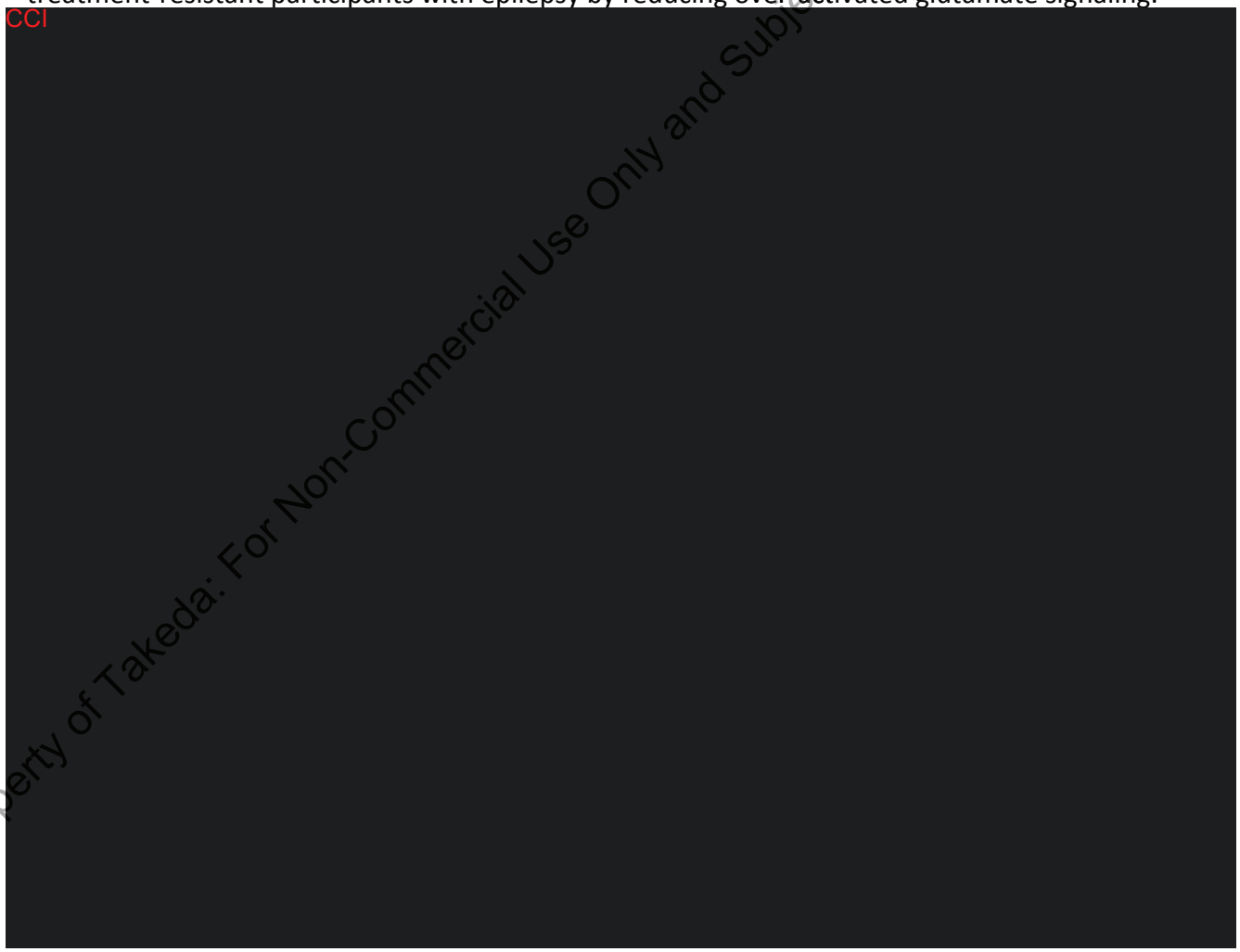

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4.1.2. Clinical Pharmacokinetics

The PK, safety, and tolerability of TAK-935 have been evaluated in 4 Phase 1 clinical studies in healthy participants and 1 Phase 1b/2a study in participants with DEE.

TAK-935 was rapidly absorbed following both single-dose (15 to 1350 mg) and multiple-dose (100 to 600 mg) oral administration as a solution or tablet formulation under fasted conditions in healthy participants. TAK-935 plasma concentration reached maximal levels within median 0.25 to 0.52 hours following single doses. Following multiple doses (10 or 14 days) of TAK-935 100 mg once daily (QD), 300 mg QD, 300 mg twice daily (BID), 400 mg QD and 600 mg QD (without up-titration) as solution under fasted condition, TAK-935 had rapid absorption with median t_{max} of 0.33 to 0.5 hours. Mean TAK-935 $t_{½z}$ was similar between Day 1 and Day 14, ranging from 3.49 to 4.83 hours. Over the 4-fold dose range of 100 to 400 mg QD after multiple-dose administration, mean TAK-935 C_{max} and AUC_{τ} on Day 14 increased by 6.08 and 6.12 folds, respectively. Doses of 100 or 400 mg QD for 14 days did not show apparent exposure accumulation on Day 14 when compared with Day 1, while 300 mg QD for 14 days showed about 1.74- and 1.42-fold increase of C_{max} and AUC_{τ} on Day 14, respectively. Approximately 0.08% to 0.25% of the administered TAK-935 dose was excreted in urine across all dose groups following a single- and multiple-oral doses. M-I metabolite showed median t_{max} values ranged from 0.5 to 1.0 hours and mean $t_{½z}$ values ranged from 2.32 to 3.88 hours. The exposure of M-I was comparable between Day 1 and Day 14 following 100, 300, and 400 mg QD of TAK-935 for 14 days, with MR decreased with increasing dose, ranging from 0.44 to 0.26 on Day 14.

The effect of food on the PK of TAK-935 was investigated. Food decreased TAK-935 C_{max} by 60%, but had little impact on the total TAK-935 exposure of the tablet formulation as AUC_{last} and AUC_{∞} decreased by only 11%. After single oral dose of TAK-935 15 to 1350 mg or multiple oral dose of TAK-935 100 to 600 mg, a generally dose-dependent decrease in plasma 24HC concentrations was observed, with more profound decreases at higher doses. In the

multiple-dose study, plasma 24HC inhibition appeared to approach steady state on Day 7, with time-matched percent change in 24HC $AUEC_{24}$ ranging from 46.82% to 62.66% on Day 14 across the doses of 100 to 400 mg QD.

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4.2. Rationale for the Proposed Study

The PK, metabolic pathways, and routes of elimination of TAK-935 have been evaluated in vitro and in vivo in preclinical species, being summarized in the IB (IB Ed 5). Further, PK of non-radiolabeled TAK-935 have been evaluated in humans in multiple studies (summarized in the IB Ed 5).

The primary purposes of the present study are to characterize the ABA (Period 1) and the absorption, metabolism, excretion, and mass balance of TAK-935 after single oral administration (Period 2) in healthy adult male participants by collecting plasma, urine, and feces samples for drug concentration analysis (via radioisotopic quantitation), and plasma, whole blood, urine, and fecal samples for total radioactivity analysis and metabolic profiling, as appropriate. The study will provide data required to evaluate the mass balance and the metabolic profile of TAK-935 in humans. Based on preclinical radioisotopic analysis, most of the radioactivity from a [14C]TAK-935 dose was eliminated within 72 hours post dose in rats and 120 hours post dose in dogs; thus, more than 90% of the radioactivity in humans should be eliminated within 120 hours post dose.

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5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Hypothesis

Not Applicable.

5.2. Study Objectives and Endpoints

Study objectives and associated endpoints are presented in Table 1. The frequency and timing of study measurements is provided in the Schedule of Assessments (Appendix 1). Information regarding sample collection and safety data collection are presented in Section 9.

Table 1: Objectives and Endpoints

	Objective	**Endpoint**
Primary	Period 1 (ABA) • To determine ABA of TAK-935 following a single microdose IV administration of 50 µg (~1 µCi) [^{14}C]TAK-935 and a single oral administration of 300 mg TAK-935.	Period 1 (ABA): • Absolute bioavailability (F) as percent F (%F) for TAK-935.
	Period 2 (ADME) • To assess the mass balance (ie, cumulative excretion of total radioactivity in urine and feces) following a single oral administration of 300 mg (~100 µCi) [^{14}C]TAK-935. • To characterize the PK of TAK-935 and M-I in plasma and urine, and total radioactivity concentration equivalents in plasma and whole blood following a single oral administration of 300 mg (~100 µCi) [^{14}C]TAK-935.	Period 2 (ADME): • Percent of total radioactivity excreted in urine (Cum%Dose[u]) and feces (Cum%Dose[f]) relative to the administered radioactive dose (Combined Cum%Dose). • Amount of total radioactive excreted in urine (Ae[u]) and feces (Ae[f]) and the percent of administered radioactive dose excreted in urine and feces within a given collection interval (urine %Dose[u]) and feces (%Dose[f]). • PK parameters C_{max}, t_{max}, $t_{1/2z}$, AUC_{∞}, AUC_t, and AUC_{last} for TAK-935 in plasma. • PK parameters C_{max}, t_{max}, $t_{1/2z}$, AUC_{∞}, AUC_t, and AUC_{last} for total

		radioactivity concentration equivalents in plasma and whole blood. • PK parameters for renal clearance (CL_R) for TAK-935 in urine. • PK parameters for amount excreted in each collection interval (Ae_{t1-t2}) for TAK-935 in urine. • The change over time in percentage of [^{14}C]radioactivity in whole blood relative to plasma (ie, whole blood:plasma partitioning ratio). • The change over time in percentage of [^{14}C]radioactivity in whole blood relative to plasma (ie, whole blood:plasma partitioning ratio).
Secondary	<u>Periods 1 (ABA)</u> • To determine the PK of [^{14}C]TAK-935 following a single IV administration of 50 µg (~1 µCi) [^{14}C]TAK-935 and the PK of TAK-935 following a single oral administration of 300 mg TAK-935. • To determine fecal and urinary excretion of the parent [^{14}C]TAK-935 following a single IV administration of 50 µg (~1 µCi) [^{14}C]TAK-935.	<u>Periods 1 (ABA)</u> • PK parameters C_{eoi} (IV infusion), C_{max} (oral), t_{max} (oral), AUC_∞, AUC_t, AUC_{last}, and $t_{1/2z}$ for TAK-935, and [^{14}C]TAK-935 in plasma. • Total radioactivity excreted and percentage of dose excreted in the feces (Ae[f] and %Dose[f]) and urine (Ae[u] and %Dose[u]) as total radioactivity following IV administration.
	<u>Period 2 (ADME)</u> • To assess the metabolic profile of TAK-935 in plasma, urine, and feces following a single oral administration of 300 mg (~100 µCi) [^{14}C]TAK-935.	<u>Period 2 (ADME)</u> • Metabolic profile of TAK-935 in plasma, urine, and feces following a single oral administration of 300 mg (~100 µCi) [^{14}C]TAK-935.

	<u>Periods 1 (ABA) and 2 (ADME)</u> • To assess the safety of TAK-935 during the ABA and ADME study periods.	<u>Periods 1 (ABA) and 2 (ADME)</u> • Tabulated TEAEs and summary statistics for clinically relevant 12-lead ECGs, vital signs, and clinical laboratory tests results.

6. INVESTIGATIONAL PLAN

6.1. Summary of Study Design

This is an open-label, 2-period, fixed-sequence, single-dose study in 6 healthy adult male participants.

On Day 1 of Period 1 (ABA Study Period), participants will receive a single unlabeled oral 300 mg dose of TAK-935 in tablet form (three 100 mg tablets). At 0.17 hours (10 minutes) post oral dosing (ie, 15 minutes prior to the median t_{max} for the oral unlabeled dose [~ 0.42 hours or 25 minutes]), participants will receive a 15-minute IV infusion of a microdose of 50 µg (equivalent to ~1 µCi) [^{14}C]TAK-935. Serial blood sampling will be performed up to 48 hours (Day 3) to determine the PK of TAK-935 and M-I metabolite (and others, if applicable) in plasma for the oral dose and [^{14}C]-total radioactivity and PK of [^{14}C]TAK-935 in the plasma for the IV dose. Urine and fecal output will also be collected up to 120 hours post dose to determine [^{14}C]-total radioactivity. Collection of urine and fecal samples will continue until one of the release criteria (participants remain in CRU) is met (ie, 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to Day 8, but no less than Day 6, for [^{14}C]-total radioactivity excretion in urine and feces. Participants who meet release criteria before Day 8, but no less than Day 6, will remain confined in the CRU until Day -1 of Period 2 and throughout Period 2 (until Period 2 discharge criteria are met).

There will be a washout period of at least 7 days between the last dose in Period 1 and the dose in Period 2.

On Day 1 of Period 2 (ADME Study Period), participants will receive a single oral dose of 300 mg (~100 µCi) [^{14}C]TAK-935 in solution. Serial blood sampling will be performed and urine and feces will be collected to determine the PK of TAK-935 and M-I metabolite in plasma and urine, and total radioactivity in plasma, whole blood, urine, and feces, and to characterize the metabolite profiles of TAK-935 in plasma, urine, and feces. Complete urinary and fecal output will be collected during the confinement period until discharge criteria are met (anticipated to be 10 days post dose or less).

In Period 2, participants will be confined in the CRU for at least 5 days post dose (ie, 120 hours) and until 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples. If less than 90% of the total dose of radioactivity administered is recovered in urine and fecal samples, participants will be confined in the clinic until a discharge criterion is met (ie, 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to

≤1% of the total administered radioactivity per 24 hour interval for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to Day 11 (ie, 240 hours).

Since up to an approximate 24-hour time lag is anticipated for radioactivity counting of samples, actual participant release from the CRU may occur 1 day after discharge criteria are met.

In both periods, any participant who experiences emesis within 1 hour post oral dosing will be excluded in the PK data analysis and may be replaced with a new participant. For a participant who drops out in Period 2, the replacement participant will be required to complete Period 2 only. If a participant experiences emesis after dosing in Period 2, vomitus will be collected throughout the study and assayed for total radioactivity.

The clinic will contact all participants (including participants who terminate the study early) 30 ± 2 days after the last study drug administration to determine if any AEs have occurred since the last study visit.

The planned dose levels of TAK-935 to be evaluated are outlined in Table 2

Table 2: Planned Dose Levels of TAK-935 and [14C]TAK-935

		Dose	Route of Administration
Period 1			
	TAK-935	300 mg	Oral tablet
	[^{14}C]TAK-935	50 µg (~1 µCi)	IV infusion
Period 2			
	[^{14}C]TAK-935	300 mg (~100 µCi)	Oral Solution

Figure 1 illustrates the study design.

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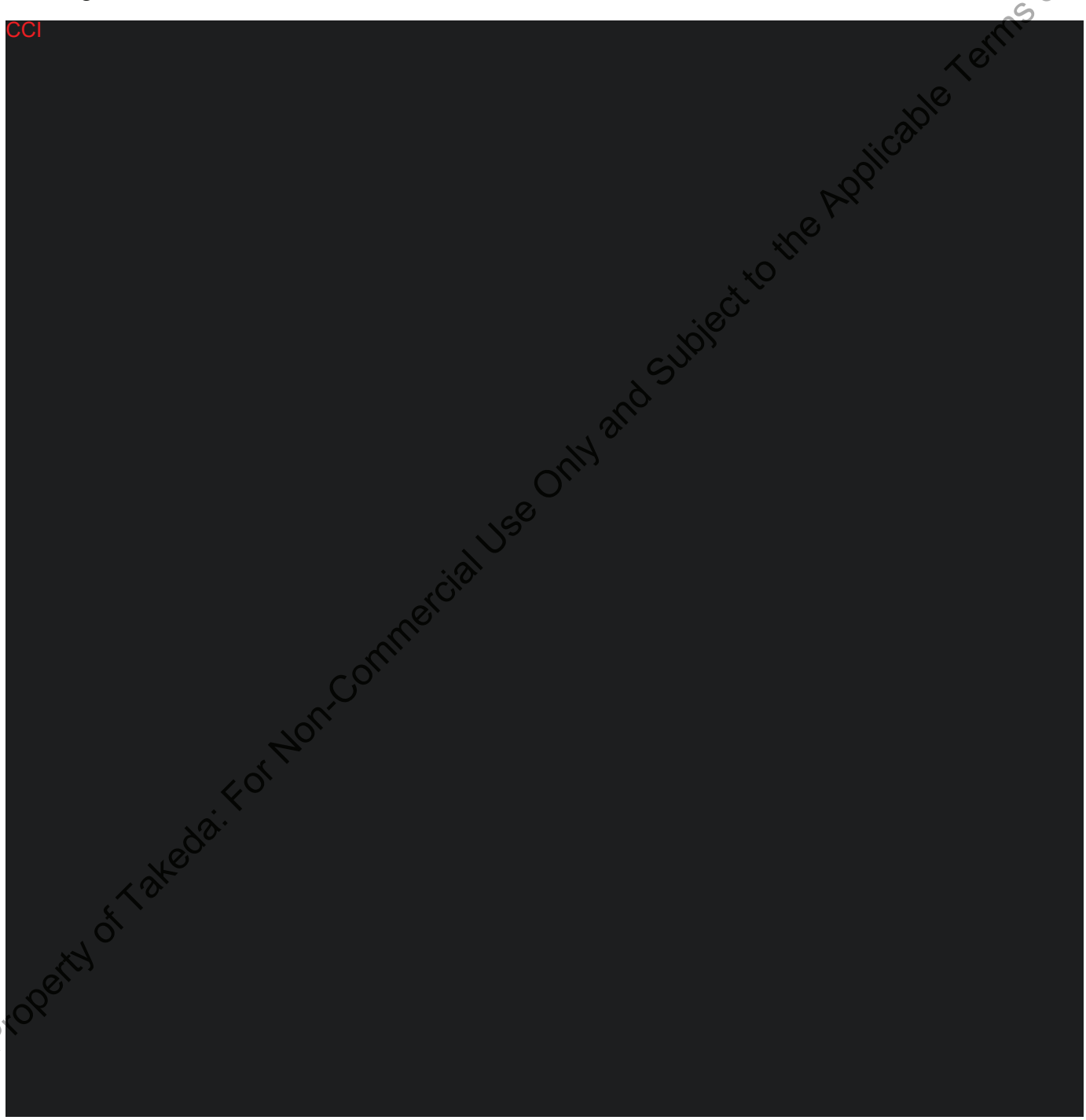

6.1.1. Confinement

In Period 1, participants will be confined in the CRU from Day -1 of Period 1 and throughout Period 2. Participants may be asked to come to CRU earlier in Period 1 to undergo additional COVID-19 precaution procedures. All participants, including participants who meet one of the release criteria (ie, 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity for at least 2 consecutive intervals where both a urine and fecal sample are collected) before Day 8 of Period 1, but no less than Day 6, will remain confined in the CRU until they meet discharge criteria in Period 2.

In Period 2, participants will be confined for at least 5 days post dose (ie, 120 hours of Period 2) and until ≥90% of the total dose of radioactivity administered has been recovered in the urine and feces samples.

If less than 90% of the total dose of radioactivity administered is recovered in urine and fecal samples, the participant will continue to stay at the CRU until a discharge criterion is met. Participants will be eligible for discharge if they meet either one of the following discharge criteria or up to Day 11 (ie, 240 hours) of Period 2:

- ≥90% of the total dose of radioactivity administered has been recovered in the urine and feces; or
- There is ≤1% of the total administered radioactivity in each of two consecutive 24 hour intervals where both a urine and fecal sample is provided.

All urine and fecal collections will be analyzed for radioactivity levels to determine if the discharge criteria are met.

It is expected that the majority (≥90%) of the administered radioactivity will be recovered within 10 days post dose or less.

Release of participants who do not meet a discharge criterion by 240 hours (Period 2) will be reviewed on a case-by-case basis.

Since up to an approximate 24-hour time lag is anticipated for radioactivity counting of samples, actual participant release from the CRU may occur 1 day after discharge criteria are met.

At all times, a participant may be required to remain at the CRU for longer at the discretion of the Investigator or designee.

6.2. Discussion of Design and Control

In Period 1 of the study, the ABA of TAK-935 will be estimated using a labeled IV microdose infusion administered 0.17 hours (10 minutes) after an unlabeled oral dose in order to characterize the disposition properties of TAK-935. In Period 1, characterization of ABA will be achieved by collecting plasma samples for drug concentration analysis, and plasma, urine, and fecal samples for total radioactivity analysis following unlabeled oral dose and labelled IV microdose of TAK-935. In order to determine ABA accurately and reliably, a healthy adult population is chosen.

Characterization of the disposition of a drug following IV administration facilitates the understanding of fundamental aspects of TAK-935's PK that cannot be determined from oral dosing alone, including bioavailability, intrinsic clearance, and volume of distribution. The results of this study will contribute to a robust understanding of the PK characteristics of TAK-935.

In Period 2 of the study, characterization of the ADME and mass balance of TAK-935 after oral administration of a single 300 mg (~100 µCi) [^{14}C]TAK-935 will be achieved by collecting plasma samples for drug concentration analysis, and plasma, urine, and fecal samples for total radioactivity analysis and metabolic profiling. The study will provide data required to evaluate the mass balance and the metabolic profile of TAK-935 in humans.

7. STUDY POPULATION

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened**.**

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

7.1. Inclusion Criteria

Participants are eligible to be included in the study only if they meet all the following criteria and none of the exclusion criteria:

1. Healthy adult male, ≥19 and ≤55 years of age at the time of first dose of study drug.
2. Weighs at least 50 kg and BMI ≥18.0 and <32.0 kg/m^2 at Screening visit.
3. Continuous nonsmoker who has not used nicotine-containing products (including vaping) for at least 3 months prior to the first dosing and throughout the study, based on participant self-reporting
4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the Investigator or designee.
5. Participants who are sexually active with a female partner of childbearing potential must use a highly effective or effective method of contraception as indicated below or true sexual abstinence, only if this is in line with the preferred and usual lifestyle of the participant. True abstinence is defined for male participants as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 90 days after the last dosing.

   Sexually active male participants (post-pubertal unless permanently sterilized by bilateral orchidectomy) must agree to use male contraception (condom) during the study and for minimum of 90 days/3 sperm cycles following the last dose of study drug. Male participants must also not donate sperm during the screening and treatment periods and for at least 90 days after the last dose of TAK-935.

   Female partners of male participants who are of childbearing potential must use a highly effective or effective method of birth control during the study and for (minimum of 3 months/3 menstrual cycles following the last dose of study drug.

   Highly effective contraceptive methods are as follows:

   a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

- Oral
- Intravaginal
- Transdermal

b. Progestogen-only hormonal contraception associated with inhibition of ovulation:

- Oral
- Injectable
- Implantable

c. Intrauterine device

d. Intrauterine hormone-releasing system

e. Bilateral tubal occlusion

Acceptable effective contraceptive methods are as follows:

a. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

b. Male or female condom with or without spermicide

c. Cap, diaphragm, or sponge with spermicide

6. Understands the study procedures and agrees to participate by providing written informed consent, and be willing and able to comply with all study procedures and restrictions.

7.2. Exclusion Criteria

Participants will be excluded from study enrollment if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the Screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History or presence of cataracts or other clinically significant vision disturbances.
4. Abnormal clinical laboratory test results at the Screening visit that suggest a clinically significant underlying disease that would compromise the well-being of the patient (if the patient has ALT and/or AST >2.5 × the ULN, the Medical Monitor should be consulted).
5. Abnormal and clinically significant ECG abnormality at Screening visit:

a. QTcF >450 ms confirmed with one repeat testing.

6. History or presence of gastritis, gastrointestinal tract, gastric bypass surgery, or hepatic disorder or other clinical condition which, in the opinion of the Investigator or designee, may affect the absorption, distribution, metabolism, or elimination of study drug.
7. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the participant by their participation in the study.
8. History or presence of alcohol or drug abuse within the past 2 years prior to Screening visit.
9. History or presence of hypersensitivity or idiosyncratic reaction to the study drug(s) or related compounds.
10. Has a risk of suicide according to the Investigator's clinical judgment (eg, per C-SSRS), or has made a suicide attempt in the previous year prior to Screening visit.
11. Positive urine drug or alcohol results at screening or first check-in.
12. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) or COVID-19.
13. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.
14. Seated heart rate is lower than 40 bpm or higher than 99 bpm at Screening visit.
15. Estimated creatinine clearance <80 mL/min at Screening visit.
16. Has tattoo(s) or scarring at or near the site of IV infusion or any other condition which may interfere with infusion site examination, in the opinion of the Investigator.
17. Has infrequent bowel movements (less than approximately once per day) within 30 days prior to first dosing.
18. Recent history of abnormal bowel movements, such as diarrhea, loose stools, or constipation, within 2 weeks prior to first dosing.
19. Has received radiolabeled substances or has been exposed to radiation sources within 12 months of first dosing or is likely to receive radiation exposure or radioisotopes within 12 months of first dosing such that participation in this study would increase their total exposure beyond the recommended levels considered safe (ie, weighted annual limit recommended by the ICRP of 3000 mrem).
20. Unable to refrain from or anticipates the use of:
    - Any drug, including prescription and nonprescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing and throughout the study, including the follow-up period. Thyroid hormone replacement medication may be

permitted if the participant has been on the same stable dose for the immediate 3 months prior to first study drug administration. After the first dose of study drug, ibuprofen (up to 1.2 g per 24 hours) may be administered at the discretion of the Investigator or designee. Milk of Magnesia (ie, magnesium hydroxide) (≤60 mL per day) may be administered to ensure defecation, at discretion of the Investigator or designee.

- Any drugs known to be significant inducers of CYP3A4, CYP2C19 or UGT, including St. John's Wort, within 28 days prior to the first dosing and throughout the study, including the follow-up period. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamic interaction with study drug(s).
- Alcohol, as defined in Table 3.

21. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing and throughout the study.
22. Donation of blood or significant blood loss within 56 days prior to the first dosing.
23. Plasma donation within 7 days prior to the first dosing.
24. Participation in another clinical study within 30 days prior to the first dosing. The 30day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

7.3. Excluded Medications, Supplements, Dietary Products

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 7.2. After the first dose of study drug, ibuprofen (up to 1.2 g per 24 hours) may be administered at the discretion of the Investigator or designee. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to first study drug administration.

Prune juice or milk of Magnesia (ie, magnesium hydroxide) (≤60 mL per day) may be administered ensure defecation, at discretion of the Investigator or designee.

If deviations occur, the Investigator or designee in consultation with the Sponsor if needed will decide on a case by case basis whether the subject may continue participation in the study.

All medications taken by subjects during the course of the study will be recorded.

Use of excluded agents (prescription or nonprescription) or dietary products is outlined in Table 3.

Table 3: Excluded Medications, Supplements, and Dietary Products

Category	Between Screening and Randomization (Days -28 to pre dose [Day 1])	Post-Randomization (Day 1) to Follow-Up
Alcohol	Prohibited from 48 hours prior to first dosing	Prohibited from 48 hours prior to first dosing until the end of PK sample (blood, urine and feces) collection in Period 2.
Xanthine and/or caffeine	Prohibited from 24 hours prior to first dosing [(a)]	Prohibited from 24 hours prior to first dosing until the end of PK sample (blood, urine and feces) collection in Period 2 [(a)].
Medications	See Sections 7.2 and 7.3	See Sections 7.2 and 7.3
Nicotine	Prohibited from 3 months prior to first dosing	Prohibited from 3 months prior to first dosing until the end of PK sample (blood, urine and feces) collection in Period 2.
Food substance		
Grapefruit/Seville orange	Prohibited from 14 days prior to first dosing	Prohibited from 14 days prior to first dosing until end of PK collection in Period 2

(a) Small amounts of caffeine derived from normal foodstuffs eg, 250 mL/8 oz/1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz chocolate bar, per day, would not be considered a deviation to this restriction.

Participants will be excluded from study enrollment if they meet any of the following criteria:

[1] Investigator site personnel directly affiliated with this study and/or their immediate family. Note: immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[2] Ovid employees, Takeda employees, or employees

[3] Currently enrolled in a clinical study involving an investigational product or nonapproved use of a drug or device (other than the investigational product used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[4] Have participated, within the last 30 days in a clinical study involving an investigational product [other than the investigational product used in this study]. If the previous investigational product has a long half-life, three months or five half-lives (whichever is longer) should have passed.

[5] Have previously completed or withdrawn from this study or any other study investigating TAK-935.

[6] Are unwilling or unable to comply with the use of a data collection device to directly record data from the participant.

7.4. Diet, Fluid, Activity

7.4.1. Diet and Fluid

Water (except water provided with each oral dosing) will be restricted 1 hour prior to and 1 hour after each oral study drug administration, but will be allowed ad libitum at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

Participants will fast overnight for at least 10 hours prior to each oral study drug administration and will continue to fast for at least 4 hours post oral dosing.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, participants will be required to fast from all food and drink except water between meals and snacks. Prune juice may be provided at any time, at the discretion of the study Investigator or designee.

7.4.2. Activity

Participants will remain ambulatory or seated upright for the first 4 hours post oral dosing, except when they are supine or semi-reclined for study procedures (eg, IV dosing on Day 1 of Period 1).

Participants will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

Participants will be prohibited from smoking and vaping throughout the study.

7.5. Discontinuations

7.5.1. Discontinuation of Participants

The criteria for enrollment must be followed explicitly. If the investigative site identifies a participant who did not meet enrollment criteria and who was inadvertently enrolled, the Sponsor must be notified. If the Sponsor identifies a participant who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the Sponsor and the Investigator to determine whether the participant may continue in the study, with or without investigational product. Inadvertently enrolled participants may be maintained in the study and on investigational product when the Sponsor agrees with the Investigator that it is medically appropriate for that participant. The participant may not continue in the study with or without investigational product if the Sponsor does not

agree with the Investigator's determination it is medically appropriate for the participant to continue. The Investigator must obtain documented approval from the Sponsor to allow the inadvertently enrolled participant to continue in the study with or without investigational product.

7.5.2. Criteria for Discontinuation or Withdrawal of a Participant

Participants are free to withdraw from the study at any time for any reason.

In addition, participants may be withdrawn from the study by the Investigator or designee for the following reasons:

- AEs.
- Positive urine drug or alcohol results.
- Difficulties in blood collection.

In Period 1 or 2, any participant who experiences emesis within 1 hour following the oral dose may be discontinued, excluded from the final data analysis, and may be replaced with a new participant. In Period 2, if a participant experiences emesis after oral dosing, vomitus will be collected throughout the study and assayed for total radioactivity.

A participant may be withdrawn by the Investigator (or designee) or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Investigator Decision [Physician Decision]
  - The investigator decides that the participant should be discontinued from the study
- Participant Decision [Withdrawal by Participant]
  - The participant requests to be withdrawn from the study
- Sponsor Decision
  - The Sponsor or its designee discontinues the study or discontinues the participant's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
  - The Sponsor or its designee stops the clinical study at a particular site

- Adverse Event
  - If the investigator decides that the participant should be withdrawn because of a serious AE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. The Sponsor or its designee is to be alerted immediately. Refer to Safety Evaluations Section 9.2.

Liver Function Test (LFT) Abnormalities:

Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a participant's laboratory profile has returned to normal/baseline status, see Section 9.1.6), if the following circumstances occur at any time during study drug treatment:

– alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (ULN), or

– ALT or AST >5 × ULN and persists for more than 2 weeks, or

– ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or

– ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

QTcF interval > 500 ms:

Study drug should be discontinued immediately with appropriate clinical follow-up if a QTcF interval >500 ms is detected by ECG and confirmed with a repeat ECG. Appropriate clinical follow-up includes a repeat ECG. Participants who discontinue the study early will have end of study procedures performed as shown in the Schedule of Assessments (Appendix 1).

7.5.3. Discontinuation of Study Sites/Site Terminated by Sponsor

Study site participation may be discontinued if the Sponsor or its designee, the investigator, or the IRB/IEC of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

7.5.4. Discontinuation of the Study/Study Terminated by Sponsor

The study will be discontinued if the Sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

8. TREATMENT

8.1. Materials and Supplies

8.1.1. Clinical Study Drug TAK-935 Tablet

A single unlabeled 300 mg dose of TAK-935 (3 x 100 mg tablets) will be administered in Period 1 of the study.

8.1.2. [^{14}C]TAK-935 IV Sterile Solution

An IV dose of 50 µg [^{14}C]TAK-935 (~1 µCi) will be administered as a 15-minute infusion at 0.17 hours (10 minutes) after the TAK-935 oral dose (see Section 6.1) in Period 1 of the study.

The drug product is prepared in the CRU pharmacy as an IV solution. The solution will be prepared and labeled by licensed pharmacy staff according to the procedures outlined in the pharmacy manual.

8.1.3. [^{14}C]TAK-935 Oral Solution

A single oral dose of 300 mg (~100 µCi) [^{14}C]TAK-935 will be administered as an oral solution in Period 2.

8.1.4. Clinical Study Drug Labeling

TAK-935 tablet, [^{14}C]TAK-935 IV solution, and [^{14}C]TAK-935 oral solution will be affixed with clinical labels in accordance with local regulatory requirements.

8.2. Clinical Study Drug Inventory and Storage

The Sponsor will supply sufficient quantities of TAK-935 products to allow completion of this study.

will provide sufficient quantities of preparation and/or dilution solutions to allow completion of the study. The same lot number will be used throughout the study.

The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report.

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drugs supplied. All TAK-935 products will be prepared and labeled by licensed pharmacy staff according to the procedures outlined in the pharmacy manual.

8.3. Treatments Administered

TAK-935 in Period 1 will be provided as 100 mg tablets;

[^{14}C]TAK-935 in Period 1 will be provided as an IV solution

[^{14}C]TAK-935 in Period 2 will be provided as an oral solution

Period 1: On Day 1, participant will receive a single unlabelled oral dose of TAK-935 300 mg tablets followed by a 15 minute IV infusion of a microdose of 50 µg (1 µCi) [^{14}C]TAK-935 at 0.17 hours (10 minutes) post oral dose.

Period 2: On Day 1, participant will receive a single oral dose of 300 mg (~100 µCi) [^{14}C]TAK-935 in solution.

Treatments in each period are described as follows:

Period 1:	300 mg TAK-935 (3 x 100mg tablets) administered orally at Hour 0 on Day 1 followed by 50 µg (~1 µCi) [^{14}C]TAK-935 IV solution administered at Hour 0.17 (10 minutes post oral dosing) for 15 minutes.
Period 2:	300 mg (~100 µCi) [14C]TAK-935 administered as an oral solution at Hour 0 on Day 1 of Period 2.

The oral doses of TAK-935 and [^{14}C]TAK-935 will be administered following an overnight fast with approximately 240 mL of water, then will be instructed to fast for an additional 4 hours. All participants may then consume water ad libitum with the exception of 1 hour before and 1 hour after oral administration. The exact clock time of oral dosing will be recorded.

The IV dose will be administered over approximately 15 minutes. The start and end time of the IV infusion will be recorded.

Participants should be instructed not to crush split or chew TAK-935 tablets in Period 1

The pharmacy at the CRU will provide the IV dose for the 15-minute infusion, the oral tablets dose in individual unit dose containers, and the oral dose solution for each participant.

8.4. Method of Assignment to Treatment

Each participant will be assigned a unique identification number upon screening. Participants who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number at the time of the first dosing, different from the screening number, and will receive the corresponding product.

Participants will receive each treatment on one occasion.

Discontinued participants may be replaced at the discretion of the Sponsor.

If replacement participant participants are used, the replacement participant number will be 100 more than the original (e.g., Participant No. 101 will replace Participant No. 1).

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8.6. Blinding

This is an open-label study.

8.7. Treatment Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral doses. A mouth check will be performed by the qualified designee to ensure that the participants have swallowed the study drug. Once a participant has finished the dosing water,

the qualified designee will use a flashlight and a tongue depressor to check the participant's mouth. Participants' hands will also be verified to ensure that the study drug was ingested.

9. STUDY ASSESSMENTS

The Schedule of Study Procedures (Appendix 1) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the Investigator or designee and/or the Sponsor for reasons related to participant safety.

For this study, the collections for blood, urine, and feces for total radioactivity, plasma and urine concentrations, and metabolite profiling for TAK-935 are the critical parameters and need to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible but can be performed prior or after the prescribed/scheduled time.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

9.1. Safety Assessments

9.1.1. Physical Examination

A full physical examination will be performed as outlined in the Schedule of Study Procedures (Appendix 1). Each examination will include the following assessments: general appearance; skin; head, ear, eye, nose, and throat; neck; lymph node; chest; heart; abdominal cavity; limb; central nervous system; and musculoskeletal.

If clinically significant changes from Screening/Baseline are noted, the changes will be documented as AEs in the AE CRF. Screening/Baseline events will be documented in the Medical History CRF. Clinical significance is defined as any variation in physical findings that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the participant until the parameter returns to Baseline or until the Investigator determines that follow-up is no longer medically necessary.

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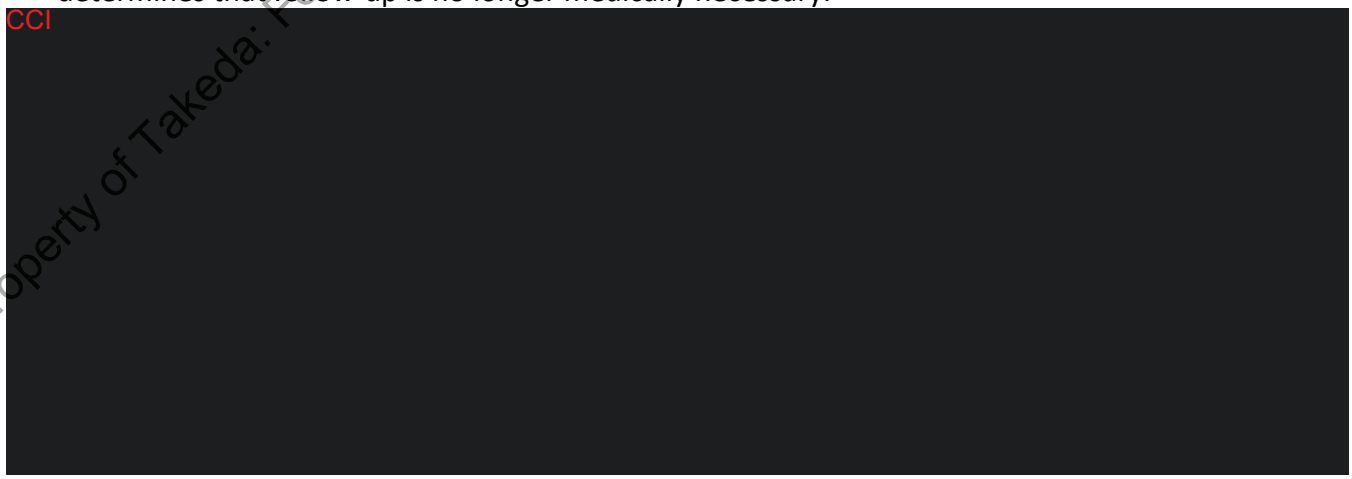

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9.1.3. Height and Weight

Body height (cm) and weight (kg) will be reported as outlined in the Schedule of Study Procedures (Appendix 1). Weight and height are to be measured while the participant is wearing indoor clothing and with shoes off.

9.1.4. BMI

BMI will be calculated based on the height and weight measured at Screening visit.

9.1.5. Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate (beats per minute), will be measured as outlined in the Schedule of Study Procedures (Appendix 1). Additional vital signs may be taken at any other times, if deemed necessary.

Vital signs should be measured at the same time of day if possible. When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 15 minutes before or after the scheduled blood draw, if possible.

All vital signs data collected will be recorded on the source documents and in the CRF. Blood pressure and heart rate measurements will be performed with participants in a seated position, except when they are supine or semi-reclined because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the Investigator or designee.

Blood pressure and heart rate will be measured within 24 hours prior to Day 1 dosing of each period for the pre dose time point. When scheduled post dose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

If clinically significant vital sign changes as compared to Screening/Baseline are noted, the changes will be documented as AEs in the AE CRF. Screening/Baseline events will be documented in the Medical History CRF. Clinical significance is defined as any variation in vital signs that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the participant until the parameter returns to Baseline or until the Investigator determines that follow-up is no longer medically necessary.

9.1.6. Serum Chemistry, Hematology, and Urinalysis

Serum chemistry, hematology, and urinalysis will be performed at the times specified in Appendix 1. Specific laboratory assessments are provided in Appendix 2.

Laboratory assessments for safety will be tested at a central laboratory facility. Laboratory reports will be made available to the Investigators in a timely manner for clinical management of participants.

It is anticipated that some laboratory values may be outside of the normal value range due to the underlying disease. As in routine practice, the Investigators should use their medical judgment when assessing clinical significance. Clinical significance is defined as any variation in laboratory measurements which has medical relevance and which results in a change in medical care. If clinically significant laboratory changes from Baseline are noted, the changes will be documented as AEs in the AE CRF. The Investigator will also assess the relationship to study treatment for all clinically significant out of range values. The Investigator will continue to monitor the participant with additional laboratory assessments until (1) values have reached normal range and/or Baseline, or (2) in the judgment of the Investigator, out of range values are not related to the administration of study drug or other protocol-specific procedures.

If participants experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma-glutamyl transferase (GGT), and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted. (Refer to Section 7.5.2 and Section 9.2.3 for the appropriate guidance on reporting abnormal liver function tests.)

If ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant participant details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 9.2.1.5).

9.1.7. 12-Lead ECG

Single 12-lead ECGs will be performed as outlined in the Schedule of Study Procedures (Appendix 1). Additional ECGs may be taken at any other times, if deemed necessary by the Investigator or designee.

ECGs will be performed with participants in a supine position. All ECG tracings will be reviewed by the Investigator or designee. ECGs will be measured within 24 hours prior to Day 1 dosing of each period for the pre dose time point. When scheduled post dose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

Study drug should be discontinued immediately with appropriate clinical follow-up if a QTcF interval >500 ms is detected by ECG and confirmed with a repeat ECG. Appropriate clinical follow-up includes a repeat ECG (Refer to Section 7.5.2 and Section 9.2.3.1 for the appropriate

guidance on QTcF measurement). The abnormality should be recorded as an AE (please refer to Section 9.2.1.5).

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9.2. Safety Evaluations

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting Ovid or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study. The participant should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the Investigator.

9.2.1. Adverse Events

An AE is any untoward medical occurrence in a participant or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to this medicinal product.

The definition of an AE also covers medication errors and uses outside what is foreseen in the protocol only if an AE results from the error, including intentional misuse, abuse, and overdose of the product.

Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital), and 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 are not AEs.

Ovid has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. Study site personnel will record the occurrence and nature of each participant's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the informed consent form (ICF) is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. If a participant experiences an AE after signing informed consent, but prior to receiving investigational product, the event will be reported, but will be classified as a pre-treatment AE unless the investigator feels the event may have been caused by a protocol procedure.

In addition, all AEs occurring after the participant receives the first dose of investigational product must be reported to Ovid or its designee via the eCRF.

9.2.1.1. Severity Assessment

Investigators will be instructed to rate the severity of AEs using the following criteria:

Mild	Events require minimal or no treatment and do not interfere with the participant's daily activities.
Moderate	Events result in a low level of inconvenience or concerns with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe	Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Change in severity of an AE should be documented based on specific guidelines in the CRF Completion Guidelines.

Severity and seriousness must be differentiated: severity describes the intensity of an AE, while the term seriousness refers to an AE that has met the criteria for an SAE.

9.2.1.2. Causality Assessment

Investigators will be instructed to report to Ovid or its designee their assessment of the potential relatedness of each AE to protocol procedure and/or study drug via the CRF.

An Investigator causality assessment (Not Related, Unlikely Related, Possibly Related or Related) must be provided for all AEs (both serious and non-serious). This assessment must be recorded in the CRF and any additional forms as appropriate.

Relationship of AEs to the defined study treatment, will be determined by the Investigator according to the following criteria. Please note that not all criteria must be present to be indicative of a particular relationship

Not Related	Exposure to the defined study treatment did not occur, or the occurrence of the AE is not reasonably related in time.
Unlikely Related	The AE occurred in a reasonable time after the defined study treatment and is doubtfully related to the investigational agent/procedure
Possibly Related	The defined study treatment and the AE were reasonably related in time, and the AE could be explained equally well by causes other than exposure to the defined study treatment
Related	The defined study treatment and the AE were reasonably related in time, and the AE was more likely explained by exposure to the defined study treatment than by other causes, or the defined study treatment was the most likely cause of the AE

If a participant's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Ovid or its designee via CRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

9.2.1.3. Serious Adverse Events

Serious adverse event collection begins after the participant has signed informed consent. If a participant experiences an SAE after signing informed consent, but prior to receiving investigational product, the event will be reported, but will be classified as a pre-treatment SAE unless the investigator feels the event may have been caused by a protocol procedure.

Planned surgeries and/or hospitalizations should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

An SAE is any AE from this study that results in one or more of the following outcomes:

- Results in death
- Requires or prolongs hospitalization
- Is life threatening (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly or birth defect

- Other medically important serious event

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events occurring up to and including the participant's last study visit will be collected, regardless of the investigator's opinion of causation.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the study may be found in the IB (IB Ed 5).

9.2.1.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance or national regulatory requirements in participating countries require the reporting of SUSARs. Ovid has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

9.2.1.5. Reporting Adverse Events

All non-serious AEs must be recorded in the CRF upon awareness.

Any AE that meets SAE criteria (Section 9.2.1.3) must immediately (i.e., within 24 hours) be sent to the Sponsor upon learning of any SAE that occurs (whether or not attributable to the study drug). It is the Investigator's responsibility to ensure that SAE reporting procedures are followed appropriately. All SAE reports and any revisions to an SAE report must be sent to the following email. All supporting source information concerning the SAE (e.g., hospital records) should also be provided by email.

Email: PPD

If there is a question concerning an SAE, the site needs guidance regarding reporting of an SAE, the site is returning a call from the Sponsor's safety specialist, or the site urgently needs to report an SAE or make the Sponsor aware of an SAE, the safety hotline should be used.

SAE Hotline: PPD

If an SAE is reported via the hotline, the site should first submit the SAE paper form and then enter the SAE in the eCRF. Any AE that meets SAE criteria must be entered into the EDC system immediately (ie, within 1 business day) after site personnel first learns about the event in addition to emailing the SAE Report form.

All SAEs must be reported starting from the time that informed consent for study participation is provided. If the Investigator becomes aware of an SAE within 30 days after the participant's last dose of study drug or within 30 days after the last study visit, the SAE must be reported. Serious AEs must be followed until the event resolves, the event or sequelae stabilize, or it is unlikely that additional information can be obtained after demonstration of due diligence with follow-up efforts (i.e., the participant or health care practitioner is unable to provide additional information, or the participant is lost to follow up). Serious AEs that occur more than 30 days after the last dose of study drug need not be reported unless the Investigator considers them related to study drug.

9.2.1.6. Sponsor Reporting Requirements

The Sponsor or its legal representative is responsible for notifying the relevant regulatory authorities of SAEs meeting the reporting criteria. This protocol will use the current IB as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by the Sponsor from the Reference Safety Information which is the IB (IB Ed 5).

9.2.1.7. Investigator Reporting Requirements

The Investigator must fulfill all local regulatory obligations required for the study Investigators. It is the PI's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all SUSAR events that occur during the clinical study. Each site is responsible for notifying its IRB/IEC of these additional SAEs.

9.2.2. Exposure During Pregnancy and/or Lactation

Exposure during pregnancy (also referred to as exposure in-utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.

If a participant's partner becomes pregnant while treated or exposed to study drug, the investigator must submit a pregnancy form to Ovid via the same method as SAE reporting. Pharmacovigilance will supply the Investigator with a copy of a "Pregnancy Reporting and Outcome Form/Breast Feeding." When the outcome of the pregnancy becomes known, the form should be completed and returned to Ovid or Ovid Pharmacovigilance delegate. If additional follow-up is required, the Investigator will be requested to provide the information.

Pregnancy is not regarded as an AE unless there is a suspicion that study drug may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet criteria for an SAE (such as ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

9.2.3. Safety Monitoring

The Ovid medical monitor and/or Pharmacovigilance physician will monitor safety data throughout the course of the study.

Ovid will review SAEs within time frames mandated by company procedures. The Ovid medical monitor will, as appropriate, consult with the functionally independent Pharmacovigilance therapeutic area physician.

9.2.3.1. Reporting of Abnormal Liver Function Tests

If a participant is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases CRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a participant is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 9.2.1.5. The investigator must contact the Medical Monitor for discussion of the relevant participant details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.6 must also be performed.

In addition, a CRF must be completed and transmitted with the SAE Report form (as per Section 9.2.1.5).

9.2.3.2. Reporting of QTcF interval increase

If a participant is noted to have QTcF interval > 500 ms on 2 consecutive occasions, the study drug should be discontinued immediately and abnormality should be recorded as an AE.

The investigator must contact the Medical Monitor for discussion of the relevant participant details and possible alternative etiologies, such as medical history/concurrent medical conditions. Follow-up ECG measurements as described in Section 9.1.7 must also be performed.

In addition, a CRF must be completed and transmitted with the SAE Report form (as per Section 9.2.1.5).

9.3. Sample Collection and Testing

9.3.1. Blood Sampling and Processing

Primary specimen collection parameters are provided in Table 4.

Instructions for whole blood, plasma, urine, fecal samples processing and handling will be provided separately.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the test runs, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

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9.3.2. PK Measurements

9.3.2.1. Whole Blood and Plasma for PK Measurements

The following PK parameters for whole blood and plasma radioactivity concentration equivalents (plasma in both Periods 1 and 2, whole blood in Period 2 only) and for plasma TAK-935 concentrations (Periods 1 and 2) will be calculated, unless otherwise specified:

- AUC_{last}: Area under the concentration-time curve from time 0 to time of the last quantifiable concentration.
- AUC_t: Area under the concentration-time curve from time 0 to time of the last common time point "t" at which total radioactivity and TAK-935 are quantifiable for all participants.
- AUC_∞: Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.
- $AUC_{extrap}\%$: Area under the curve from the last quantifiable concentration to infinity calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_∞.
- C_{max}: Maximum observed concentration.
- λ_z: Terminal disposition phase rate constant.
- t_{max}: Time of first occurrence of C_{max}.
- $t_{1/2z}$: Terminal disposition phase half-life.

The following PK parameters for plasma concentrations of [^{14}C]TAK-935 following IV infusion (Period 1) will be calculated, unless otherwise specified:

- AUC_{last}: Area under the concentration-time curve from time 0 to time of the last quantifiable concentration.
- AUC_t: Area under the concentration-time curve from time 0 to time of the last common time point "t" at which plasma total radioactivity and plasma TAK-935 are quantifiable for all participants.
- AUC_∞: Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.

AUC_{extrap}%:	Area under the curve from the last quantifiable concentration to infinity calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞}.
C_{eoi}:	Concentration at the end of infusion.
λ_z:	Terminal disposition phase rate constant.
$t_{1/2z}$:	Terminal disposition phase half-life.

No value for λ_z, AUC_{∞}, AUC_{extrap}%, or $t_{1/2z}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

No PK parameters will be calculated for participants with detectable concentrations or radioactivity concentration equivalents at 2 or fewer consecutive time points.

Individual and mean plasma concentration- or radioactivity concentration equivalent-time curves (both linear and log-linear) will be included in the final report.

The ABA parameters for TAK-935 (Period 1) will be calculated as follows:

F:	Absolute bioavailability, calculated for plasma TAK-935.
%F:	Percent absolute bioavailability, calculated for plasma TAK-935 as [Dose (IV) x AUC_{∞} (oral)] / [Dose (oral) x AUC_{∞} (IV)] x 100.

9.3.3. Urine for PK Measurements

The following PK parameters for urine [^{14}C]TAK-935 concentrations (Period 1; IV dose), and for urine TAK-935 concentrations and urine total radioactivity (both Periods 1 and 2) will be calculated, unless otherwise specified:

Ae_{t1-t2}:	Amount of drug excreted in urine from time 1 to time 2.
Ae(u):	Cumulative amount excreted in urine.
%Dose(u):	Percent of administered radioactive dose excreted in urine within a given collection interval.
Cum%Dose(u):	Cumulative percent of administered dose excreted in urine.
CL_R:	Renal clearance.

Total radioactivity excreted in urine will be presented in mass equivalent units.

9.3.4. Feces for PK Measurements

The following PK parameters for fecal [^{14}C]TAK-935 concentrations (Period 1; IV dose), and for fecal total radioactivity (both Periods 1 and 2) will be calculated, unless otherwise specified:

Ae(f):	Cumulative amount of total radioactivity excreted in feces.
%Dose(f):	Percent of administered radioactive dose excreted in feces within a given collection interval.
Cum%Dose(f):	Cumulative percent of administered dose excreted in feces.

Total radioactivity excreted in feces will be presented in mass equivalent units.

9.3.5. Additional PK Measurements

The following PK parameters for combined urine and fecal total radioactivity (Period 1, IV dose and Period 2) will be calculated, unless otherwise specified:

Combined Cum%Dose:	Cumulative combined percent of administered dose excreted in urine and feces.

9.3.6. Biomarker Measurements

Not applicable

9.4. Data Collection and Storage

All clinical raw data will be recorded promptly, accurately, and legibly, either directly into the data capture system as e-source data, or indelibly on paper (eg, ECG readings). A detailed list of the type (electronic or paper) and location for all source data will be included in the Trial Master File. When recorded electronically, case report forms will be electronically generated. All raw data will be preserved to maintain data integrity. The investigator or designee will assume the responsibility of ensuring the completeness, accuracy, and timeliness of the clinical data.

The electronic data capture system is fully validated and Code of Federal Regulations Title 21 Part 11 compliant. The electronic data capture system will maintain a complete audit trail of all data changes. At each scheduled monitoring visit, the Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each participant receiving study drug.

10. STATISTICAL METHODS AND PLANNED ANALYSES

10.1. General Considerations

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a SAP. The SAP will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

10.2. Determination of Sample Size

The sample size of 6 male healthy participants was selected without statistical considerations and is deemed adequate to meet the study objectives. In addition, this sample size is limited based on clinical considerations for this type of study and in order to limit exposure to radioactivity.

10.3. Analysis Sets

10.3.1. Pharmacokinetic Set

All participants who comply sufficiently with the protocol and display an evaluable PK profile (eg, exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses.

10.3.2. Safety Set

All participants who received at least one dose of the study drug will be included in the safety evaluations.

10.4. Demographics and Other Baseline Characteristics

Continuous demographic data (ie, age, weight, height, and BMI) will be listed and summarized using appropriate summary statistics. Categorical demographic data (ie, sex, race, and ethnicity) will also be listed and tabulated.

10.5. Participant Disposition

All participants who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

10.6. Pharmacokinetic Analysis

Descriptive statistics will be provided for the total radioactivity (whole blood, plasma, urine, feces, and if applicable, emesis), TAK-935 concentrations and PK parameters (plasma and urine), and [^{14}C]TAK-935 plasma, urine, feces radioactivity concentrations equivalent, using appropriate summary statistics to be fully specified in the SAP.

PK parameters for whole blood and plasma concentrations (as appropriate) and total radioactivity will be calculated as described in Section 9.3.2.1 and for urine and feces, as described in Sections 9.3.3 and 9.3.4, respectively.

ABA of TAK-935 (Period 1) will be estimated using a 90% CI constructed for the difference in LS mean on the log scale for dose normalized AUC_{∞} between a single oral dose and the IV microdose. Exponentiating the log-scale 90% CI will provide a 90% CI for the dose normalized AUC_{∞} geometric mean ratio (TAK-935 administered as oral dose / [^{14}C]TAK-935 administered as IV microdose). AUC_{last} will be analyzed in a similar fashion if AUC_{∞} cannot be calculated.

10.6.1. Analysis of Mass Balance

In Period 2, mass balance will be calculated as a sum of the percent of the total radioactivity recovered in urine and feces plus any radioactivity dose lost due to emesis (if any occurred) relative to the administered radioactivity dose.

10.6.2. Whole Blood to Plasma Partitioning Ratio

In Period 2, ratios of the concentration of [^{14}C] radioactivity and TAK-935 in whole blood relative to plasma will be estimated (eg, whole blood:plasma partitioning ratio). The ratio of AUC_{∞} total radioactivity in blood and plasma will also be calculated.

10.6.3. Metabolite Profiling

In Period 2, TAK-935 metabolite profiling will be performed in plasma, urine, and feces containing sufficient amounts of radioactivity. The percent of dose represented by each of the metabolites, if any, will be calculated using the radioactivity concentration equivalent data combined with the metabolite profiling data. The percentage of each identified metabolite, if any, to total radioactivity in the plasma will be estimated based on plasma metabolite profiling data.

10.7. PD Analysis

Not applicable.

10.8. Safety Analysis

All safety data will be listed in the listings.

Dosing dates and times will be listed by participant.

Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

10.8.1. Adverse Events

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA® version 21 or higher) available and summarized by treatment for the number of participants reporting the TEAE and the number of TEAEs reported. A by participant AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided. AE listing will be provided.

10.8.2. Clinical Laboratory Evaluation

Clinical laboratory results will be summarized by treatment and point of time of collection and a shift table describing out of normal range shifts will be provided.

10.8.3. Vital Signs

Vital signs assessments will be summarized by treatment and point of time of collection.

10.8.4. Other Safety Parameters

Physical examination findings will be presented in the data listings.

ECGs will be summarized by treatment and point of time of collection.

Medical history, and concurrent conditions will be coded using the MedDRA® and concomitant medications will be coded using the World Health Organization drug and will be listed by participant.

C-SSRS findings will be presented in the data listings.

10.9. Interim Analysis and Criteria for Early Termination

Not applicable

10.10. Other Statistical Issues

Significance Levels:

There is no hypothesis test for this study, only summary statistics will be provided. No significance level is specified.

10.10.1. Missing or Invalid Data

Techniques for handling missing data will be specified in detail in the SAP.

10.10.2. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Sponsor personnel will be consulted to determine whether it is necessary to amend the protocol.

Details of all statistical analyses are contained in the study SAP.

11. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

11.1. Informed Consent

The investigator is responsible for ensuring that the participant understands the potential risks and benefits of participating in the study, including answering any questions the participant may have throughout the study and sharing in a timely manner any new information that may be relevant to the participant's willingness to continue his participation in the study.

The ICF will be used to explain the potential risks and benefits of study participation to the participant in simple terms before the participant is entered into the study, and to document that the participant is satisfied with his understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each participant. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.

11.1.1. Informed Consent Procedure

Informed consent must be obtained before the participant enters into the study, and before any protocol-directed procedures are performed.

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the participants in non-technical terms. Participants or their legally authorized representative will be required to read, sign and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Participants and/or their legally authorized representative will be given a copy of their signed ICF.

A unique participant identification (ID) number (participant number) will be assigned to each participant and will be used throughout the study.

The investigator is responsible throughout the study for ensuring that the participant understands the potential risks and benefits of participating in the study, including answering any questions the participant may have throughout the study and sharing in a timely manner any new information that may be relevant to the participant's willingness to continue his participation in the study.

The ICF will be used to explain the potential risks and benefits of study participation to the participant in simple terms before the participant is entered into the study, and to document

that the participant is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The Investigator is responsible for ensuring that informed consent is given by each participant. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

11.2. Administrative Procedures

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the sponsor, its designee, US FDA, Health Authorities, Ethics Committees, and/or IRBs.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.3. Ethical Review

The Sponsor or its representatives must approve all ICFs before they are used at investigative sites(s). All ICFs must be compliant with the ICH guideline on GCP.

Documentation of IRB/IEC approval of the protocol and the ICF must be provided to the Sponsor before the study may begin at the investigative site(s). The IRB/IEC(s) will review the protocol as required.

The study site's IRB/IEC(s) should also be provided with the following:

- The current IB and updates during the study (IB Ed 5)
- ICF
- Relevant curricula vitae

Only a Sponsor and IRB/IEC approved protocol and ICF may be used by the investigative site.

11.4. Regulatory Considerations

This study will be conducted in accordance with:

1. Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2. The ICH GCP Guideline [E6]
3. Applicable FDA regulations
4. Applicable laws and regulations

The investigator or designee will promptly submit the protocol to applicable IRB/IEC(s).

An identification code assigned by the investigator to each participant will be used in lieu of the participant's name to protect the participant's identity when reporting AEs and/or other study-related data.

11.5. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the sponsor, its designee, US Food and Drug Administration, Health Authorities, Ethics Committees, and/or IRBs. The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.5.1. Investigator Information

PPD

11.5.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Sponsor representative.

11.5.3. Final Report Signature

The investigator will sign the final clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The Sponsor's responsible medical officer and statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

11.6. Publication Policy

The full terms regarding publication of the results of this study are outlined in the Clinical Study Agreement, Statement of Agreement, or the Master Clinical Study Agreement. Publication is permitted only after multi-center results are available and all disclosure requirements for clinical study registries have been met. Any data to be submitted for publication, including abstract submissions or presentations, are required to be submitted PPD for review at least 30 days prior to submission.

12. LIST OF REFERENCES

21CFR361.1 FDA CFR Code of Federal Regulations Title 21, Volume 5, 01 Apr 2019

ICRP Draft 2005 Recommendations on Radiological Protection: People Against Radiation Exposure In The Aftermath Of A Radiological Attack April 2004 (A Report from a Task Group of the ICRP)

OV/TAK-935 Global Investigator Brochure Ed 5 22 Jan 2019.

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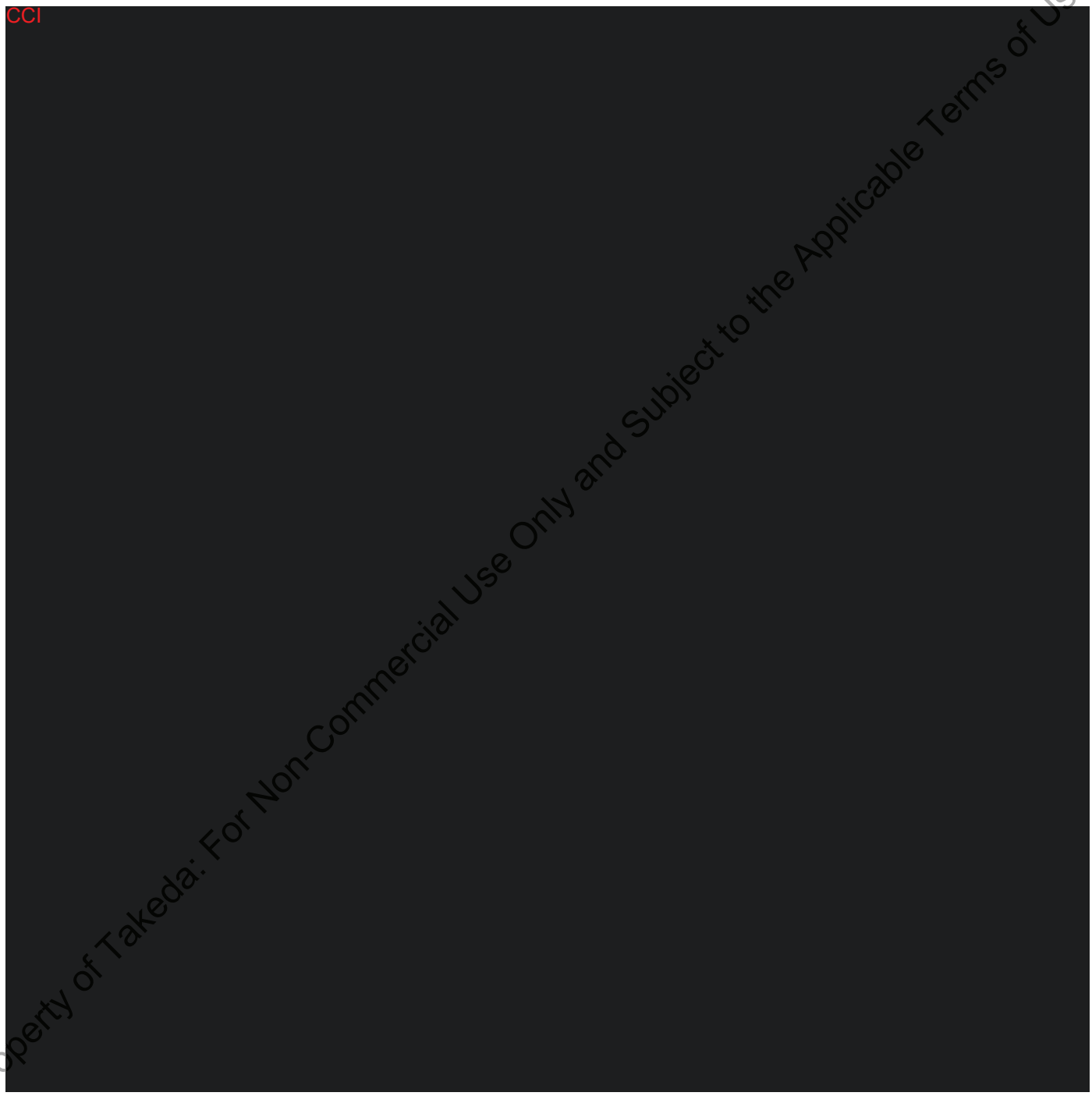

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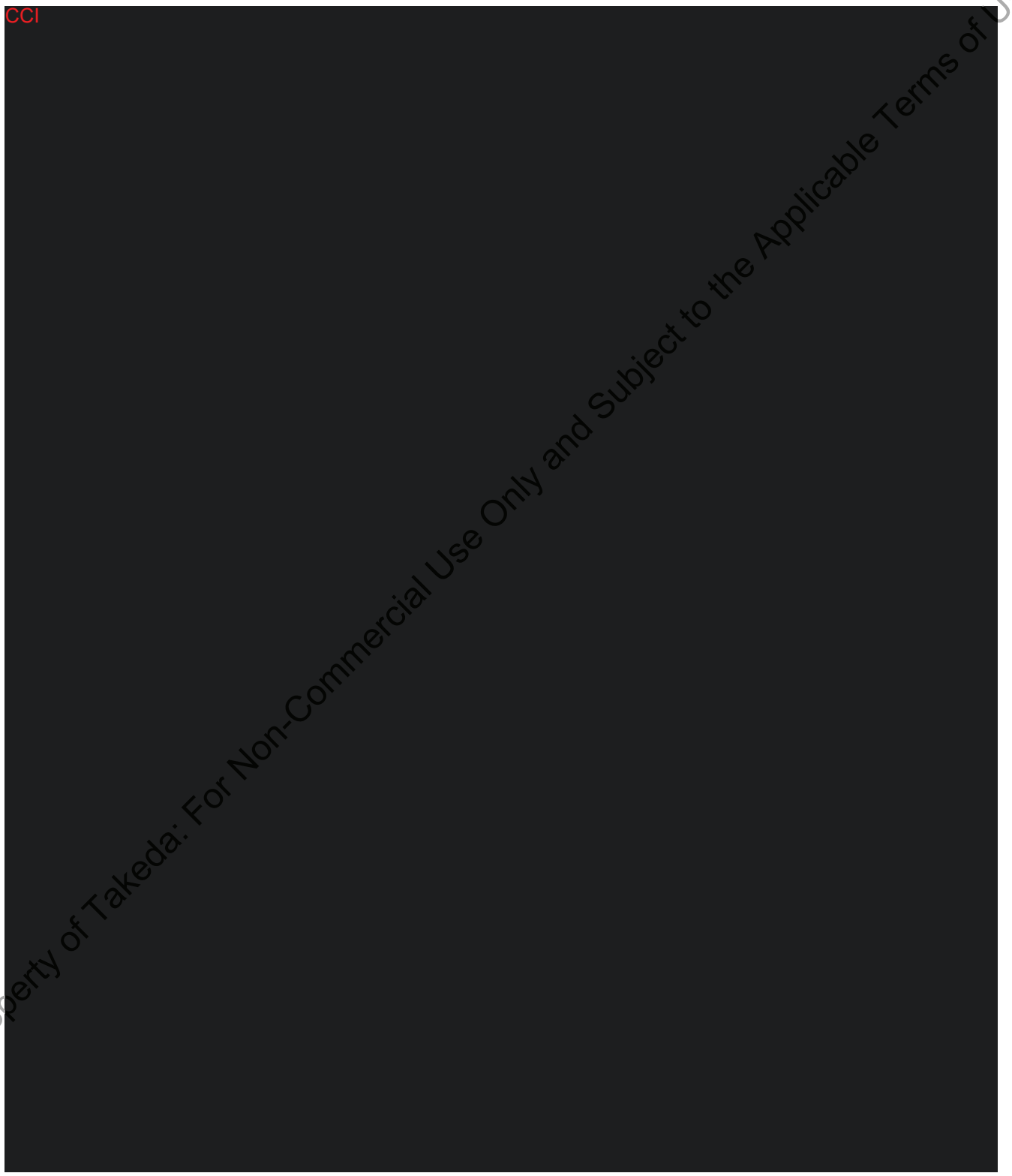

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APPENDIX 2. CLINICAL LABORATORY TESTS (STUDY TAK-935-20-001 [OV935]):

Protocol TAK-935-20-001 (OV935): Clinical Laboratory Tests

Hematology:

Erythrocytes

Hemoglobin

Hematocrit

Red blood cell indices

Mean corpuscular volume reticulocytes

Ret. mean corpuscular hemoglobin

Ret. corpuscular hemoglobin content

Reticulocyte distribution width

White blood cell count and differential

Neutrophils, segmented

Lymphocytes

Monocytes

Eosinophils

Basophils

Platelets

Mean platelet volume

Coagulation:

Prothrombin time/INR

Activated partial thromboplastin time

Urinalysis:

pH

Protein

Glucose

Clinical Chemistry:

Sodium

Potassium

Total bilirubin

Direct bilirubin

Indirect bilirubin

Alkaline phosphatase

Alanine aminotransferase (ALT)

Aspartate aminotransferase (AST)

Gamma-glutamyl transferase (GGT)

Blood urea nitrogen (BUN)

Creatinine

Urea

Calcium

Phosphate

Glucose, fasting

Albumin

Protein

Alpha1-acidic glycoprotein (AGP) (screening only)

Carbon dioxide

Magnesium

Chloride

Ketones

Bilirubin

Erythrocytes

Leukocyte esterase

Nitrite

Urobilinogen

Calcium

Calcium/Creatinine

Microscopy

Other Laboratory Tests

COVID-19

HIV

HBsAg

HCV

Urine alcohol screen

Urine drug screen

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