Official Title: An Open-Label Study Assessing the Mass Balance, Pharmacokinetics, and Metabolite Profiles of a Single Oral Dose of [14C]INCB099280 in Healthy Male Participants

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Clinical Study Protocol

INCB 99280-102

An Open-Label Study Assessing the Mass Balance, Pharmacokinetics, and Metabolite Profiles of a Single Oral Dose of [^{14}C]INCB099280 in Healthy Male Participants

Product:	**INCB099280**
IRAS ID Number:	**1009235**
Phase of Study:	**1**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803 USA**
Original Protocol:	**15 DEC 2023**
Amendment 1:	**25 MAR 2024**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Brazil 2013) and conducted in adherence to the study Protocol, applicable Good Clinical Practices, and applicable laws and country-specific regulations, including WMO (Medical Research Involving Human Participants Act) and Clinical Trials Regulation (EU) No. 536/2014, in which the study is being conducted.

INVESTIGATOR'S AGREEMENT

I have read the INCB 99280-102 Protocol Amendment 1 (dated 25 MAR 2024) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

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(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
A_e	amount of drug excreted in the urine over sampling interval
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AME	absorption, metabolism, and excretion
ARSAC	Administration of Radioactive Substances Advisory Committee
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the steady-state plasma concentration-time curve from time = 0 to 24 hours
AUC_{0-t}	area under the steady-state plasma or serum concentration-time curve up to the last measurable concentration
$AUC_{0-\infty}$	area under the single-dose plasma or serum concentration-time curve extrapolated to time of infinity
BID	twice daily
BMI	body mass index
bpm	beats per minute
CFR	Code of Federal Regulations
CL/F	apparent oral dose clearance
CL_R	renal clearance
C_{max}	maximum observed plasma or serum concentration
COVID-19	coronavirus disease 2019
CRU	clinical research unit
CSPM	Clinical Sample Processing Manual
C_t	last quantifiable concentration
CYP	cytochrome P450
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ET	early termination
FDA	Food and Drug Administration
f_e	percent of unchanged drug dose excreted in the urine
FSH	follicle-stimulating hormone

Abbreviations and Special Terms	Definition
GI	gastrointestinal
GCP	Good Clinical Practice
GCV	geometric coefficient of variation
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-a-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICRP	International Commission on Radiological Protection
IEC	independent ethics committee
IMP	investigational medicinal product
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	oral(ly)
Q24H	every 24 hours
QD	once daily
QTcF	QT interval corrected using Fridericia's formula
RSI	Reference Safety Information
SAE	serious adverse event
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
$t_{½}$	apparent terminal-phase disposition half-life
TEAE	treatment-emergent adverse event

Abbreviations and Special Terms	Definition
t_{max}	time to maximum concentration
ULN	upper limit of normal
UK	United Kingdom
V_{ss}	volume of distribution at steady state
V_z/F	apparent oral dose volume of distribution
WBC	white blood cell
WOCBP	women of childbearing potential
WHO	World Health Organization
λ_z	apparent terminal-phase disposition rate constant

1. PROTOCOL SUMMARY

Protocol Title: An Open-Label Study Assessing the Mass Balance, Pharmacokinetics, and Metabolite Profiles of a Single Oral Dose of [^{14}C]INCB099280 in Healthy Male Participants

Protocol Number: INCB 99280-102

Objectives and Endpoints:

Table 1 presents the primary and secondary objectives and endpoints.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the route of elimination and mass balance of [^{14}C]INCB099280 after administration of a single dose of INCB099280 400 mg PO followed by an oral dose solution containing [redacted] of [^{14}C]INCB099280 (not more than [redacted]	Total recovery of radioactivity from urine and feces.
To characterize the metabolic profile and identify circulating and excreted metabolites of INCB099280 after administration of a single dose of INCB099280 400 mg PO followed by an oral dose solution containing [redacted] of [^{14}C]INCB099280 (not more than [redacted]	Quantitative metabolite profile in plasma, urine, and feces.
Secondary	
To evaluate the PK of total radioactivity and the parent compound after administration of a single dose of INCB099280 400 mg PO followed by an oral dose solution containing [redacted] of [^{14}C]INCB099280 (not more than [redacted]	PK for plasma INCB099280 (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{½}$, λ_z, CL/F, and V_z/F).
	PK for whole blood and plasma total radioactivity (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{½}$, λ_z, CL/F, and V_z/F).
To evaluate the safety of a single dose of INCB099280 400 mg PO followed by an oral dose solution containing [redacted] of [^{14}C]INCB099280 (not more than [redacted]	Incidence of AEs, assessed by changes in ECGs and vital signs and through physical examinations and clinical laboratory sample evaluations.

Overall Design:

Table 2 presents the key study design elements. Further study details are presented after the table.

Table 2: Key Study Design Elements

Study Phase	Phase 1
Clinical Indication	Healthy participants
Population	Healthy male participants aged 35 to 55 years, inclusive
Number of Participants	Up to 7 participants will be enrolled to ensure 6 participants complete the study
Study Design	A single-center, open-label, mass balance study of [^{14}C]INCB099280
Estimated Duration of Study Participation	Up to 27 days for screening, 1 day for admission, a single administration of study treatment on Day 1, and 18 to 24 days for follow-up after the dose of study drug. It is estimated that an individual will participate for approximately 2 months from screening to follow-up.
Data Safety Monitoring Board	No

Treatment Groups and Duration:

This is a Phase 1, single-center, open-label, mass balance study of [^{14}C]INCB099280 in healthy male participants. Study treatment will consist of a single dose of INCB099280 400 mg administered in tablet form (4 × 100-mg tablets) with 240 mL of water followed approximately 10 minutes later by an oral dose solution containing [redacted] of [^{14}C]INCB099280 (not more than [redacted] Participants will receive study treatment on Day 1 after an overnight fast of at least 8 hours, with food intake allowed no sooner than 4 hours postdose. In addition, except for the water provided for dose administration, water will be restricted for 1 hour before INCB099280 tablet administration until 1 hour postdose.

Participants will be admitted to the CRU on Day –1 at a time determined by the clinic. Participants will remain in the CRU until at least Day 6, but potentially up to Day 12, based on satisfying both of the following discharge criteria:

- ≥ 90% of the administered radioactive dose is recovered in excreta (urine and feces combined).
- < 1% of the administered radioactive dose is recovered in excreta (urine and feces combined) in 2 consecutive, 24-hour, urine and fecal samples in which both samples are provided.

If the discharge criteria are not met, then participants will be discharged no later than Day 12 (264 hours postdose on the morning of Day 12). Participants may be provided with sample pots for home collection of urine and/or feces; this would be decided on a case-by-case basis following discussion between the investigator and the sponsor.

The follow-up period will include a follow-up phone call 21 (± 3) days after the dose of study treatment.

Adherence to the study design requirements, including those specified in the SoA (see Table 3), is essential and required for study conduct.

Table 3: Schedule of Activities

Visit Day (Range)	Screening Days –28 to –2	Admission Day –1	Treatment Day 1	 Day 2	 Day 3	 Days 4-5	 Days 6-12	ET	Follow-Up Day 22 (± 3 days)	Notes
Administrative procedures										
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Demographics	X									
Height and weight	X	X								Height at screening only. BMI calculated.
Medical history	X	X								Interim medical history at admission.
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	
INCB099280 + [^{14}C]INCB099280 administration			X							Study treatment administration will occur after an overnight fast of at least 8 hours, and participants will refrain from food for an additional 4 hours post–tablet administration. A single 400-mg dose of INCB099280 tablet formulation will be taken, followed approximately 10 minutes later by an oral dose solution of [^{14}C]-INCB099280.
Admission to CRU		X								
Confined to CRU		X	X	X	X	X	X			Participants will remain in the CRU until at least Day 6 but potentially up to Day 12 based on satisfying both of the following discharge criteria: ≥ 90% of the administered radioactive dose is recovered and < 1% of the administered radioactive dose is recovered in excreta in 2 consecutive, 24-hour, urine and fecal samples (combined). Participants not meeting these criteria will be discharged at the maximum confinement on Day 12.
Discharge from CRU							X	X		
Safety assessments										
AE assessments	X	X	X	X	X	X	X	X	X	Participants will undergo AE assessments on each day from signing of the ICF until CRU discharge and at the follow-up phone call.
Vital signs	X	X	X*				X†	X†		* Performed at 0 hour (predose) and approximately 1, 2, 4, and 6 hours post–tablet administration. † Performed on the day of discharge or ET.

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening Days –28 to –2	Admission Day –1	Treatment Day 1	Day 2	Day 3	Days 4-5	Days 6-12	ET	Follow-Up Day 22 (± 3 days)	Notes
Comprehensive physical examination	X	X					X*	X*		* Performed on the day of discharge or ET. A targeted physical examination can be conducted at the discretion of the investigator at any time during the study period (see Section 8.3.2).
Single, 12-lead ECG	X	X	X*				X†	X†		* Performed at 0 hour (predose) and 4 hours post–tablet administration. † Performed on the day of discharge or ET.
Clinical laboratory assessments										
Serum chemistry	X	X		X			X*	X*		Scheduled blood samples will be taken following an 8-h fast. * Performed on the day of discharge or ET.
Hematology	X	X		X			X*	X*		Scheduled blood samples will be taken following an 8-h fast. * Performed on the day of discharge or ET.
Urinalysis	X	X					X*	X*		* Performed on the day of discharge or ET.
Serology	X									
Thyroid panel	X						X*	X*		* Performed on the day of discharge or ET.
Urine drug screen	X	X								
Alcohol and carbon monoxide breath test	X	X								
Blood sampling for PK and radioactivity			X	X	X	X	X	X		Samples will be collected as outlined in Table 6.
Blood sampling for metabolite profiling			X	X	X	X	X	X		Samples will be collected as outlined in Table 6.
Urine sampling for PK, radioactivity, and metabolite profiling			X	X	X	X	X	X		Urine will be collected at the following intervals relative to INCB099280 tablet administration: −12 to 0 hours (predose void [spot sample only]); 0 to 6, 6 to 12, and 12 to 24 hours postdose; and continuing in 24-hour intervals until discharge.
Fecal sampling for radioactivity and metabolite profiling			X	X	X	X	X	X		Fecal samples will be collected at the following intervals relative to INCB099280 tablet administration: −12 to 0 hours (predose [spot sample only]; whenever possible), 0 to 24 hours postdose, and continuing in 24-hour intervals until discharge.

2. INTRODUCTION

2.1. Background

INCB099280 is a potent, orally bioavailable, selective small molecule that targets PD-L1 (also known as CD274) that is being developed for the treatment of advanced malignant diseases.

2.1.1. Pharmacology

PD-1, also known as CD279, is a cell surface receptor expressed on activated T cells, natural killer T cells, B cells, and macrophages. It functions as an intrinsic negative feedback system to prevent the activation of T cells, which in turn reduces autoimmunity and promotes self-tolerance. In addition, PD-1 is also known to play a critical role in the suppression of antigen-specific T-cell response in diseases like cancer and viral infection. PD-1 binds to PD-L1, which is highly upregulated on many types of tumor cells as well as immune cells; therefore, targeting PD-L1 is an alternative approach for the treatment of cancer. Anti–PD-L1 antibodies have demonstrated unequivocal therapeutic benefit in multiple clinical studies across different tumor types, resulting in their approval as anticancer agents.

INCB099280 has been evaluated against a panel of targets to assess the potential for unintended pharmacological activity. There was no cross-reactivity in any of the 55 in vitro binding assays in which INCB099280 was tested. INCB099280 has also been evaluated in 2 separate kinase profiling assays. In the first assay, IC_{50} values for the 56 kinases evaluated were at least 840-fold higher than the unbound clinical steady-state C_{max} after administration of 400 mg BID; in a separate kinase profiling assay (172 kinases) at a concentration of 100 nM, INCB099280 did not inhibit the activity of any kinase by more than 50%. In a GLP, in vitro, voltage-clamped, cell-based, hERG channel assay, the functional IC_{50} for hERG inhibition was estimated to be 3.0 μM, which is approximately 300-fold higher than the unbound clinical steady-state C_{max} after administration of 400 mg BID. There have been no adverse findings in in vivo safety pharmacology assessments of INCB099280, including respiratory and central nervous system function studies at doses up to 1000 mg/kg in rats and an in vivo cardiovascular study at doses up to 225 mg/kg in conscious, radiotelemetry-implanted cynomolgus monkeys. Absence of neurological and cardiovascular findings in nonclinical GLP toxicology studies as well as the collective in vitro and functional results support the conclusion that the risk of unintended pharmacological activity is expected to be low.

2.1.2. Nonclinical Pharmacokinetics and Drug Metabolism

The absorption, distribution, metabolism, and excretion of INCB099280 have been characterized in rats, dogs, and monkeys. Following IV administration, clearance was low (14%-21% of hepatic blood flow) and the V_{ss} was moderate (1.27-2.56 L/kg) across nonclinical species. The $t_{½}$ was moderate in rats (3.4 hours), dogs (5.5 hours), and monkeys (4.8 hours). In vitro protein binding of INCB099280 was high (unbound fraction of 0.3%) in human, which is similar to the ex vivo unbound fraction in rat (0.4%) and monkey (0.6%) plasma. INCB099280 has limited penetration across the rat blood-brain barrier.

In vitro experiments using human recombinant CYPs and human liver microsomes with selective chemical inhibitors showed INCB099280 is predominately metabolized by CYP3A, which was

confirmed by monitoring metabolites formed by recombinant CYPs. This suggests that INCB099280 may be subject to CYP3A4/CYP3A5 victim DDI upon coadministration with CYP3A4/CYP3A5 inhibitors. INCB099280 is not a potent reversible or time-dependent inhibitor of any of the CYPs tested; thus, the potential for INCB099280 to cause clinical drug interactions via reversible or time-dependent inhibition of CYPs is low. Results from a cultured primary human hepatocyte study demonstrated that INCB099280 is not an in vitro inducer of CYP1A2, CYP2B6, or CYP3A4.

The 3 most abundant, while still minor, metabolites (M2, M3, and M19) identified in human subcellular fraction and/or hepatocytes at ≥ 1% of drug-related peak area by mass spectrometry were also detected in other species at similar or higher levels. Thus, there was no evidence of human disproportionate metabolites. There was no evidence of reactive metabolites in either in vivo or in vitro biotransformation studies.

2.1.3. Nonclinical Toxicology

The INCB099280 nonclinical toxicology has been evaluated in Sprague Dawley rats and cynomolgus monkeys for up to 3 months. The program also includes genotoxicity studies, a core battery of safety pharmacology studies (central nervous system, respiratory, and cardiovascular), and an in vitro hERG inhibition evaluation.

The INCB099280 batch used in GLP nonclinical toxicology studies was fully characterized with regard to the identity, purity, and composition.

The primary finding from a pivotal, 28-day, rat GLP study was generally reversible mononuclear cell infiltration of the mandibular salivary gland and liver in all groups dosed with INCB099280 without a clear dose response and in the kidney in females and in the thyroid gland in males at ≥ 300 mg/kg per day. The only finding considered adverse was the marked mononuclear cell infiltration of the thyroid gland in a single 300-mg/kg per day male based on morphology disruption and loss of thyroid follicles. These findings were considered likely pharmacology-driven and occurred at an exposure (AUC) of 136 μM·h total, which is approximately 4.3-fold higher than steady-state clinical exposure after administration of 400 mg BID. In addition, increased hematopoiesis in the bone marrow was noted for males at 1000 mg/kg per day; exposure in this group was > 10-fold higher than steady-state clinical exposure after administration of 400 mg BID.

In a 90-day oral toxicity study in rats, immune-mediated pancreatic lesions resulting in mortality occurred at all doses. The cause of morbidity/deaths at all dose levels was considered to be decreased cellularity in the islets of Langerhans (minimal to marked) in the pancreas of males and females at all doses. There was also mononuclear cell (primarily lymphocytic) infiltration (mild to marked) in the pancreas at all doses. Death or euthanasia in extremis generally occurred after Day 45 and was preceded by rapid decline in animal condition with only minimal clinical signs and/or body weight loss. The primary microscopic lesion evident in both moribund and found-dead animals was marked lymphocytic infiltration in pancreatic islets leading to islet inflammation/atrophy. Based on the marked lymphocytic infiltrate, the observed pancreatic lesions are considered likely an immune-mediated effect. The no-observed-adverse-effect level was not identified. At the lowest dose in this study (100 mg/kg per day), the steady-state AUC_{0-24} was 80.6 μM·h, (both sexes combined), which is approximately 1.4-fold the clinical exposure at 800 mg BID (56.8 μM·h).

There were no adverse findings in a pivotal, 28-day, monkey GLP study that evaluated doses up to 225 mg/kg per day. However, in a range-finding monkey study, administration of INCB099280 at 500 mg/kg per day for 14 days caused adverse clinical signs (inappetence, swollen eyes, hunched posture, and body weight loss), marked elevation of liver function tests (ALT, AST, and bilirubin) associated with hepatocyte degeneration with occasional necrotic hepatocytes, and gastric ulceration/erosion with necrosis/loss of glandular mucosa with focal inflammation. Steady-state exposure (AUC) at 500 mg/kg per day was 1360 μM·h total, approximately 43-fold higher than steady-state clinical exposure after administration of 400 mg BID.

INCB099280 is not genotoxic. INCB099280 was negative in a bacterial reverse mutation assay, an in vitro chromosomal aberrations study in human peripheral blood lymphocytes, and an in vivo micronucleus study in rats. Carcinogenesis and reproductive and developmental toxicity studies have not been performed with INCB099280. INCB099280 is not expected to be phototoxic on the basis of a neutral red uptake study in BALB/c 3T3 mouse fibroblasts.

2.1.4. Clinical Summary

Administration of single doses of INCB099280 up to 150 mg have been generally well tolerated in healthy participants. In Study INCB 99280-101, 76 participants received a single dose of INCB099280 25, 75, or 150 mg, and no participants had serious TEAEs, TEAEs with fatal outcomes, or TEAEs leading to study drug discontinuation. Across all INCB099280 treatment groups, TEAEs occurred in 57.9% of participants. Treatment emergent AEs occurring in more than 1 participant were headache (17.1%); catheter site pain and dizziness (5.3% each); back pain, muscle spasms, paresthesia, and presyncope (3.9% each); and diarrhea, lethargy, dry lip, mouth ulceration, and viral upper respiratory tract infection (2.6% each).

As of 22 JUN 2023, 172 participants with advanced solid tumors have received INCB099280 up to 1600 mg daily. Treatment-emergent AEs occurred in 95.3% of participants; the most common TEAEs were asthenia (30.2%), decreased appetite (27.3%), nausea (25.0%), vomiting (22.7%), and fatigue (20.3%). Serious TEAEs occurred in 26.2% of participants; the serious TEAEs occurring in more than 1 participant were pyrexia (4 participants [2.3%]); pneumonia and sepsis (3 participants [1.7%] each); and anemia, dyspnea, hypercalcemia, large intestinal obstruction, pneumothorax, and urinary tract infection (2 participants [1.2%] each). Six participants (3.5%) had a fatal TEAE as follows: multiple organ dysfunction syndrome and sepsis (in 1 participant) and COVID 19, pneumonia, death, large intestinal obstruction, and subdural hematoma (in 1 participant each). All fatal events were assessed as not related to INCB099280 by the investigator. Eight participants (4.7%) had TEAEs leading to INCB099280 discontinuation as follows: increased ALT and increased AST in 3 participants (1.7%) each and COVID-19, confusional state, dyspnea, increased gamma-glutamyl transferase, immune-mediated hepatitis, and large intestinal obstruction in 1 participant (0.6%) each.

2.1.4.1. Clinical Pharmacology

INCB 99280-101 is a completed study in healthy participants. After single-dose treatment of 25, 75, or 150 mg under fasting conditions, INCB099280 attained peak plasma concentration at approximately 4 hours (ranging from 1 to 6 hours) and then was eliminated in a multiphasic manner. The mean PK exposures after a single dose of 150 mg seemed to increase proportionally

as dose increased from 75 to 150 mg, whereas such exposures appeared to increase supraproportionally as dose increased from 25 to 75 mg. The geometric means of the $t_{½}$ were between 10 and 12 hours across the 3 single-dose levels studied, with up to 20% GCV, suggesting the dose supraproportionality between 25 and 75 mg was likely attributable to drug absorption rather than elimination. The interindividual variabilities were 91% GCV in C_{max} and 75% GCV in $AUC_{0-\infty}$ for the dose level of 150 mg but were moderate (39% to 70% GCV) for lower dose levels. There was a minimal extent of renal excretion.

After a high-fat meal and following a single dose of INCB099280 150 mg, the plasma exposures (C_{max} and $AUC_{0-\infty}$) of INCB099280 were 57% and 43% lower, respectively, than under the fasting condition in 12 healthy participants. The time to peak concentration was significantly longer than under fasting conditions, with the median t_{max} changed from 4 to 6 hours. The $t_{½}$ was estimated as 15 to 16 hours, not different between fasting and fed states. After a medium-fat meal and following a single dose of INCB099280 150 mg, the plasma exposures (C_{max} and $AUC_{0-\infty}$) of INCB099280 were 36% and 26% lower, respectively, than under the fasting condition in 12 healthy participants. The time to peak concentration under fed status was significantly longer than under fasting, with the median t_{max} changed from 4 to 7 hours. The means of estimated $t_{½}$ were approximately 12 to 13 hours, not different between fasting and fed states.

2.2. Study Rationale

As of 22 JUN 2023, 172 participants with advanced solid tumors have received INCB099280 with a total daily dose of between 100 and 1600 mg. The median duration of INCB099280 exposure was 57.0 days (range: 3-669 days). Across all tested dose levels, TEAEs occurred in 164 participants (95.3%). The most frequent TEAEs were asthenia (30.2%), decreased appetite (27.3%), nausea (25.0%), vomiting (22.7%), and fatigue (20.3%). An assessment for GI toxicities including nausea, vomiting, and diarrhea was performed. Preliminary safety data after the first day of INCB099280 administration that included doses of 300 mg BID, 400 mg BID, 600 mg BID, 800 mg QD, and 800 mg BID in 172 participants showed there were GI toxicities in 11 participants. Seven participants had nausea (n = 3), diarrhea (n = 3), or vomiting (n = 1), which were considered study drug–related. All of these Day 1 GI toxicities were Grade 1 except for 1 Grade 2 event of diarrhea. In addition, for the QD dosing regimens in Study INCB 00928-112, which included 100 mg, 200 mg and 600 mg, there were no immune-related AEs reported within the first 7 days of dosing.

The purpose of this study is to determine the AME of [^{14}C]INCB099280 and to characterize and determine the metabolites present in plasma, urine, and, where possible, feces in healthy male participants following a single oral administration. Knowledge of the metabolism and excretion of a parent drug and its metabolites is useful for evaluating the metabolites in safety testing requirements elucidated in the FDA guidance (FDA 2020) and ICH M3 (ICH 2009), the likelihood of effects of renal or hepatic impairment on the disposition of INCB099280, and the likelihood for DDIs with INCB099280. The results from this study may guide future study designs using special populations or evaluating the potential for additional DDIs of the metabolites present in plasma, urine, or feces.

2.2.1. Scientific Rationale for Study Design

The present [^{14}C]INCB099280 AME study will be a single-dose study in 7 healthy male adult participants, which is a study design and study population typically used for human AME studies (Penner et al 2009). This study design allows for adequate collection of data while exposing as few participants as possible to radiation.

The ARSAC recommends that, whenever possible, healthy participants selected for radiopharmaceutical research projects should be aged over 50 years (ARSAC 2023). However, the current study is designed to generate data for supporting the investigation of the human absorption, metabolism, and elimination of INCB099280 as well as generating samples for metabolite profiling and structural identification. In order to address these 2 main objectives of an AME study, investigation of the drug under development is required in a population with normal physiological function, as it is recognized that certain physiological processes (eg, renal function) deteriorate with age. Therefore, it is preferable to use as healthy a population as possible to mitigate against factors that may make interpretation of the data difficult. A healthy participant population is ideal given the relatively stable physiological, biochemical, and hormonal statuses, which removes any disease-related variations and variations due to concomitant medications. Considering the objectives of this AME study, the target age range will be 35 to 55 years old.

Female participants will be excluded to align with regulatory guidance. The principle prescribed by the ICRP (1991) recommends that radiation exposure to participants should be kept as low as reasonably achievable; therefore, if no specific reason exists to include female participants (ie, no available data suggest the metabolism of INCB099280 is different in females versus males), then the radiation exposure to female participants should ideally be kept at zero by only enrolling and administering study drug to male participants.

2.2.2. Justification for Dose

A total (tablets plus solution) INCB099280 dose of not more than 405.3 mg was selected for the present study, which is within the dose range evaluated in Phase 1 (up to 800 mg BID). The dose linearity for INCB099280 ranges from 400 mg BID to 800 mg BID with high variability observed for PK parameters and demonstrated a lack of linearity down to the 100-mg dose. The dose of 400 mg was selected because of the questionable PK linearity to lower doses and because this approximates the efficacious dose of 400 mg BID that is being investigated in patients with cancer. A total of approximately 127 participants who received doses ≥ 400 mg had mostly Grade 1 AEs following the first dose administration. Therefore, a single 405.3-mg dose of INCB099280 is expected to be safe and well tolerated in healthy participants.

The exact total dose of IMP is dependent on the weight of INCB099280 free-base equivalent in the 4.4-mg (2.9 MBq) [^{14}C]INCB099280 concentrate for oral solution; this will be determined based on the radioactive potency of the radiolabeled drug substance, the weight of active pharmaceutical ingredient will be altered to achieve the target radioactivity dose (2.9 MBq). The target chemical dose of IMP is 4.4 mg; however, this may vary by up to 20% (ie, 80% to 120%), resulting in an IMP range of 3.5 to 5.3 mg per dose of [^{14}C]INCB099280. The dose of the INCB099280 tablets is fixed, and as such, the INCB099280 dose will be no more than 405.3 mg in this study.

The dose of radioactivity has been determined following review of human dosimetry data calculations from LabCorp. A target dose of [^{14}C]INCB099280 [redacted] will be administered to each participant. Allowing for measurement and manufacturing tolerances, this equates to a single dose of not more than [redacted] The effective dose that participants will receive from 1 administration of [redacted] will not exceed 1.16 mSv. This radiation exposure falls within ICRP guidelines for Category IIb studies (ICRP 1991). The radioactive dose is an acceptable dose to give to healthy participants and is considered necessary to define the disposition of [^{14}C]INCB099280.

The committed effective radiation doses delivered by the radiolabeled study drug have been calculated by Labcorp (Madison, WI) based on the results of a preclinical mass-balance study and a quantitative whole-body autoradiography study. The effective radiation dose is defined as being within the variations of natural background radiation (Category I study; WHO 1977) with a minor associated risk (Risk Category IIa; ICRP 1991).

To ensure [^{14}C]INCB099280 does not exceed the limit for radioactive dose approved by the ARSAC, the target-specific activity of the drug substance will be set at 90% of 90% of the threshold radioactive dose limit. This will allow for tolerances in the manufacturing processes for both drug substance and drug product, thereby providing continued assurance for compliance with the ARSAC-approved limit for drug product radioactivity dose.

In order to provide the optimal conditions for the objectives of the study to be met, following calculation, the radioactive dose considered for administration and the bioanalytical data from the preclinical studies have been reviewed by the study's medical physics expert and the ARSAC practitioner to ensure radioactivity concentrations in urine, feces, and plasma are detectable for sufficient periods postdose.

Oral dose administration was chosen since this is the intended clinical route of administration. Based on the nonclinical data and the known PK of INCB099280, the sample collection timing and duration of this study are considered adequate to achieve the study objectives.

2.3. Benefit/Risk Assessment

Participants will not receive any health benefit (beyond that of an assessment of their medical status) from participating in this study. The risks of participation are primarily those associated with adverse reactions to the study drug, although there may also be some discomfort associated with the collection of blood samples and other study procedures.

Gastrointestinal toxicities occurred in approximately 11 of 172 participants who received INCB099280, of which only 6 were study-drug related. No other AEs have been observed following a single dose of INCB099280.

The [^{14}C]INCB099280 solution will contain a radionuclide, not more than [redacted] so participants will be exposed to ionizing radiation. The effective dose that each participant will receive from 1 administration of [^{14}C]INCB099280 will not exceed 1.16 mSv. This is equivalent to approximately 5 months of the average radiation exposure received in the UK each year (2.7 mSv; Oatway et al 2016) and is less than the radiation dose from 1 computed tomography head (1.4 mSv). It is believed that any increase in the amount of radiation that is received above natural radiation carries a risk of developing serious and possibly fatal conditions such as cancer. Extrapolation of data from epidemiological studies of cancers induced by radiation exposure

indicates that the risk factor for an adult (age range: 18 to 64) in the UK is 5×10^{-2} per Sv. From this, it can be estimated that the lifetime risk of inducing a fatal cancer in a healthy individual from an exposure of 1.16 mSv is approximately 1 in 17,200. For comparison, the lifetime risk of being diagnosed with cancer in the UK is around 1 in 2 (50%), indicating that this additional risk from the maximum possible radiation exposure in this study is minimal and considered to be acceptable.

Blood sample collection may cause pain, swelling, bruising, light headedness, fainting and, very rarely, clot formation, nerve damage, and/or infection at the site of needle stick or cannulation. During cannulation, more than 1 attempt may be needed to insert the cannula, and it is possible that bleeding, bruising, or inflammation may occur at the site of cannulation. Adhesive electrodes for ECGs may cause some local irritation to the chest and limbs and may be uncomfortable to remove.

INCB099280 has been evaluated against a panel of targets to assess the potential for unintended pharmacological activity. There was no cross-reactivity in any of the 55 in vitro binding assays in which INCB099280 was tested. INCB099280 has also been evaluated in 2 separate kinase profiling assays. In the first assay, IC_{50} values for the 56 kinases evaluated were at least 840-fold higher than the unbound clinical steady-state C_{max} after administration of 400 mg BID; in a separate kinase profiling assay (172 kinases) at a concentration of 100 nM, INCB099280 did not inhibit the activity of any kinase by more than 50%. In a GLP, in vitro, voltage-clamped, cell-based, hERG channel assay, the functional IC_{50} for hERG inhibition was estimated to be 3.0 μM, which is approximately 300-fold higher than the unbound clinical steady-state C_{max} after administration of 400 mg BID. There have been no adverse findings in in vivo safety pharmacology assessments of INCB099280, including respiratory and central nervous system function studies at doses up to 1000 mg/kg in rats and an in vivo cardiovascular study at doses up to 225 mg/kg in conscious, radiotelemetry-implanted cynomolgus monkeys. Absence of neurological and cardiovascular findings in nonclinical GLP toxicology studies as well as the collective in vitro and functional results support the conclusion that the risk of unintended pharmacological activity is expected to be low.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of INCB099280 may be found in the IB.

2.3.1. COVID-19 Related Risks and Risk Mitigation Measures

Against the background of the COVID-19 pandemic, the potential risk of a participant developing COVID-19 has been considered in terms of the risk-benefit evaluation. The mode of action of INCB099280 as a PD-L1 inhibitor has been considered alongside available preclinical and clinical data (including class effects), and it is considered that the risk of a single dose of INCB099280 in a healthy participant is minimal.

General risk mitigation against COVID-19 will be implemented in accordance with the study site's monitoring and prevention control measures. COVID-19 testing may be performed based on current infection rates and availability of tests. The decision on COVID-19 testing and the definition of the testing timepoints are subject to change based on the current risk mitigation in place and will be agreed by the study team and documented in the investigator site file. Risk mitigation measures, where applicable, will be amended based on emerging government guidance.

Approved (including health authority conditional marketing authorization) COVID-19 vaccinations may be permitted up to 14 days prior to the administration of INCB099280. Thereafter, to ensure that any side effects from vaccination have fully abated prior to the INCB099280 dose and that the study data are not confounded by concomitant vaccination use, vaccinations will not be permitted until after study discharge.

It is unlikely that administration of INCB099280 would substantially interfere with a COVID-19 vaccination response; however, no specific preclinical or clinical investigations have been conducted in this regard.

3. OBJECTIVES AND ENDPOINTS

Table 4 presents the objectives and endpoints.

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the route of elimination and mass balance of [^{14}C]INCB099280 after administration of a single dose of INCB099280 400 mg PO followed by an oral dose solution containing [redacted] of [^{14}C]INCB099280 (not more than [redacted]	Total recovery of radioactivity from urine and feces.
To characterize the metabolic profile and identify circulating and excreted metabolites of INCB099280 after administration of a single dose of INCB099280 400 mg PO followed by an oral dose solution containing [redacted] of [^{14}C]INCB099280 (not more than [redacted]	Quantitative metabolite profile in plasma, urine, and feces.
Secondary	
To evaluate the PK of total radioactivity and the parent compound after administration of a single dose of INCB099280 400 mg PO followed by an oral dose solution containing [redacted] of [^{14}C]INCB099280 (not more than [redacted]	PK for plasma INCB099280 (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{½}$, λ_z, CL/F, and V_z/F).
	PK for whole blood and plasma total radioactivity (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{½}$, λ_z, CL/F, and V_z/F).
To evaluate the safety of a single dose of INCB099280 400 mg PO followed by an oral dose solution containing [redacted] of [^{14}C]INCB099280 (not more than [redacted].	Incidence of AEs, assessed by changes in ECGs and vital signs and through physical examinations and clinical laboratory sample evaluations.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, single-center, open-label, mass balance study of [^{14}C]INCB099280. Study treatment will consist of a single dose of INCB099280 400 mg administered in tablet form (4 × 100-mg tablets) with 240 mL of water followed approximately 10 minutes later by an oral dose solution containing [redacted] of [^{14}C]INCB099280 (not more than [redacted]

Healthy male participants will receive study treatment on Day 1 after an overnight fast of at least 8 hours, with food intake allowed no sooner than 4 hours postdose. In addition, except for the water provided for dose administration, water will be restricted for 1 hour before INCB099280 tablet administration until 1 hour postdose.

Participants will be admitted to the CRU on Day –1 at a time determined by the clinic. Participants will remain in the CRU until at least Day 6, but potentially up to Day 12, based on satisfying both of the following discharge criteria:

- ≥ 90% of the administered radioactive dose is recovered in excreta (urine and feces combined).
- < 1% of the administered radioactive dose is recovered in excreta (urine and feces combined) in 2 consecutive, 24-hour, urine and fecal samples in which both samples are provided.

If the discharge criteria are not met, then participants will be discharged no later than Day 12 (264 hours postdose on the morning of Day 12).

4.2. Overall Study Duration

Each participant will undergo a screening period, a treatment period, and a follow-up period. During the screening period (up to 27 days), participants will sign an ICF and will be assessed for eligibility. Participants will enter the CRU on Day –1 and remain in the CRU during the treatment period until at least Day 6 but potentially up to Day 12 (264 hours postdose on the morning of Day 12). If the discharge criteria are not met, then participants will be discharged no later than Day 12. The follow-up period will include a follow-up phone call 21 ± 3 days after the dose of study drug. It is estimated that study participation will last approximately 2 months per individual.

The study will begin when the first participant signs the ICF and will be complete when the last participant has completed the safety follow-up phone call. A participant is considered to have completed the study if they have completed all visits of the study, including the follow-up phone call.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract, without consultation with the MHRA, IEC, ARSAC practitioner, or ARSAC. The investigator is to notify the MHRA, IEC, the ARSAC practitioner, and ARSAC (if ARSAC research application has been submitted or approved) of the study's

completion or early termination in writing, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively if, for example, required by regulatory decision. If the study is terminated prematurely, the sponsor will notify the investigators, the IEC, and the regulatory bodies of the decision and reason for termination of the study. Notification of early termination should be provided to the IEC and MHRA within 15 days. A description of follow-up measures taken for safety reasons, if applicable, will also be provided.

5. STUDY POPULATION

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or participant safety. Therefore, adherence to the criteria as specified in this Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

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

1. Ability to comprehend and willingness to sign a written ICF for the study.
2. Healthy males, as determined by the investigator based upon physical examinations, ECGs, vital signs, and safety laboratory assessments, aged 35 to 55 years, inclusive, at the time of signing the ICF.
3. Body mass index between 18.0 and 32.0 kg/m^2, inclusive, at the time of screening.
4. No clinically significant findings in screening evaluations (eg, clinical, laboratory, vital signs, and ECG) at screening and Day −1.
5. Ability to swallow and retain oral medication.
6. Willingness to avoid fathering children based on the criteria below.
    a. Participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 93 days (5 half-lives plus a spermatogenesis cycle) after the dose of study drug and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
7. Must have regular bowel movements (ie, average of ≥ 1 and ≤ 3 stools per day).
8. Must be willing and able to communicate and participate throughout the entirety of the study.

5.2. Exclusion Criteria

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

1. History of clinically significant respiratory, renal, gastrointestinal, endocrine, hematopoietic, psychiatric, and/or neurological disease as judged by the investigator.
2. History of cardiovascular, cerebrovascular, peripheral vascular, or thrombotic disease or uncontrolled hypertension (systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mmHg at screening, confirmed by repeat testing).
3. History of rheumatologic/autoimmune disorders, except for minor eczema and rosacea.
4. Resting pulse < 40 bpm or > 100 bpm, confirmed by repeat testing at screening.
5. History or presence of an abnormal ECG (QTcF interval > 450 milliseconds, QRS interval > 120 milliseconds, and PR interval > 220 milliseconds) at screening or predose on Day 1 that, in the investigator's opinion, is clinically significant.
6. Presence of a malabsorption syndrome (eg, Crohn's disease or chronic pancreatitis) that could possibly affect drug absorption.
7. Hemoglobin level, WBC count, platelet count, or absolute neutrophil count at screening or admission that is out of the laboratory's range, unless considered clinically insignificant by the investigator.
8. Hepatic transaminases (ie, ALT and AST), ALP, or total bilirubin greater than the laboratory-defined ULN at screening or admission, confirmed by repeat testing (except participants with Gilbert's disease, for which total bilirubin must be ≤ 2.0 × ULN).
9. History of malignancy within 5 years of screening, with the exception of cured basal cell or squamous cell carcinoma of the skin.
10. Current or recent (within 6 months before screening), clinically significant, gastrointestinal disease or surgery (including cholecystectomy, excluding appendectomy) that could affect the absorption of study drug.
11. Any major surgery within 6 months of screening.
12. Donation of blood to a blood bank or in a clinical study (except a screening visit) within 3 months before screening (within 2 weeks for plasma donation).
13. Blood transfusion within 4 weeks before admission (Day −1).
14. Chronic or current active infectious disease requiring systemic antibiotic, antifungal, or antiviral treatment (includes any history of tuberculosis).
15. Positive test for HBV, HCV, or HIV at screening. Participants whose HBV results are compatible with prior immunization or immunity due to infection may be included at the discretion of the investigator.
16. History of alcohol dependency within 3 years before screening.
17. Regular alcohol consumption > 21 units per week (1 unit = 8 oz of beer or a 25-mL shot of a 40% spirit; 1.5 to 2 units = a 125-mL glass of wine, depending on type).

18. Consumption of alcohol 72 hours before admission (Day −1) until CRU discharge.
19. Positive breath test for alcohol or positive urine screen for drugs of abuse (confirmed by repeat) at screening or admission (Day −1).
20. Treatment with another investigational medication within 90 days or 5 half-lives (whichever is longer) before Day 1 or current enrollment in another investigational drug study.
21. Participation in any clinical study involving a ^{14}C-radiolabeled investigational product within 12 months prior to admission (Day −1).
22. Radiation exposure, including that from the present study, excluding background radiation but including diagnostic x-rays and other medical exposures, exceeding 5 mSv in the last 12 months or 10 mSv in the last 5 years. No occupationally exposed worker, as defined in the Ionising Radiation Regulations 2017, shall participate in the study.
23. Treatment within 15 days or 5 half-lives (whichever is longer) before Day 1 with any medications known to be an inducer or inhibitor of CYP3A4 or P-gp (refer to the Drug Interaction Database [2023] for prohibited medications).
24. Consumption of Seville oranges, grapefruit, pomelos, exotic citrus fruits, grapefruit hybrids, or any fruit juices (including but not limited to juices containing Seville oranges, grapefruits, pomelos, exotic citrus fruits, or grapefruit hybrids) within 72 hours prior to study treatment administration until CRU discharge.
25. Consumption of poppy seeds within 7 days prior to screening and admission (Day –1).
26. Consumption of caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) within 72 hours prior to study treatment administration until CRU discharge.
27. History of any significant drug allergy (such as anaphylaxis or hepatotoxicity) deemed clinically relevant by the investigator. Hay fever is allowed unless it is active.
28. Known hypersensitivity or severe reaction to INCB099280 or any excipients of INCB099280 (refer to the IB).
29. Inability to undergo venipuncture or tolerate venous access.
30. Inability or unlikeliness of the participant to comply with the dose schedule or study evaluations, in the opinion of the investigator.
31. History of tobacco- or nicotine-containing product use within 1 month before screening. Consumption of tobacco- or nicotine-containing products 72 hours before admission (Day −1) until CRU discharge is not permitted. Breath test for carbon monoxide > 10 ppm (confirmed by repeat) at screening or admission (Day −1).
32. Participation in unaccustomed strenuous exercise within 7 days before admission (Day −1) until CRU discharge.

33. Use of prescription drugs within 14 days before Day 1 or nonprescription medications/products (including vitamins, minerals, and phytotherapeutic, herbal, or plant-derived preparations) within 7 days before Day 1 until CRU discharge. However, paracetamol up to 4000 mg Q24H and ibuprofen up to 600 mg Q24H are permitted.
34. Use or intention to use any COVID-19 vaccine within 14 days prior to Day 1 and through CRU discharge.
35. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
36. An eGFR < 90 mL/min/1.73 m^2 based on the site's preferred formula at screening.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants will refrain from consuming Seville oranges, grapefruits, pomelos, exotic citrus fruits, grapefruit hybrids, or any fruit juices (including but not limited to juices containing Seville oranges, grapefruits, pomelos, exotic citrus fruits, or grapefruit hybrids) from 72 hours prior to study treatment administration until CRU discharge.

Participants will refrain from consuming poppy seeds within 7 days prior to screening and admission (Day −1).

Participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) from 72 hours prior to study treatment administration until CRU discharge.

Participants will abstain from alcohol and tobacco- or nicotine-containing products from 72 hours before admission (Day −1) until CRU discharge.

Participants will receive the study treatment, INCB099280 tablets taken with 240 mL of water followed approximately 10 minutes later by an oral dose solution of [^{14}C]INCB099280, after an overnight fast of at least 8 hours, with food intake allowed no sooner than 4 hours postdose. In addition, water will be restricted for 1 hour before INCB099280 tablet administration until 1 hour postdose (except for the water provided for dose administration).

Prune juice may be administered as needed to aid with bowel function and will not be considered a concomitant medication.

5.3.2. Activity

Participants will abstain from unaccustomed and strenuous exercise from 7 days before admission (Day −1) until CRU discharge. Participants may participate in light recreational activities during the study (eg, watching television, reading, walking).

5.3.3. Other Restrictions

Participants must not donate blood or plasma (outside of this study) from admission (Day −1) through at least 90 days after the dose of study medication.

Participants will not be permitted to shower for 24 hours postdose (to ensure the collection of all samples).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study.

Results from the screening evaluations will be reviewed to confirm participant eligibility before study treatment administration. Tests with results that fail eligibility requirements (except for positive alcohol or drug screen) may be repeated once during screening or on Day −1 with permission of the investigator.

Participants meeting all inclusion and no exclusion criteria will be advised of their eligibility to participate in the study and may return to the site on Day −1. Participants who fail screening may repeat the screening process 1 time if the investigator believes there has been a change in eligibility status. Participants who rescreen must reconsent and will be assigned a new participant number.

5.5. Recruitment Strategy and Retention of Participants

Not applicable.

5.6. Replacement of Participants

Up to 7 male participants will be enrolled in order to have 6 complete the study. At the discretion of the sponsor and investigator, additional participants may be enrolled to ensure 6 complete the study. Participants withdrawn due to IMP-related AEs will not be replaced.

6. STUDY TREATMENT

6.1. Study Treatments Administered

Table 5 presents the study treatment information.

Table 5: Study Treatment Information

	Study Treatment 1	Study Treatment 2
Study treatment name:	INCB099280	[^{14}C]INCB099280
Dose formulation:	Tablet	Solution
Unit dose strength(s)/ dose level(s):	100 mg/400 mg	4.4 [3.5-5.3] mg/dose[a] (Not more than [redacted]
Administration instructions:	Administered orally with approximately 240 mL of water in the fasted state.	The dose of [^{14}C]INCB099280 solution will be administered orally in the fasted state, approximately 10 minutes after the INCB099280 tablet administration, with a total volume of 240 mL (dose volume + container rinses + room-temperature water chaser).
Packaging and labeling:	INCB099280 will be provided in a bottle. Each bottle will be labeled as required per country requirement.	[^{14}C]INCB099280 will be provided as a concentrate for oral solution and will be prepared from bulk supplies. The concentrate will be diluted with simple syrup immediately prior to administration. Each unit dose container will be labeled as required per country requirement.
Storage	Must be refrigerated. Store at 2°C-8°C (36°F-46°F).	Store as indicated in the Pharmacy Manual.
Status of treatment in participating countries	Investigational	Investigational

[a] The target chemical dose of IMP is 4.4 mg; however, this may vary by up to 20% (ie, 80% to 120%), resulting in an IMP range of 3.5 to 5.3 mg per dose of [^{14}C]INCB099280.

The IMPs are unlicensed medicinal products for use only in this study. INCB099280 100-mg tablets will be supplied by the sponsor, and radiolabeled INCB099280 solution will be supplied by Pharmaron, Inc along with the batch/lot numbers and certificates of analysis. The study site will manufacture and label the radiolabeled study drug from bulk supplies such that each unit dose contains not more than [redacted] of [^{14}C]INCB099280. The weight of INCB099280 free-base equivalent in each dose will be determined based on the specific activity of the radiolabeled INCB099280.

Immediately after administration of [^{14}C]INCB099280, the dose vessel will be rinsed with water and participants will consume the rinse solution. Participants will then consume water for a total volume of 240 mL (including the dose volume and volume used to rinse the dose vessel). The manufacturing process will be documented in the Pharmaceutical Development and Control Strategy Report.

All excipients for the [^{14}C]INCB099280 solution will be sourced by the study site. Specific instructions regarding dose preparation will be mutually agreed upon between the sponsor and the appropriate site staff and will be presented in a separate document.

All study treatments will be stored according to the instructions on the label at the study site in a location that is locked with restricted access.

Participants will be administered study treatment in numerical order (see Table 5) while seated and will not be permitted to lie supine for 2 hours after administration of [^{14}C]INCB099280, except as necessitated by the occurrence of an AE and/or study procedure.

6.2. Preparation, Handling, and Accountability

The investigator (or designee) must confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator (or designee) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document the following:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Participant use of the study drug, including pill counts from each supply dispensed.

The investigational product must be used only in accordance with the Protocol. The investigator or designee will also maintain records adequately documenting that the participants were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

Completed accountability records will be archived by the site. The investigator, or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee the destruction of any remaining study drug according to institutional SOPs. If, however, local procedures do not allow on-site destruction, shipment of the study drug back to the sponsor is allowed. In this case, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, nonbiased study with objective PK endpoints.

6.4. Study Treatment Compliance

Participants will be confined to the CRU during the treatment period of the study. Compliance will be ascertained by inspection of the oral cavity and hands of the participant after study treatment administration.

6.5. Dose Modifications

Treatment interruptions and modifications are not allowed in this study.

6.6. Concomitant Medications and Procedures

6.6.1. Permitted Medications and Procedures

All concomitant medications and treatments must be recorded in the eCRF, including any prior medication received up to 14 days before study treatment administration. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.2. Restricted Medications and Procedures

Paracetamol up to 4000 mg Q24H and ibuprofen up to 600 mg Q24H for pain and discomfort are permitted.

6.6.3. Prohibited Medications and Procedures

The following medications/measures are not permitted during the study:

- Any medications known to affect CYP enzymes or P-gp activity (refer to the Drug Interaction Database [2023]). Use of these prohibited medications within 15 days or 5 half-lives (whichever is longer) before study treatment administration (Day 1), or the anticipated use during the study, will result in exclusion or withdrawal of the participant from the study.
- Any investigational medication other than the study treatment. Use of such medication within 90 days or 5 half-lives (whichever is longer) before study treatment administration (Day 1) and during the study is prohibited. Any such use or anticipated use of these medications will result in the participant being excluded or withdrawn from the study.
- Any prescription drugs within 14 days or 5 half-lives (whichever is longer) before study treatment administration (Day 1).
- Any nonprescription medications/products (including vitamins, minerals, and phytotherapeutic, herbal, or plant-derived preparations) within 7 days or 5 half-lives (whichever is longer) before study treatment administration (Day 1). Occasional paracetamol and ibuprofen use is permitted (see Section 6.6.2).

6.7. Treatment After the End of the Study

Not applicable.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

Participants **must** be discontinued from study treatment for the following reasons:

- Consent is withdrawn.

  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case, no further data, except data in the public domain, may be solicited from or collected on the participant.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity as noted in Section 7.1.3.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IEC.
- The participant is found not to have met eligibility criteria.

A participant **may** be discontinued from study treatment as follows:

- If a participant is noncompliant with study procedures or study treatment administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the ET visit should be conducted. Reasonable efforts should be made to have the participant complete the follow-up phone call. These visits are described in Table 3.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record, and the primary reason for discontinuation must be included in the eCRF.
- The ET visit should be performed and the date recorded.
- Participants must be followed for safety until the time of the follow-up phone call or until study treatment–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the participant discontinues study treatment and actively withdraws consent for collection of safety follow-up data, then no additional data collection should occur; however, participants will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety assessments.

7.1.3. Study Stopping Rules

The study will be halted, and the risk to other participants will be evaluated, if any of the following criteria are met:

- A serious adverse reaction (ie, an SAE considered at least possibly related to the IMP) occurs in 1 participant.
- Severe, nonserious, adverse reactions (ie, severe, nonserious AE considered at least possibly related to the IMP) in 2 participants, independent of the SOC.
- One or more immune-related AEs (any grade).

Relatedness to the IMP will be determined by the investigator.

If the study is halted, a temporary halt will be submitted to the MHRA and IEC in the form of a Protocol Amendment. The study may be resumed or terminated; however, it will not be resumed until a further Protocol Amendment to resume the study is submitted and approved by the MHRA and IEC. The ARSAC practitioner will also be informed of the temporary halt.

7.2. Participant Withdrawal From the Study

Participants **must** be withdrawn from the study for the following reasons:

- The participant has a confirmed (confirmed by 1 repeat test) decline in eGFR of 35% or greater compared with the baseline value (screening or Day −1). The assessment is based on measurements of serum creatinine and subsequent calculation of eGFR using the site's preferred formula. This assessment is to be conducted at investigator discretion after screening.
- The participant has a confirmed (confirmed by 1 repeat test) prolongation of QTcF ≥ 60 milliseconds relative to baseline (defined as Day 1 predose) or an absolute QTcF ≥ 500 milliseconds.
- The participant has an elevation of ALT > 3 × ULN (confirmed by 1 repeat test).
- The participant has a serious or severe (Grade 3 or higher) AE.
- Consent is withdrawn.

  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected on the participant.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IEC.
- At the discretion of the investigator.

A participant **may** be withdrawn from the study as follows:

- If a participant is noncompliant with study procedures or study treatment administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.
- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be withdrawn from the study.
- An AE or laboratory abnormality occurs that, in the opinion of the investigator, may constitute a potential risk for continued participation by the participant.

A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. If a participant requests to leave the CRU earlier than planned, they may be provided with sample pots for home collection of urine and/or feces; this would be decided on a case-by-case basis following discussion between the investigator and the sponsor.

If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

See Table 3 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if they are unable to be contacted by the study site. The following actions must be taken if a participant is unable to be contacted:

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted.
  - Informed consent must be obtained using the most current IEC-approved version in a language that is native and understandable to the participant. An ICF template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template, and all site-specific changes must be approved by the IEC and the sponsor or its designee. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements including optional samples/procedures (eg, optional biopsy) and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the country in which the study is being conducted as well as the IEC or study center.
- The participant must be informed that their personal data collected for the study will be used in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.
- The medical record must include the date and time of informed consent to document that written informed consent was obtained before the participant was enrolled in the study. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date and if the ICF template has not been modified and reapproved by the IEC.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is enrolled in the study. Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Results from the screening visit evaluations will be reviewed to confirm eligibility before enrollment or administration of study treatment. Tests with results that fail eligibility requirements (except for positive alcohol or drug screen) may be repeated once during screening or on Day −1 if the investigator believes there has been a change in eligibility status or the results to be in error. For screening assessments that are repeated, the most recent available result before treatment administration will be used to determine eligibility.

See Sections 5.4 and 5.6 for information regarding screen failures and replacement of participants, respectively.

8.1.3. Demography and Medical History

8.1.3.1. Demographics and General Medical History

Demographic data will be collected at screening and general medical history will be collected at screening and admission by the investigator or qualified designee and will include date of birth, race, ethnicity, medical and surgical history, and current illnesses.

8.2. Efficacy Assessments

Not applicable.

8.2.1. Health Economics

Not applicable.

8.3. Safety Assessments

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 18 days after the dose of study treatment or the follow up telephone call, whichever is later. Adverse events for enrolled participants that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study treatment. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver or surrogate). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, that are considered related to the study treatment/procedures, or that caused the participant to withdraw from the study. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal

questioning of the participant, such as "How are you feeling?", is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

All SAEs will be reported to the sponsor or designee by the investigator immediately without undue delay and not later than 24 hours of obtaining knowledge of the events. The investigator will also submit any updated SAE data to the sponsor immediately without undue delay and not later than 24 hours of obtaining knowledge of the update.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, a physician assistant, or an advanced registered nurse practitioner, as local law permits. Abnormalities identified after the dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, or require concomitant therapy. Investigators should pay special attention to clinical signs related to previous serious illnesses.

At admission (Day −1) and on the day of discharge or ET, a comprehensive physical examination should be conducted (see Table 3). The comprehensive physical examination will include assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination that will include assessments of the central nervous system, peripheral nervous system, and cerebellar function.

A targeted physical examination may be conducted at any time at the investigator's discretion. Participants will be assessed by the investigator or medically qualified designee per institutional standard of care. These assessments should be an evaluation as indicated by participant symptoms, AEs, or other findings and documented on the Adverse Events Form in the eCRF.

Height will be assessed at screening. Body weight will be assessed and BMI will be calculated at both screening and admission.

8.3.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory and PK tests, except during screening) include blood pressure, pulse, respiratory rate, and body temperature. See Table 3 for the timing and frequency. Blood pressure and pulse will be taken with the participant in the supine position after 5 minutes of rest. All measurements will be performed singly and repeated once (within 15 minutes) if outside the relevant clinical reference range. Abnormal vital sign results identified after the dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, or require concomitant therapy.

8.3.4. Electrocardiograms

Single, 12-lead ECGs will be obtained as outlined in Table 3 (to be taken before blood collection for laboratory and PK tests, except during screening) using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTcF intervals. All 12-lead ECGs will be performed with the participant in a supine position after 5 minutes of rest.

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate participant management. Single, 12-lead ECGs will be repeated once if the investigator deems a repeat is indicated. Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. The decision to include or exclude a participant based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs. The predose ECG will serve as baseline for the purposes of calculating change-from-baseline intervals.

8.3.5. Laboratory Assessments

See Appendix B for the list of clinical laboratory tests to be performed and Table 3 for the timing and frequency. Scheduled chemistry and hematology samples will be taken following an 8-hour fast. A certified laboratory local to the investigative site will perform all clinical blood laboratory assessments for safety (ie, serum chemistries, hematology and serology assessments, and thyroid panel). Urinalysis will be performed on site by a trained clinical staff member using a dipstick. If urine microscopy or microbiology is required, samples will be sent to a certified laboratory local to the investigative site. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated. All Protocol-required laboratory assessments must be conducted in accordance with the CSPM and the SoA (see Table 3). Information regarding collection, processing, and shipping of laboratory samples will be provided to the site in the CSPM.

Clinically significant abnormal laboratory findings are those that are not associated with an underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

Screening laboratory assessments must be performed within 28 days before Day 1. If laboratory samples are collected on Day 1, they must be performed before study treatment administration.

See Section 9.1 for information regarding laboratory abnormalities that should be recorded as an AE in the eCRF. Additionally, if laboratory values from laboratory assessments performed at the institution's local laboratory require a change in participant management (eg, require treatment) or are considered clinically significant by the investigator (eg, SAE or AE), then the result(s) of the specific laboratory assessment(s) must be recorded in the eCRF.

8.3.5.1. Serology

Hepatitis and HIV screening assessments will be performed at the screening visit to rule out infection; required analytes are shown in Appendix B. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

8.4. Pharmacokinetic Assessments

8.4.1. Blood Sample Collection

All scheduled sample collection timepoints are relative to INCB099280 tablet administration. Blood samples will be collected for the determination of total radioactivity in whole blood and plasma. Plasma INCB099280 concentrations will also be determined using a validated bioanalytical method. Timing of blood PK sample collections is outlined in Table 6. A maximum of 3 samples for determination of total radioactivity and 3 samples for metabolite profiling may be collected per participant at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor.

Sample collection, processing, storage, and shipping instructions will be provided in the Sample Management Instructions.

The participant's dose date and time associated with the serial blood and plasma sampling will be recorded on source documents and in the eCRF. The actual date and time (24-hour clock time) of each sample will be recorded. Missed, lost, or damaged samples must be recorded on the source documents and as a comment in the participant's eCRF.

After the predose PK sample is drawn, participants will begin the study treatment. Predose is defined as within 90 minutes before administration of study treatment.

Table 6: Pharmacokinetic Blood Sample Timing

Sample Type	Pharmacokinetic Sample Collection Day						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7-12[a]
Plasma INCB099280 concentrations	0 h (predose) and 0.5, 1, 2, 4, 6, 8, 12, and 16 h postdose	24 and 36 h postdose	48 h postdose	72 h postdose	96 h postdose	120 h postdose	Not required
Total radioactivity (plasma and blood)	0 h (predose) and 0.5, 1, 2, 4, 6, 8, 12, and 16 h postdose	24 and 36 h postdose	48 h postdose	72 h postdose	96 h postdose	120 h postdose	Q24H until discharge
Metabolite profiling	0 h (predose) and 1, 2, 4, 8, 12, and 16 h postdose	24 and 36 h postdose	48 h postdose	72 h postdose	96 h postdose	120 h postdose	Q24H until discharge

Note 1: Participants withdrawn from the study prematurely will have PK samples collected at ET.
Note 2: PK windows will be listed in the eCRF clinical guidelines.
[a] As needed.

8.4.2. Urine Sample Collection

Urine samples will be collected over the following intervals in relation to INCB099280 tablet administration: −12 to 0 hours (predose void [spot sample only]); 0 to 6, 6 to 12, and 12 to 24 hours postdose; and continuing in 24-hour intervals until the participant is discharged from the CRU. If a urine sample is not provided, it will not be considered a deviation. Total radioactivity analysis of urine samples will occur until study discharge criteria are met. Urine collections will be used to assess the excretion of total radioactivity and for metabolite profiling. Urine INCB099280 concentrations will also be determined using a validated bioanalytical method. Processing, storage, and shipping instructions for these urine samples will be provided in the Sample Management Instructions. Missed samples, spillage, or other loss of sample that results in incomplete urine collection must be recorded on the study source documents and as a comment in the eCRF.

8.4.3. Fecal Sample Collection

Fecal samples for total radioactivity analysis and metabolite profiling will be collected at the following time intervals in relation to INCB099280 tablet administration: −12 to 0 hours (predose [spot sample only]; whenever possible), 0 to 24 hours postdose, and continuing in 24-hour intervals until CRU discharge). If a predose fecal sample cannot be obtained, the participant will still be administered study treatment. If a sample is not provided, it will not be considered a deviation. Total radioactivity analysis of fecal samples will occur until study discharge criteria are met. Processing, storage, and shipping instructions for these fecal samples will be provided in the Sample Management Instructions.

8.4.4. Emesis Sample Collection

For participants with emesis within 4 hours after dose administration, vomitus will be collected and stored for possible radioactivity analysis. The time and date of collection will be recorded on the participant's source documents and in the eCRF. Vomitus will be analyzed as deemed appropriate. The sponsor will decide whether the participant should be replaced.

8.4.5. Bioanalytical Methodology and Sample Analysis

Pharmacokinetic blood samples will be centrifuged, and plasma will be harvested for bioanalysis. The plasma samples will be analyzed for INCB099280 using a validated bioanalytical method. Blood, plasma, urine, feces, and vomitus (if applicable) total radioactivity will be determined with liquid scintillation counting.

8.4.6. Pharmacokinetic Analysis

Standard noncompartmental PK methods will be used to analyze the plasma and blood total radioactivity and plasma INCB099280 concentration data using Phoenix WinNonlin v8.0 or higher (Certara, Princeton, NJ). The actual times of postdose sample collections will be used. Predose PK samples will be assigned Time 0.

The PK parameters to be calculated for each matrix and analyte are presented in Table 7.

Metabolite-to-parent compound (INCB099280) molar ratio of C_{max} and AUC (AUC_{0-t}, $AUC_{0-\infty}$, when available) will be calculated if metabolites are measurable. The linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations will be used to calculate AUC_{0-t}. The $AUC_{0-\infty}$ will be calculated as $AUC_{0-t} + C_t / \lambda_z$.

Table 7: Pharmacokinetic Parameters

Matrix and Analyte	Parameters
Whole blood and plasma total radioactivity	C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{½}$, CL/F, and V_z/F
Plasma INCB099280 concentration	C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{½}$, CL/F, and V_z/F
Urine INCB099280 concentration	A_e, f_e, and CL_R

8.5. Pharmacodynamic and Translational Assessments

Not applicable.

8.6. Storage and Future Use of Biological Samples

Biological samples (eg, PK) may be stored from the date of the last participant's last visit to perform study-related research. Additional research outside of study-related research will not be performed. Pseudonymized participant samples will be transported to the sponsor or designated vendor for analysis as detailed in the laboratory-specific study manual(s). Pharmacokinetic samples will be destroyed after the final bioanalysis report or CSR.

8.7. Unscheduled Visits

Not applicable.

8.8. Early Termination

If the participant is withdrawing from the study early, the ET visit should be conducted. The participant should be encouraged to complete all ET procedures and the follow-up phone call 21 (± 3) days after the dose of study treatment.

8.9. Follow-Up

The follow-up period is the interval between CRU discharge and the scheduled follow-up telephone call, which should occur 21 (± 3) days after the dose of study treatment. Adverse events and SAEs must be reported up until 1) at least 18 days after the dose of study treatment or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant contacted for the follow-up phone call and report any AEs that may occur during this period.

9. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related. • An AE can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to disease progression) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition that develops after the start of study treatment is to be reported as an AE. • New conditions detected or diagnosed after the start of study treatment administration are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from dose administration errors of a study treatment (eg, overdose) or a concomitant medication are to be reported as an AE. • A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after obtaining informed consent. If the condition is present before entering the study, then it should be captured as medical history. • Pre-existing diseases, pre-existing conditions, or new conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization or death due to disease progression).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurs. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been **admitted** as an inpatient at the hospital or emergency department for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Emergency department visits that do not result in admission to the hospital should be evaluated for one of the other serious criteria (eg, life-threatening, required intervention to prevent permanent impairment or damage, other medically important event). Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE. Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) is not considered an SAE.
d. Results in persistent or significant disability/incapacity The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is an important medical event An important medical event is an event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers; intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

9.3. Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Events Form in the eCRF. All AEs/SAEs should be reported for enrolled participants, but only SAEs need to be reported for screen failure participants. For enrolled participants, conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF. For detailed information, refer to the eCRF guidelines.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator (or designee) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the Adverse Events Form in the eCRF.
- There may be rare instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted by the site staff on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the Study Reference Manual or as per SAE completing guidelines.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

To the extent possible, each AE/SAE should be evaluated to determine the following:

- The severity grade (Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [FDA 2007] Grade 1 to 4). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up call.
- The action taken with regard to study treatment as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Events Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures, and Non-Drug Therapy).

Assessment of Intensity

The severity of AEs will be assessed using Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA 2007) Grades 1 through 4. If an event is not classified by this scale, the severity of the AE will be graded according to the scale below to estimate the grade of severity.

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the RSI in the IB for study treatment in making their assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and have provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change their opinion of causality in light of follow-up information and submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • Once an AE is detected, it should be followed in the Adverse Events Form in the eCRF until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome. • When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology. • Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (in the SAE EDC CRF) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. • Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) immediately without undue delay but not later than 24 hours of receipt of the information.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study treatment or study procedure[s]), all SAEs occurring after the participant has signed the ICF through the follow-up phone call (or 18 days after the dose of study treatment, whichever is longer) must be reported to the sponsor (or designee) immediately without undue delay but not later than 24 hours of obtaining knowledge of its occurrence unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) immediately without undue delay but not later than 24 hours of obtaining knowledge of the update.

Investigators are not obligated to actively seek SAE information after the follow-up phone call. If the investigator learns of any SAE, including death, at any time during this period, and they consider the event to be reasonably related to the study treatment or study participation, then the investigator must notify the sponsor (or designee) immediately but no later than 24 hours of becoming aware of the event.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

Prompt notification by the investigator to the sponsor regarding an SAE is essential so that legal obligations and ethical responsibilities for the safety of participants and the safety of a study treatment under clinical investigation are met.

If the SAE is not documented in the RSI of the IB for the study treatment (new occurrence) and is thought to be related to the study treatment, the sponsor or its designee may urgently require

further information from the investigator for expedited reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities including EudraVigilance, as applicable, and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries. Suspected unexpected serious adverse reactions are also subject to expedited reporting to the ARSAC practitioner (when related to radiation exposure).

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IEC, and investigators.

Investigator safety report notifications must be prepared by the sponsor for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IEC, if appropriate, according to local requirements.

Serious Adverse Event Reporting

- Information about all SAEs is collected and recorded on the Adverse Events Form in the eCRF.
- The investigator must report immediately but no later than 24 hours of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available). The contact information for notifying Incyte Pharmacovigilance by email/fax is listed in the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor without undue delay but not later than 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form. Once the EDC system is functional, the SAE report should be retroactively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form for details and for the email address or fax number).
- Incyte Pharmacovigilance will issue queries for missing or discrepant information directly into the applicable EDC system.
- Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study treatment because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

9.5. Potential Drug-Induced Liver Injury

See Section 7.1.3.

9.6. Events of Clinical Interest

Not applicable.

9.7. Emergency Unblinding of Treatment Assignment

Not applicable.

9.8. Pregnancy

When a pregnancy has been confirmed in a participant's partner during paternal exposure to study treatment, the investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluations with the consent of the pregnant partner. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study treatment to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

If an abnormal pregnancy outcome (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) is reported in a study participant's partner, the event should be reported to the sponsor on the Clinical Trial Pregnancy Form.

9.9. Warnings and Precautions

Special warnings or precautions for the study treatment, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study as necessary. If new significant risks are identified, they will be added to the ICF.

9.10. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or their designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be recorded as described in Section 9.3.

If the investigator is asked to return the product for investigation, they will return a copy of the product complaint communication with the product.

9.11. Treatment of Overdose

Overdose is not an SAE unless it meets the criteria of an SAE (see Section 9.2).

For this study, any dose of study treatment greater than the Protocol dose + 10% will be considered an overdose and recorded in the eCRF.

There has been no clinical experience with overdose of INCB099280. Treatment of overdose should consist of general supportive measures. Overdose with concomitant medication treatment will not be recorded in the eCRF unless it resulted in an AE.

In the event of an overdose, the investigator should do the following:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically.
- Obtain a plasma sample for PK analysis within 2 days from the date of the dose of study treatment if requested by the medical monitor or if possible (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

10. STATISTICS

10.1. Sample Size Determination

Up to 7 participants will be enrolled into this study in order to have 6 participants complete the study (study completion is defined in Section 4.2). The sample size is not based on formal power calculation because the study is only designed to provide an assessment of the characteristics of the AME of a single oral dose of INCB099280 400 mg followed by an oral dose solution of not more than [redacted] of [^{14}C]INCB099280. The sample size used is typical for studies of this nature.

10.2. Populations for Analysis

The populations for analysis are provided in Table 8.

Table 8: Populations for Analysis

Population	Description
Safety	All participants who received the study treatment. All safety analyses will be conducted using the safety population. In addition, the safety population will also be used for summary of demographics, baseline characteristics, and participant disposition.
PK-evaluable	All participants who received the study treatment and provided at least 1 postdose PK sample. The PK-evaluable population will be used for all PK analyses.

10.3. Level of Significance

This is an exploratory, Phase 1 study, and no formal efficacy hypotheses will be tested.

10.4. Statistical Analyses

10.4.1. Pharmacokinetic Analysis

The PK-evaluable population will be used for all PK analyses.

The PK parameters, as described in Table 7, will be summarized by total radioactivity and INCB099280 concentration in plasma using descriptive statistics. Individual participant and group mean radioactivity-time profiles in blood and plasma and the INCB099280 concentration-time profiles in plasma will also be generated in both linear and semilogarithmic scales.

10.4.2. Excretion and Mass Balance

Radioactivity in urine and feces will be reported as the percentage of the administered radioactivity excreted at each time interval and the total percentage of dose excreted (cumulative recovery). The mass balance of administered radioactivity will be determined by the summation of the percentage of dose excreted in both urine and feces during the study period. Renal clearance of unchanged INCB099280 may be calculated based on metabolite profiling data.

10.4.3. Safety Analyses

Safety analyses will be conducted for the safety population. Adverse events will be coded by the MedDRA dictionary, and TEAEs (ie, AEs reported for the first time or the worsening of a pre-existing event after study treatment administration) will be tabulated by preferred term and SOC for all events, related events, and events of Grade 3 or higher. Quantitative safety variables (eg, laboratory assessments, vital signs) and their changes from baseline will be summarized with descriptive statistics. Clinically notable abnormal values will be flagged and tabulated based on predefined criteria.

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into toxicity grades (FDA 2007) and tabulated. The baseline value for laboratory assessments will be the last nonmissing measurement obtained before administration of the INCB099280 tablet.

Descriptive statistics and mean change from baseline will be determined for each ECG and vital sign parameter at each assessment time. The baseline value for ECG assessments will be the predose ECG. The baseline value for vital sign assessments will be the last nonmissing measurement obtained before the administration of the INCB099280 tablet.

Electrocardiogram and vital signs results will be reviewed for clinically notable abnormalities according to predefined criteria (see Table 9 and Table 10, respectively). Participants exhibiting clinically notable ECG and vital sign abnormalities will be listed.

Table 9: Normal Ranges for Electrocardiogram Intervals

Parameter	High Threshold	Low Threshold
QTcF	≤ 450 ms	≥ 295 ms
PR	≤ 220 ms	≥ 120 ms
QRS	≤ 120 ms	≥ 50 ms
QT	≤ 500 ms	≥ 300 ms
RR	≤ 1500 ms	≥ 600 ms

Table 10: Normal Ranges for Vital Sign Values

Parameter	High Threshold	Low Threshold
Systolic blood pressure	≤ 140 mmHg	≥ 90 mmHg
Diastolic blood pressure	≤ 90 mmHg	≥ 50 mmHg
Pulse	≤ 100 bpm	≥ 40 bpm
Temperature	≤ 38°C	≥ 35.5°C
Respiratory rate	≤ 24 breaths/min	≥ 10 breaths/min

10.5. Interim Analysis

No formal interim analysis is planned in this study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol Amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IEC by the investigator. All documents must be reviewed and approved by the IEC and health authorities before the study is initiated. The sponsor will be responsible for submitting all documents in participating countries.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both health authorities and the IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Any amendments related to the administration of radioactive substances will be reviewed by the ARSAC practitioner prior to submission to ARSAC as required by the current ARSAC guidance (2023). The ARSAC practitioner will also be notified of any amendments to the Participant Information Sheet, ICF, and Protocol.
- The investigator will be responsible for the following:
  - Recording and documenting AEs or laboratory abnormalities identified in the Protocol as critical to the safety evaluation and reporting them to the sponsor according to the reporting requirements specified in the Protocol.
  - Recording and documenting all AEs, unless the Protocol provides different guidance in Section 9.
  - Reporting to the sponsor all SAEs occurring to participants treated by them in the clinical study unless the Protocol provides different guidance in Section 9.
  - Reporting an SAE to the sponsor per Section 9 procedures and timelines if they become aware of an SAE with a suspected causal relationship to the study treatment that occurs after the end of the study.
  - Providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC.
  - Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures.
  - Ensuring (along with the sponsor) that the clinical study is conducted in accordance with the Protocol and with the principles of GCP.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IEC requirements, institutional requirements, and applicable laws and country-specific regulations.

  - Assigning tasks among the members of the team of investigators in a way that does not compromise the safety of participants or the reliability and robustness of the data generated at the clinical study site.

- The investigator will adhere to the Protocol as described in this document and agree that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- The investigator will retain the content of the clinical trial master file, essential documents, AE documentation, and medical and other study records in accordance with all local, national, and regulatory laws but for a minimum period of at least 30 years after completion or discontinuation of the study or as described in the final executed copy of the individual site agreement, or at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after formal discontinuation of clinical development of the test article and the regulatory authority is notified, whichever is longer, to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study during the retention period without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.2. Data Management

Data management will be performed in a validated EDC system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each participant.

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the Protocol, such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and as designated by the sponsor, will have their own data flow management plans, study charters, or biomarker plans, as applicable.

The sponsor (or designee) will be responsible for the following:

- Managing the integrity of the data and the quality of the conduct of the study, such as ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved Protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Managing and reconciling the data generated and/or collected, including documents and results such as laboratory or imaging data analyzed centrally by a designated vendor of the sponsor.

The investigator will be responsible for the following:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, biomarker data, photographs, diary data) or as otherwise specified in the Protocol.
- Maintaining adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are, in general, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; participants' files; and e-records/records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study).
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.
- Sending participants' data, either as unique samples, copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
- Permitting study-related monitoring, sponsor audits, IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Quality Assurance

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations). The sponsor or designee is responsible for the data management of this study, including quality checking of the data. Further, monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues, Protocol deviations, and monitoring techniques (eg, central, remote, or on-site monitoring) are provided in the monitoring plan or equivalent.

Quality tolerance limits will be predefined in the operational manual or equivalent, to identify systematic issues that can impact participants' safety, efficacy results and analysis, and/or reliability of study results. These predefined parameters will be monitored during the study and can be adjusted during the study upon data review. Important deviations from the quality tolerance limits and remedial actions taken, including reporting to IECs and health authorities if applicable, will be summarized in the CSR.

11.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable, and the sponsor operates comprehensive data privacy and data security programs that are applicable to this study. Appropriate notice, or notice and consent (as may be required by each applicable jurisdiction), for collection, use, disclosure, and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws. Appropriate data protection terms that comply with applicable laws will be included in relevant study agreements.

To ensure confidentiality of records and protect personal data, participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

In the event of a data breach involving participant data, the sponsor or its designee will follow the sponsor's incident response procedures. The precise definition of a data breach varies in accordance with applicable law but may generally be understood as a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data. In accordance with its incident response procedures, the sponsor will assess the breach to consider its notification and remediation obligations under applicable law.

11.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 CFR Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure Form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research participants, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Clinical Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

11.6. Publication Policy

By signing the study Protocol, the investigator and their institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

11.7. Study and Site Closure

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

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

Further, reasons for the early closure of a study site (eg, premature termination) by the sponsor, investigator, or the IEC may include but are not limited to the following:

- Failure of the investigator to comply with the Protocol, the requirements of the IEC or local health authorities, the sponsor's procedures or site agreement, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.

- Circumstances beyond the control of the sponsor or investigator that make it unreasonable to require the continuation of the study or site.
- Failure to carry out the study in the interest of the health of the participants.
- Failure to demonstrate that the continuation of an IEC-approved study (ie, the IEC had previously issued a positive decision on the study) has scientific merit.
- Financial reasons (eg, the sponsor is declared insolvent or a bankruptcy petition has been filed).

12. REFERENCES

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Penner N, Klunk LJ, Prakash C. Human radiolabeled mass balance studies: objectives, utilities and limitations. Biopharm Drug Dispos 2009;30:185-203.

World Health Organization. Use of ionising radiation and radionuclides on human beings for medical research, training, and nonmedical purposes. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser 1977;611:1-39.

APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

WOCBP: A woman who is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal with 1 of the following:[a]
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.

For male participants of reproductive potential[b]

The following methods during the Protocol-defined timeframe in Section 5.1 are highly effective:

- Use of a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant
- Vasectomy with medical assessment of the surgical success (verified by site personnel's review of the participant's medical records)
- Sexual abstinence[c]
  - Abstinence from penile-vaginal intercourse

The following methods have been identified as acceptable methods of contraception when used in conjunction with a male condom and spermicide:

- Hormonal injection
- Combined oral contraceptive pill or progestin/progestogen-only pill associated with inhibition of ovulation
- Combined hormonal patch
- Combined hormonal vaginal ring
- Hormonal implant
- Hormonal or non-hormonal intrauterine device
- Bilateral tubal occlusion

The following are **not** acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method
- Male condom with cap, diaphragm, or sponge with spermicide
- Male and female condom used together

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Note: Contraception requirements only apply to heterosexual relationships.

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

[b] If the male participant has a partner of childbearing potential, the partner should also use contraceptives.

[c] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

Source: Clinical Trials Facilitation and Coordination Group 2020.

APPENDIX B. REQUIRED LABORATORY ANALYTES

<table>
<tr><th>Serum Chemistries[a]</th><th>Hematology[a]</th><th>Urinalysis</th></tr>
<tr><td rowspan="2">Albumin
ALP
ALT
Amylase (at screening only)
AST
Bicarbonate
Blood urea nitrogen
Calcium
Chloride
Creatinine
Creatine kinase
Glucose
Gamma-glutamyl transferase
Lactate dehydrogenase
Lipase (at screening only)
Magnesium
Phosphate
Potassium
Sodium
Total bilirubin
Total serum protein
eGFR (per sites standard method)</td><td rowspan="2">Hematocrit
Hemoglobin
Mean corpuscular volume
Platelet count
Red blood cell count
Reticulocyte count (absolute and percentage)
WBC count
WBC differential in absolutes and percentages (6 part):
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils</td><td>Color and appearance
Nitrite
pH and specific gravity
Bilirubin
Protein
Glucose
Urobilinogen
Ketones
Leukocytes
Blood</td></tr>
<tr><td>Urine Drug Screen</td></tr>
<tr><td></td><td></td><td>Amphetamines
Methamphetamines
Barbiturates
Benzodiazepines
Cocaine (metabolite)
Tetrahydrocannabinol/cannabinoids
Methadone
Opiates
Phencyclidine
Tricyclic antidepressants</td></tr>
<tr><th>Thyroid Panel</th><th>Serology</th><th>Other</th></tr>
<tr><td>Free triiodothyronine
Free thyroxine
Thyroid-stimulating hormone</td><td>HBsAg
HBsAg antibody
Hepatitis B core antibody
HCV antibody
HIV</td><td>Alcohol breath test
Carbon monoxide breath test</td></tr>
</table>

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data or to rule out a diagnosis.

[a] To be taken after an 8-hour fast.

APPENDIX C. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	25 MAR 2024

Amendment 1 (25 MAR 2024)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to address health authority comments. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 1: Primary and Secondary Objectives and Endpoints; Table 3: Schedule of Activities); Section 2.2.2, Justification of Dose; Section 3, Objectives and Endpoints (Table 4: Objectives and Endpoints); Section 4.1, Overall Design; Section 6.1, Study Treatments Administered (Table 5: Study Treatment Information); Section 10.1, Sample Size Determination**

   Description of change: Changed the tablet dose from 600 mg to 400 mg (100 mg × 4 tablets).

   Rationale for change: Regulatory authority request and the latest decision from Incyte's Clinical Development Team on efficacious dose selection of 400 mg BID.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities)**

   Description of change: Added comprehensive physical examination at screening.

   Rationale for change: Investigator request.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities)**

   Description of change: Added serum chemistry and hematology assessments at Day 2.

   Rationale for change: Regulatory authority request.

4. **Section 2.2, Study Rationale**

   Description of change: Added background safety data.

   Rationale for change: Regulatory authority request.

5. **Section 5.2, Exclusion Criteria (Exclusion Criterion 8)**

   Description of change: Changed the exclusion criterion for hepatic transaminases to greater than the laboratory-defined ULN.

   Rationale for change: Regulatory authority request.

6. **Section 7.1.3, Study Stopping Rules**

   Description of change: Added a study stopping rule of 1 or more immune-related AEs (any grade).

   Rationale for change: Regulatory authority request.

7. **Incorporation of administrative changes.** Other administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Signature Page for VV-CLIN-025234 v2.0

Approval Task	[redacted] [redacted] Clinical Pharmacology 25-Mar-2024 19:08:05 GMT+0000
Approval Task	[redacted] [redacted] 25-Mar-2024 19:18:01 GMT+0000
Approval Task	[redacted] Approver [redacted] Clinical Pharmacology, Pharmacometrics & QSP 25-Mar-2024 19:20:28 GMT+0000
Approval Task	[redacted] Approver [redacted] Clinical Pharmacology 25-Mar-2024 19:49:26 GMT+0000
Approval Task	[redacted] Approver [redacted] Clinical Operations 26-Mar-2024 12:26:13 GMT+0000

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