Official Title: A Phase 2 Study of INCB086550 (Oral PD-L1 Inhibitor) in Participants Who Are Immune Checkpoint Inhibitor–Naïve With Selected Solid Tumors

NCT Number: NCT04629339

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Clinical Study Protocol

INCB 86550-203

A Phase 2 Study of INCB086550 (Oral PD-L1 Inhibitor) in Participants Who Are Immune Checkpoint Inhibitor–Naïve With Selected Solid Tumors

Product:	**INCB086550**
IND Number:	**139,900**
EudraCT Number:	**2020-000157-27**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803**
Original Protocol (Version 1):	**01 APR 2020**
Amendment 1 (Version 2):	**08 MAR 2021**

INVESTIGATOR'S AGREEMENT

I have read the INCB 86550-203 Protocol Amendment 1 (Version 2 dated 08 MAR 2021) 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.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine transaminase
anti-HBc	anti–hepatitis B core
anti-HCV	hepatitis C virus antibody
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
BCG	Bacillus Calmette–Guérin
BID	twice daily
CAR-T	chimeric antigen receptor T-cell therapy
CBC	complete blood cell count
cfDNA	cell-free DNA
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
COVID-19	coronavirus disease 2019
CPS	composite performance score
CR	complete response
CrCl	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Group
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid

Abbreviations and Special Terms	Definition
EGFR	epidermal growth factor receptor
EOT	end of treatment
ER/PR	estrogen and progesterone receptors
ESMO	European Society for Medical Oncology
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act of 1996
HPV	human papillomavirus
IB	Investigator's Brochure
IC_{50}	concentration that results in 50% inhibition
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IHC	immunohistochemistry
IFNγ	interferon gamma
INR	international normalized ratio
irAE	immune-related adverse events
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSI-H	microsatellite instability – high
mTOR	mammalian target of rapamycin
NSCLC	non–small cell lung cancer

Abbreviations and Special Terms	Definition
ORR	objective response rate
[redacted]	[redacted]
[redacted]	[redacted]
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death-ligand 1
[redacted]	[redacted]
P-gp	P-glycoprotein
PHL	potential Hy's law
[redacted]	[redacted]
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia's formula
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SoA	schedule of activities
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
TPS	tumor proportion score
UC	urothelial carcinoma
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
WBC	white blood cell

1. PROTOCOL SUMMARY

Protocol Title:

A Phase 2 Study of INCB086550 (Oral PD-L1 Inhibitor) in Participants Who Are Immune Checkpoint Inhibitor–Naïve With Selected Solid Tumors

Protocol Number: INCB 86550-203

Objectives and Endpoints:

Table 1 presents the primary and major/key secondary endpoints and objectives.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints[a]
Primary	
To determine the ORR of participants treated with INCB086550.	ORR, defined as the percentage of participants with a best overall response of CR or PR confirmed by at least 1 repeat assessment ≥ 28 days later according to RECIST v1.1 as determined by the investigator.
Secondary	
To determine the efficacy of INCB086550 in participants with advanced solid tumors in respect to DCR.	DCR, defined as the percentage of participants with a best overall response of CR or PR confirmed by at least 1 repeat assessment ≥ 28 days later, or SD for ≥ 12 weeks, by investigator assessment per RECIST v1.1.
To determine the efficacy of INCB086550 in participants with advanced solid tumors in respect to DOR.	DOR, defined as the time from the earliest date of CR or PR confirmed by at least 1 repeat assessment ≥ 28 days later until the earliest date of disease progression by investigator assessment per RECIST v1.1, or death due to any cause, if occurring sooner than progression.
To evaluate the safety of INCB086550 in participants with advanced solid tumors.	Safety is determined by monitoring the frequency and severity of AEs, including the evaluation of laboratory tests, vital signs, and ECGs

[a] The primary and secondary endpoints will be analyzed after all participants are considered evaluable for response according to the RECIST evaluable population.

Overall Design:

Table 2 presents the key study design elements. Further study details are presented after the table. Figure 1 presents the study design schema. Adherence to the study design requirements, including those specified in the SoA (see Table 3, Table 4, Table 5, and Table 6), is essential and required for study conduct.

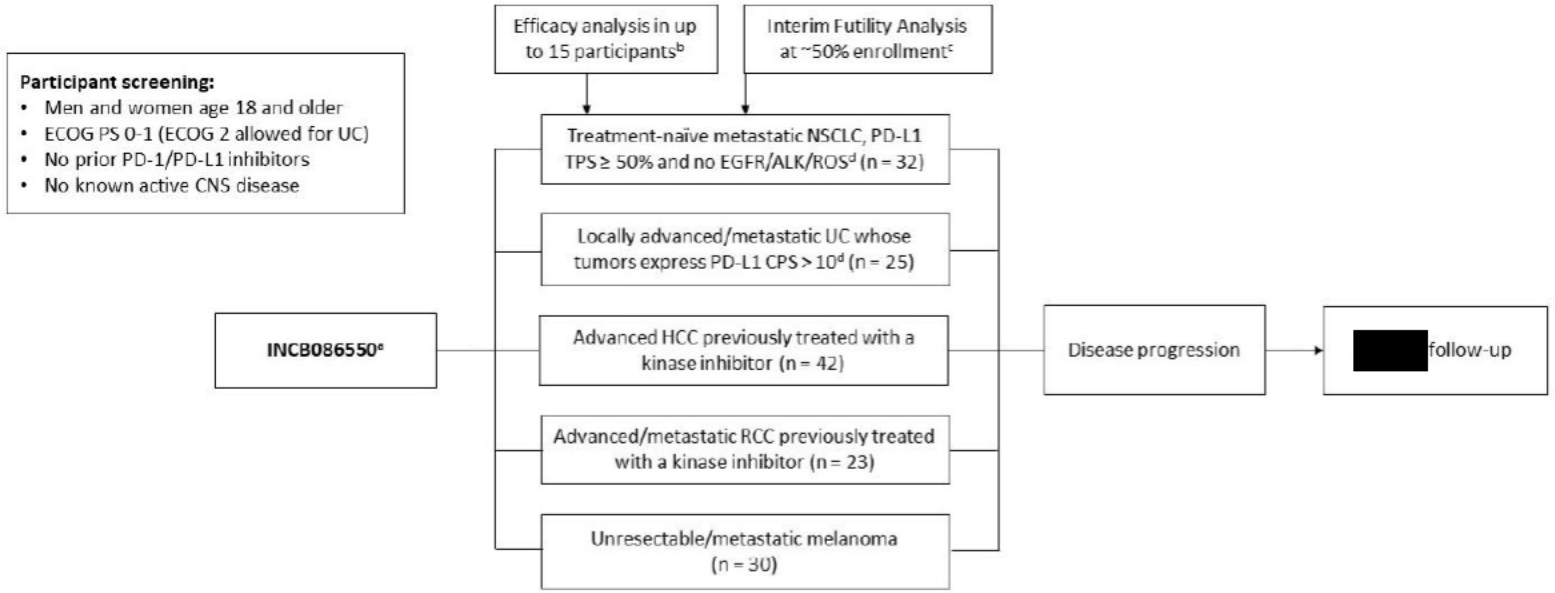
Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indications	Treatment of participants with recurrent or metastatic solid tumors who are immunotherapy naïve and may or may not have been treated with prior therapy for their disease.
Population	Male and female participants at least 18 years of age with 1 of the following solid tumors: • Participants with treatment-naïve, stage IV NSCLC (AJCC v8) whose tumors express PD-L1 TPS ≥ 50% using the Dako PD-L1 IHC 22C3 assay and who have no known activating genomic tumor aberrations that require targeted therapy (eg, EGFR, ALK, ROS, BRAF). • Participants with locally advanced, and unresectable or metastatic UC of the renal pelvis, ureter, bladder, or urethra (including transitional cell and mixed transitional or nontransitional cell histologies) who are cisplatin-ineligible, who are immune checkpoint inhibitor–naïve, and whose tumors express high PD-L1 (CPS ≥ 10) using the Dako PD-L1 IHC 22C3 assay. • Participants with advanced HCC that is not amenable to curative surgery or local treatment who have received at least 1 previous line of systemic therapy (ie, sorafenib or lenvatinib) or who were intolerant of sorafenib or lenvatinib treatment. Participants must be immune checkpoint inhibitor–naïve. • Participants with advanced or metastatic RCC with a clear cell component with or without sarcomatoid features who have received prior systemic therapy for their disease (up to 2 previous regimens of a VEGF or mTOR inhibitor) and who are immune checkpoint inhibitor–naïve. • Participants with unresectable stage III or IV melanoma (excluding ocular/uveal melanoma) who are immune checkpoint inhibitor–naïve and have known BRAF V600 mutational status.
Number of Participants	Up to approximately 304 participants will receive INCB086550 and be enrolled into disease-specific cohorts of 23-42 participants.
Study Design	This is a Phase 2, open-label, nonrandomized, multicohort, global, multicenter study.
Estimated Duration of Study Participation	The study consists of 3 periods: screening, study drug treatment, and follow-up. Up to 28 days for screening, treatment for up to 2 years as long as participants are receiving benefit and have not met any criteria for study withdrawal, and 30 (± 7) days and 90 (± 14) days for safety follow-up, [redacted] every 12 weeks (± 14) days for up to 2 years from EOT.
DMC	Yes

Treatment Groups and Duration:

Disease-specific cohorts receiving single-agent INCB086550 (up to 2 years of treatment).

Figure 1: Study Design Schema



ECOG PS = Eastern Cooperative Group Performance Score; HCC = hepatocellular carcinoma; NSCLC = non–small cell lung cancer; RCC = renal cell carcinoma; UC = urothelial carcinoma.

[a] Information on dosing are included in Section 2.2.2 and Section 2.2.3.

[b] Nonbinding efficacy run-in are planned after enrollment of up to 15 participants in select disease-specific cohorts are evaluable for response using the RECIST evaluable population.

[c] Nonbinding interim futility analyses are planned after approximately 50% of the participants in each disease-specific cohort are evaluable for response using the RECIST evaluable population.

[d] PD-L1 staining assessed using the Dako PD-L1 IHC 22C3 pharmDx assay.

Table 3: Schedule of Activities for Schedule A (Continuous, 2-Week and 3-Week Intermittent, or 2-Week and 3-Week Step-Down Treatment Schedules in a 28-Day Cycle)

	Screening	Treatment						Follow-Up				
		Cycle 1		Cycles 2-6		Cycles 7+		Safety		[redacted]	[redacted]	
Visit Day (Range)	**Day −28**	**Day 1**	**Day 14**	**Day 1**	**Day 15**	**Day 1**	**EOT**	**EOT + 30 d**	**EOT + 90 d**	**Q8W**	**Q12W**	**Notes**
Evaluation Window			*	± 3 d	± 3 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	*± 3 days for continuous and 3-week treatment schedule; −3 days for 2-week treatment schedule
Administrative procedures												
Informed consent	X											Section 8.1.1.
Tumor tissue for PD-L1 expression (NSCLC or UC only)	X											Section 8.6.
Contact IRT	X	X		X		X	X					Section 8.1.3.
Inclusion/exclusion criteria	X	X										Section 5.
General and disease medical history	X											Section 8.1.5.
Document baseline biomarker history	X											Section 8.1.5.3.
Prior/concomitant medications	X	X	X	X	X	X	X	X	X			Section 6.6 and Section 8.1.5.
Dispense INCB086550		X		X		X						Section 6.1, Appendix C, and Pharmacy Manual.
Administer INCB086550 in clinic [redacted]		X	X									
Distribute dosing diary and participant information cards	X	X	X	X	X	X	X	X	X	X*		*If applicable. Section 8.1.4.
Assess compliance			X	X	X	X	X					Section 6.4.

Table 3: Schedule of Activities for Schedule A (Continuous, 2-Week and 3-Week Intermittent, or 2-Week and 3-Week Step-Down Treatment Schedules in a 28-Day Cycle) (Continued)

	Screening	Treatment						Follow-Up				
		Cycle 1		Cycles 2-6		Cycles 7+		Safety		[redacted]	[redacted]	
Visit Day (Range)	**Day −28**	**Day 1**	**Day 14**	**Day 1**	**Day 15**	**Day 1**	**EOT**	**EOT + 30 d**	**EOT + 90 d**	**Q8W**	**Q12W**	**Notes**
Evaluation Window			*	± 3 d	± 3 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	*± 3 days for continuous and 3-week treatment schedule; −3 days for 2-week treatment schedule
Safety assessments												
AE assessments	X	X	X	X	X	X	X	X	X			Section 8.3.1.
Telephone AE assessment		X*	X*	X*	X*	X**						*Performed on Days 8 and 22 (±3 d) in Cycles 1-6. **Performed on Day 15 of each cycle (± 3 days) in Cycle 7 and beyond. Section 8.3.1.1.
Physical examination/body weight and height*	X	X	X	X	X	X	X	X**				*Comprehensive examination at screening, targeted physical examination thereafter. Height at screening only. **If EOT visit occurs ≥ 30 days from last dose of study treatment, an EOT + 30 days visit is not required. Section 8.3.2.
Neurologic examination*		X	X	X	X	X	X	X				*Should include assessment of motor system, muscle reflexes, sensory system, coordination, and gait and stance. Section 8.3.2.1.
Vital signs	X	X	X	X	X	X	X	X				Section 8.3.3.
ECOG performance status	X	X		X		X	X	X				Section 8.3.4.
12-lead ECG	X	X*	X*	X**		X**	X					*C1D1 and C1D14: Predose and 2 and 4 hours postdose. **Beginning in C3 and every 2 cycles thereafter (eg, C3, C5, C7). Section 8.3.5.

Table 3: Schedule of Activities for Schedule A (Continuous, 2-Week and 3-Week Intermittent, or 2-Week and 3-Week Step-Down Treatment Schedules in a 28-Day Cycle) (Continued)

	Screening	Treatment						Follow-Up				
		Cycle 1		Cycles 2-6		Cycles 7+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 14	Day 1	Day 15	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	Notes
Evaluation Window			*	± 3 d	± 3 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	*± 3 days for continuous and 3-week treatment schedule; −3 days for 2-week treatment schedule
Efficacy assessments												
Radiologic tumor imaging and response assessment (CT/MRI)	X			X*		X*				X**		*Every 8 weeks (56 ± 7 days) until disease progression. After 6 months of study treatment, imaging frequency may be reduced to every 12 weeks (84 ± 14 days). Imaging should not be delayed for delays in cycle starts. Section 8.2. **Imaging during follow-up will only be performed for participants continuing to be followed [redacted]. Complete response or PR should be confirmed by imaging at least 4 weeks after initial documentation Section 8.2 and Section 8.2.1.3.
Bone scan	X*			X**		X**				X**		*Required at baseline within 28 days before first dose. **If positive at baseline, follow same schedule as CT/MRI. During follow-up, can be done per standard of care. Follow same schedule if treatment is discontinued for reason other than disease progression. Section 8.2.1.
Post-treatment anticancer therapy status								X	X	X		Section 8.9.

Table 3: Schedule of Activities for Schedule A (Continuous, 2-Week and 3-Week Intermittent, or 2-Week and 3-Week Step-Down Treatment Schedules in a 28-Day Cycle) (Continued)

	Screening	Treatment						Follow-Up				
		Cycle 1		Cycles 2-6		Cycles 7+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 14	Day 1	Day 15	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	Notes
Evaluation Window			*	± 3 d	± 3 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	*± 3 days for continuous and 3-week treatment schedule; −3 days for 2-week treatment schedule
Efficacy assessments (continued)												
[redacted]								X	X		X*	*During [redacted], participants should be contacted by telephone, email, or visit at least every 12 weeks for maximum of 2 years after EOT. Section 8.9.3.
Local laboratory assessments												
Blood chemistry panel	X	X	X	X	X	X	X	X				Section 8.3.6.
Hematology panel	X	X	X	X	X	X	X	X				Additional unscheduled CBCs may be performed. Section 8.3.6.
Coagulation panel	X			X*		X*	X					*If clinically indicated, only on Cycle 2 and then every other cycle (eg, 4, 6, 8). Section 8.3.6.
Endocrine panel	X	X		X*		X*	X					*Cycle 2 and then every other cycle (eg, 4, 6, 8). If a participant has an endocrine irAE, additional assessments may be performed. Section 8.3.6.
Lipid panel	X						X					Section 8.3.6.
Serology	X											Section 8.3.6.2.
HBV/HCV viral load (HCC participants with viral hepatitis only)*	X			X**		X**	X**					*HBV DNA and/or HCV RNA depending on underlying disease. **Every 2 cycles beginning at Cycle 3. Section 8.3.6.

Table 3: Schedule of Activities for Schedule A (Continuous, 2-Week and 3-Week Intermittent, or 2-Week and 3-Week Step-Down Treatment Schedules in a 28-Day Cycle) (Continued)

	Screening	Treatment						Follow-Up				
		Cycle 1		Cycles 2-6		Cycles 7+		Safety		[redacted]	[redacted]	
Visit Day (Range)	**Day −28**	**Day 1**	**Day 14**	**Day 1**	**Day 15**	**Day 1**	**EOT**	**EOT + 30 d**	**EOT + 90 d**	**Q8W**	**Q12W**	**Notes**
Evaluation Window			*	**± 3 d**	**± 3 d**	**± 3 d**	**± 7 d**	**± 7 d**	**± 14 d**	**± 7 d**	**± 14 d**	*± 3 days for continuous and 3-week treatment schedule; −3 days for 2-week treatment schedule
Local laboratory assessments (continued)												
Urinalysis	X			X*		X*						*Cycle 2 and then every 3 cycles (eg, 5, 8, 11). Section 8.3.6.
Pregnancy testing	X*	X**		X**		X**	X*					*Serum pregnancy test for women of childbearing potential. Additionally, monthly telephone visits should take place to check pregnancy status (may be home pregnancy tests) during the period when contraception is mandatory (190 days after the last dose of study drug). **Urine pregnancy test for women of childbearing potential. Section 8.3.6.1.
[redacted]												

Table 3: Schedule of Activities for Schedule A (Continuous, 2-Week and 3-Week Intermittent, or 2-Week and 3-Week Step-Down Treatment Schedules in a 28-Day Cycle) (Continued)

	Screening	Treatment						Follow-Up				
		Cycle 1		Cycles 2-6		Cycles 7+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 14	Day 1	Day 15	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	Notes
Evaluation Window			*	± 3 d	± 3 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	*± 3 days for continuous and 3-week treatment schedule; −3 days for 2-week treatment schedule
[redacted]												
Tumor/tissue biopsy collection												
Tumor biopsy	X*											*Fresh or archival. Section 8.5.6.
Tumor biopsy quality control evaluation	X*											*Performed as per local laboratory practice. Section 8.5.6.

Table 3: Schedule of Activities for Schedule A (Continuous, 2-Week and 3-Week Intermittent, or 2-Week and 3-Week Step-Down Treatment Schedules in a 28-Day Cycle) (Continued)

	Screening	Treatment						Follow-Up				
		Cycle 1		Cycles 2-6		Cycles 7+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 14	Day 1	Day 15	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	Notes
Evaluation Window			*	± 3 d	± 3 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	*± 3 days for continuous and 3-week treatment schedule; −3 days for 2-week treatment schedule
[redacted]												

Table 4: Schedule of Activities for Schedule B (1-Week Intermittent or Step-Down Treatment Schedules in a 28-Day Cycle)

	Screening	Treatment						Follow-Up				
		Cycle 1		Cycles 2-6		Cycles 7+		Safety		[redacted]	[redacted]	
Visit Day (Range)	**Day −28**	**Day 1**	**Day 7**	**Day 1**	**Day 15**	**Day 1**	**EOT**	**EOT + 30 d**	**EOT + 90 d**	**Q8W**	**Q12W**	
Evaluation Window				**± 3 d**	**± 3 d**	**± 3 d**	**± 7 d**	**± 7 d**	**± 14 d**	**± 7 d**	**± 14 d**	**Notes**
Administrative procedures												
Informed consent	X											Section 8.1.1.
Tumor tissue for PD-L1 expression (NSCLC or UC only)	X											Section 8.6.
Contact IRT	X	X		X		X	X					Section 8.1.3.
Inclusion/exclusion criteria	X	X										Section 5.
General and disease medical history	X											Section 8.1.5.
Document baseline biomarker history	X											Section 8.1.5.3.
Prior/concomitant medications	X	X	X	X	X	X	X	X	X			Section 6.6 and Section 8.1.5.
Dispense INCB086550		X		X		X						Section 6.1, Appendix C, and Pharmacy Manual.
Administer INCB086550 in clinic [redacted]		X*	X									*C1D1 to occur Tuesday through Friday only [redacted]
Distribute dosing diary and participant information cards	X	X	X	X	X	X	X	X	X	X*		*If applicable. Section 8.1.4.
Assess compliance			X	X	X	X	X					Section 6.4.
Safety assessments												
AE assessments	X	X	X	X	X	X	X	X	X			Section 8.3.1.
Telephone AE assessment		X*	X*	X**	X**	X***						*Performed on Days 15 and 22 (± 3 days) in Cycle 1. **Performed on Days 8 and 22 (± 3 days) in Cycles 2-6. ***Performed on Day 15 of each cycle (± 3 days) in Cycle 7 and beyond. Section 8.3.1.1.

Table 4: Schedule of Activities for Schedule B (1-Week Intermittent or Step-Down Treatment Schedules in a 28-Day Cycle) (Continued)

	Screening	Treatment						Follow-Up				
		Cycle 1		Cycles 2-6		Cycles 7+		Safety		[redacted]	[redacted]	
Visit Day (Range)	**Day −28**	**Day 1**	**Day 7**	**Day 1**	**Day 15**	**Day 1**	**EOT**	**EOT + 30 d**	**EOT + 90 d**	**Q8W**	**Q12W**	
Evaluation Window				**± 3 d**	**± 3 d**	**± 3 d**	**± 7 d**	**± 7 d**	**± 14 d**	**± 7 d**	**± 14 d**	**Notes**
Safety assessments (continued)												
Physical examination/body weight and height*	X	X	X	X	X	X	X	X**				*Comprehensive examination at screening, targeted physical examination thereafter. Height at screening only. **If EOT visit occurs ≥ 30 days from last dose of study treatment, an EOT + 30 days visit is not required. Section 8.3.2.
Neurologic examination*		X	X	X	X	X	X	X				*Should include assessment of motor system, muscle reflexes, sensory system, coordination, and gait and stance. Section 8.3.2.1.
Vital signs	X	X	X	X	X	X	X	X				Section 8.3.3.
ECOG performance status	X	X		X		X	X	X				Section 8.3.4.
12-lead ECG	X	X*	X*	X**		X**	X					*C1D1 and C1D7: Predose and 2 and 4 hours postdose. **Beginning in C3, every 2 cycles thereafter (eg, C3, C5, C7). Section 8.3.5.

Table 4: Schedule of Activities for Schedule B (1-Week Intermittent or Step-Down Treatment Schedules in a 28-Day Cycle) (Continued)

	Screening	Treatment						Follow-Up				
		Cycle 1		Cycles 2-6		Cycles 7+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 7	Day 1	Day 15	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	
Evaluation Window				± 3 d	± 3 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	Notes
Efficacy assessments												
Radiologic tumor imaging and response assessment (CT/MRI)	X			X*		X*				X**		*Every 8 weeks (56 ± 7 days) until disease progression. After 6 months of study treatment, imaging frequency may be reduced to every 12 weeks (84 ± 14 days). Imaging should not be delayed for delays in cycle starts. Section 8.2. **Imaging during follow-up will only be performed for participants continuing to be followed [redacted] Complete response or PR should be confirmed by imaging at least 4 weeks after initial documentation. Section 8.2 and Section 8.2.1.3.
Bone scan	X*			X**		X**				X**		*Required at baseline within 28 days before first dose. **If positive at baseline, follow same schedule as CT/MRI. During follow-up, can be done per standard of care. Follow same schedule if treatment is discontinued for reason other than disease progression. Section 8.2.1.
Post-treatment anticancer therapy status								X	X	X		Section 8.9.

Table 4: Schedule of Activities for Schedule B (1-Week Intermittent or Step-Down Treatment Schedules in a 28-Day Cycle) (Continued)

	Screening	Treatment						Follow-Up				
		Cycle 1		Cycles 2-6		Cycles 7+		Safety		[redacted]	[redacted]	
Visit Day (Range)	**Day −28**	**Day 1**	**Day 7**	**Day 1**	**Day 15**	**Day 1**	**EOT**	**EOT + 30 d**	**EOT + 90 d**	**Q8W**	**Q12W**	
Evaluation Window				**± 3 d**	**± 3 d**	**± 3 d**	**± 7 d**	**± 7 d**	**± 14 d**	**± 7 d**	**± 14 d**	**Notes**
Efficacy assessments (continued)												
[redacted]								X	X		X*	*During [redacted] participants should be contacted by telephone, email, or visit at least every 12 weeks for maximum of 2 years after EOT. Section 8.9.3.
Local laboratory assessments												
Blood chemistry panel	X	X	X	X	X	X	X	X				Section 8.3.6.
Hematology panel	X	X	X	X	X	X	X	X				Additional unscheduled CBCs may be performed. Section 8.3.6.
Coagulation panel	X			X*		X*	X					*If clinically indicated, only on Cycle 2 and then every other cycle (eg, 4, 6, 8). Section 8.3.6.
Endocrine panel	X	X		X*		X*	X					*Cycle 2 and then every other cycle (eg, 4, 6, 8). If a participant has an endocrine irAE, additional assessments may be performed. Section 8.3.6.
Lipid panel	X						X					Section 8.3.6.
Serology	X											Section 8.3.6.2.
HBV/HCV viral load (HCC participants with viral hepatitis only)*	X			X**		X**	X**					*HBV DNA and/or HCV RNA depending on underlying disease. **Every 2 cycles beginning at Cycle 3. Section 8.3.6.
Urinalysis	X			X*		X*						*Cycle 2 and then every 3 cycles (eg, 5, 8, 11). Section 8.3.6.

Table 4: Schedule of Activities for Schedule B (1-Week Intermittent or Step-Down Treatment Schedules in a 28-Day Cycle) (Continued)

	Screening	Treatment						Follow-Up				
		Cycle 1		Cycles 2-6		Cycles 7+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 7	Day 1	Day 15	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	
Evaluation Window				± 3 d	± 3 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	Notes
Local laboratory assessments (continued)												
Pregnancy testing	X*	X**		X**		X**	X*					*Serum pregnancy test for women of childbearing potential. Additionally, monthly telephone visits should take place to check pregnancy status (may be home pregnancy tests) during the period when contraception is mandatory (190 days after the last dose of study drug). **Urine pregnancy test for women of childbearing potential. Section 8.3.6.1.
[redacted]												

Table 4: Schedule of Activities for Schedule B (1-Week Intermittent or Step-Down Treatment Schedules in a 28-Day Cycle) (Continued)

	Screening	Treatment						Follow-Up				
		Cycle 1		Cycles 2-6		Cycles 7+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 7	Day 1	Day 15	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	Notes
Evaluation Window				± 3 d	± 3 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	
[redacted]												
Tumor/tissue biopsy collection												
Tumor biopsy	X*											*Fresh or archival. Section 8.5.6.
Tumor biopsy quality control evaluation	X*											*Performed as per local laboratory practice. Section 8.5.6.
[redacted]												

Table 5: Schedule of Activities for Schedule C (2-Week Intermittent or Step-Down Treatment Schedules in a 21-Day Cycle)

	Screening	Treatment				Follow-Up				
		Cycle 1		Cycles 2+		Safety		[redacted]	[redacted]	
Visit Day (Range)	**Day −28**	**Day 1**	**Day 14**	**Day 1**	**EOT**	**EOT + 30 d**	**EOT + 90 d**	**Q8W**	**Q12W**	
Evaluation Window			**−3 d**	**± 3 d**	**± 7 d**	**± 7 d**	**± 14 d**	**± 7 d**	**± 14 d**	**Notes**
Administrative procedures										
Informed consent	X									Section 8.1.1.
Tumor tissue for PD-L1 expression (NSCLC or UC only)	X									Section 8.6.
Contact IRT	X	X		X	X					Section 8.1.3.
Inclusion/exclusion criteria	X	X								Section 5.
General and disease medical history	X									Section 8.1.5.
Document baseline biomarker history	X									Section 8.1.5.3.
Prior/concomitant medications	X	X	X	X	X	X	X			Section 6.6 and Section 8.1.5.
Dispense INCB086550		X		X						Section 6.1, Appendix C, and Pharmacy Manual.
Administer INCB086550 in clinic [redacted]		X	X							
Distribute dosing diary and reminder cards	X	X	X	X	X	X	X	X*		*If applicable. Section 8.1.4.
Assess compliance		X	X	X	X					Section 6.4.
Safety assessments										
AE assessments	X	X	X	X	X	X	X			Section 8.3.1.
Telephone AE assessment		X*	X*	X**						*Performed on Day 8 only in Cycle 1. **Performed on Day 8 and Day 15 during Cycles 2-6. Performed on Day 8 or Day 15 during Cycles 7+. Section 8.3.1.1.

Table 5: Schedule of Activities for Schedule C (2-Week Intermittent or Step-Down Treatment Schedules in a 21-Day Cycle) (Continued)

	Screening	Treatment				Follow-Up				
		Cycle 1		Cycles 2+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 14	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	Notes
Evaluation Window			−3 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	
Safety assessments (continued)										
Physical examination/body weight and height*	X	X	X	X	X	X**				*Comprehensive examination at screening, targeted physical examination thereafter. Height at screening only. **If EOT visit occurs ≥ 30 days from last dose of study treatment, an EOT + 30 days visit is not required. Section 8.3.2.
Neurologic examination*		X	X	X	X	X				*Should include assessment of motor system, muscle reflexes, sensory system, coordination, and gait and stance. Section 8.3.2.1.
Vital signs	X	X	X	X	X	X				Section 8.3.3.
ECOG performance status	X	X		X	X	X				Section 8.3.4.
12-lead ECG	X	X*	X*	X**	X					*Predose and 2 and 4 hours postdose. **Beginning in C3 every 2 cycles thereafter (eg, C3, C5, C7). Section 8.3.5.

Table 5: Schedule of Activities for Schedule C (2-Week Intermittent or Step-Down Treatment Schedules in a 21-Day Cycle) (Continued)

	Screening	Treatment				Follow-Up				
		Cycle 1		Cycles 2+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 14	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	Notes
Evaluation Window			−3 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	
Efficacy assessments										
Radiologic tumor imaging and response assessment (CT/MRI)	X			X*				X**		*Every 8 weeks (56 ± 7 days) until disease progression. After 6 months of study treatment, imaging frequency may be reduced to every 12 weeks (84 ± 14 days). Imaging should not be delayed for delays in cycle starts. Section 8.2. **Imaging during follow-up will only be performed for participants continuing to be followed [redacted]. Complete response or PR should be confirmed by imaging at least 4 weeks after initial documentation. Section 8.2 and Section 8.2.1.3.
Bone scan	X*			X**				X**		*Required at baseline within 28 days before first dose. **If positive at baseline, follow same schedule as CT/MRI. During follow-up, can be done per standard of care. Follow same schedule if treatment is discontinued for reason other than disease progression. Section 8.2.1.

Table 5: Schedule of Activities for Schedule C (2-Week Intermittent or Step-Down Treatment Schedules in a 21-Day Cycle) (Continued)

	Screening	Treatment				Follow-Up				
		Cycle 1		Cycles 2+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 14	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	Notes
Evaluation Window			−3 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	
Efficacy assessments (continued)										
Post-treatment anticancer therapy status						X	X	X		Section 8.9.
[redacted]						X	X		X*	*During [redacted] participants should be contacted by telephone, email, or visit at least every 12 weeks for maximum of 2 years after EOT. Section 8.9.3.
Local laboratory assessments										
Blood chemistry panel	X	X	X	X	X	X				Section 8.3.6.
Hematology panel	X	X	X	X	X	X				Additional unscheduled CBCs may be performed. Section 8.3.6.
Coagulation panel	X			X*	X					*If clinically indicated, only on Cycle 2 and then every other cycle (eg, 4, 6, 8). Section 8.3.6.
Endocrine panel	X	X		X*	X					*Cycle 2 and then every other cycle (eg, 4, 6, 8). If a participant has an endocrine irAE, additional assessments may be performed. Section 8.3.6.
Lipid panel	X				X					Section 8.3.6.
Serology	X									Section 8.3.6.2.

Table 5: Schedule of Activities for Schedule C (2-Week Intermittent or Step-Down Treatment Schedules in a 21-Day Cycle) (Continued)

	Screening	Treatment				Follow-Up				
		Cycle 1		Cycles 2+		Safety		[redacted]	[redacted]	
Visit Day (Range)	**Day −28**	**Day 1**	**Day 14**	**Day 1**	**EOT**	**EOT + 30 d**	**EOT + 90 d**	**Q8W**	**Q12W**	
Evaluation Window			**−3 d**	**± 3 d**	**± 7 d**	**± 7 d**	**± 14 d**	**± 7 d**	**± 14 d**	**Notes**
Local laboratory assessments (continued)										
HAV/HBV/HCV viral load (HCC participants with viral hepatitis only)*	X			X**	X**					*HAV IgM, HBV DNA, and/or HCV RNA depending on underlying disease. **Every 2 cycles beginning at Cycle 3. Section 8.3.6.2.
Urinalysis	X			X*						*Cycle 2 and then every 3 cycles (eg, 5, 8, 11). Section 8.3.6.
Pregnancy testing	X*	X**		X**	X*					*Serum pregnancy test for women of childbearing potential. Additionally, monthly telephone visits should take place to check pregnancy status (may be home pregnancy tests) during the period when contraception is mandatory (190 days after the last dose of study drug). **Urine pregnancy test for women of childbearing potential. Section 8.3.6.1.

Table 5: Schedule of Activities for Schedule C (2-Week Intermittent or Step-Down Treatment Schedules in a 21-Day Cycle) (Continued)

	Screening	Treatment				Follow-Up				
		Cycle 1		Cycles 2+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 14	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	
Evaluation Window			−3 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	Notes
[redacted]										

Table 5: Schedule of Activities for Schedule C (2-Week Intermittent or Step-Down Treatment Schedules in a 21-Day Cycle) (Continued)

	Screening	Treatment				Follow-Up				
		Cycle 1		Cycles 2+		Safety		[redacted]	[redacted]	
Visit Day (Range)	**Day −28**	**Day 1**	**Day 14**	**Day 1**	**EOT**	**EOT + 30 d**	**EOT + 90 d**	**Q8W**	**Q12W**	
Evaluation Window			**−3 d**	**± 3 d**	**± 7 d**	**± 7 d**	**± 14 d**	**± 7 d**	**± 14 d**	**Notes**
Tumor/tissue biopsy collection										
Tumor biopsy	X*									*Fresh or archival. Section 8.5.6.
Tumor biopsy quality control evaluation	X*									*Performed as per local laboratory practice. Section 8.5.6.
[redacted]										

Table 6: Schedule of Activities for Schedule D (1-Week Intermittent or Step-Down Treatment Schedules in a 21-Day Cycle)

	Screening	Treatment				Follow-Up				
		Cycle 1		Cycles 2+		Safety		[redacted]	[redacted]	
Visit Day (Range)	**Day −28**	**Day 1**	**Day 7**	**Day 1**	**EOT**	**EOT + 30 d**	**EOT + 90 d**	**Q8W**	**Q12W**	
Evaluation Window			**−1 d**	**± 3 d**	**± 7 d**	**± 7 d**	**± 14 d**	**± 7 d**	**± 14 d**	**Notes**
Administrative procedures										
Informed consent	X									Section 8.1.1.
Tumor tissue for PD-L1 expression (NSCLC or UC only)	X									Section 8.6.
Contact IRT	X	X		X	X					Section 8.1.3.
Inclusion/exclusion criteria	X	X								Section 5.
General and disease medical history	X									Section 8.1.5.
Document baseline biomarker history	X									Section 8.1.5.3.
Prior/concomitant medications	X	X	X	X	X	X	X			Section 6.6 and Section 8.1.5.
Dispense INCB086550		X		X						Section 6.1, Appendix C, and Pharmacy Manual.
Administer INCB086550 in clinic [redacted]		X*	X							*C1D1 to occur Tuesday through Friday only [redacted]
Distribute dosing diary and reminder cards	X	X	X	X	X	X	X	X*		*If applicable. Section 8.1.4.
Assess compliance		X	X	X	X					Section 6.4.

Table 6: Schedule of Activities for Schedule D (1-Week Intermittent or Step-Down Treatment Schedules in a 21-Day Cycle) (Continued)

	Screening	Treatment				Follow-Up				
		Cycle 1		Cycles 2+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 7	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	Notes
Evaluation Window			−1 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	
Safety assessments										
AE assessments	X	X	X	X	X	X	X			Section 8.3.1.
Telephone AE assessment		X*	X*	X**						*Performed on Day 15 only in Cycle 1. **Performed on Day 8 and Day 15 during Cycles 2 to 6. Performed on Day 8 or Day 15 during Cycles 7+. Section 8.3.1.1.
Physical examination/body weight and height*	X	X	X	X	X	X**				*Comprehensive examination at screening, targeted physical examination thereafter. Height at screening only. **If EOT visit occurs ≥ 30 days from last dose of study treatment, an EOT + 30 days visit is not required. Section 8.3.2.
Neurologic examination*		X	X	X	X	X				*Should include assessment of motor system, muscle reflexes, sensory system, coordination, and gait and stance. Section 8.3.2.1.
Vital signs	X	X	X	X	X	X				Section 8.3.3.
ECOG performance status	X	X		X	X	X				Section 8.3.4.

Table 6: Schedule of Activities for Schedule D (1-Week Intermittent or Step-Down Treatment Schedules in a 21-Day Cycle) (Continued)

	Screening	Treatment				Follow-Up				
		Cycle 1		Cycles 2+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 7	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	
Evaluation Window			−1 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	Notes
Safety assessments (continued)										
12-lead ECG	X	X*	X*	X**	X					*Predose and 2 and 4 hours postdose. **Beginning in C3, every 2 cycles thereafter (eg, C3, C5, C7). Section 8.3.5.
Efficacy assessments										
Radiologic tumor imaging and response assessment (CT/MRI)	X			X*				X**		*Every 8 weeks (56 ± 7 days) until disease progression. After 6 months of study treatment, imaging frequency may be reduced to every 12 weeks (84 ± 14 days). Imaging should not be delayed for delays in cycle starts (Section 8.2). **Imaging during follow-up will only be performed for participants continuing to be followed [redacted]. Complete response or PR should be confirmed by imaging at least 4 weeks after initial documentation (Section 8.2 and Section 8.2.1.3).

Table 6: Schedule of Activities for Schedule D (1-Week Intermittent or Step-Down Treatment Schedules in a 21-Day Cycle) (Continued)

	Screening	Treatment				Follow-Up				
		Cycle 1		Cycles 2+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 7	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	Notes
Evaluation Window			−1 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	
Efficacy assessments (continued)										
Bone scan	X*			X**				X**		*Required at baseline within 28 days before first dose. **If positive at baseline, follow same schedule as CT/MRI. During follow-up, can be done per standard of care. Follow same schedule if treatment is discontinued for reason other than disease progression. Section 8.2.1.
Post-treatment anticancer therapy status						X	X	X		Section 8.9.
[redacted]						X	X		X*	*During [redacted] participants should be contacted by telephone, email, or visit at least every 12 weeks for maximum of 2 years after EOT. Section 8.9.3.
Local laboratory assessments										
Blood chemistry panel	X	X	X	X	X	X				Section 8.3.6.
Hematology panel	X	X	X	X	X	X				Additional unscheduled CBCs may be performed. Section 8.3.6.
Coagulation panel	X			X*	X					*If clinically indicated, only on Cycle 2 and then every other cycle (eg, 4, 6, 8). Section 8.3.6.

Table 6: Schedule of Activities for Schedule D (1-Week Intermittent or Step-Down Treatment Schedules in a 21-Day Cycle) (Continued)

	Screening	Treatment				Follow-Up				
		Cycle 1		Cycles 2+		Safety		[redacted]	[redacted]	
Visit Day (Range)	**Day −28**	**Day 1**	**Day 7**	**Day 1**	**EOT**	**EOT + 30 d**	**EOT + 90 d**	**Q8W**	**Q12W**	
Evaluation Window			**−1 d**	**± 3 d**	**± 7 d**	**± 7 d**	**± 14 d**	**± 7 d**	**± 14 d**	**Notes**
Local laboratory assessments (continued)										
Endocrine panel	X	X		X*	X					*Cycle 2 and then every other cycle (eg, 4, 6, 8). If a participant has an endocrine irAE, additional assessments may be performed. Section 8.3.6.
Lipid panel	X				X					Section 8.3.6.
Serology	X									Section 8.3.6.2.
HAV/HBV/HCV viral load (HCC participants with viral hepatitis only)*	X			X**	X**					*HAV IgM, HBV DNA and/or HCV RNA depending on underlying disease. **Every 2 cycles beginning at Cycle 3. Section 8.3.6.2.
Urinalysis	X			X*						*Cycle 2 and then every 3 cycles (eg, 5, 8, 11). Section 8.3.6.

Table 6: Schedule of Activities for Schedule D (1-Week Intermittent or Step-Down Treatment Schedules in a 21-Day Cycle) (Continued)

	Screening	Treatment				Follow-Up				
		Cycle 1		Cycles 2+		Safety		[redacted]	[redacted]	
Visit Day (Range)	**Day −28**	**Day 1**	**Day 7**	**Day 1**	**EOT**	**EOT + 30 d**	**EOT + 90 d**	**Q8W**	**Q12W**	**Notes**
Evaluation Window			**−1 d**	**± 3 d**	**± 7 d**	**± 7 d**	**± 14 d**	**± 7 d**	**± 14 d**	
Local laboratory assessments (continued)										
Pregnancy testing	X*	X**		X**	X*					*Serum pregnancy test for women of childbearing potential. Additionally, monthly telephone visits should take place to check pregnancy status (may be home pregnancy tests) during the period when contraception is mandatory (190 days after the last dose of study drug). **Urine pregnancy test for women of childbearing potential. Section 8.3.6.1.
[redacted]										

Table 6: Schedule of Activities for Schedule D (1-Week Intermittent or Step-Down Treatment Schedules in a 21-Day Cycle) (Continued)

	Screening	Treatment				Follow-Up				
		Cycle 1		Cycles 2+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 7	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	
Evaluation Window			−1 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	Notes
[redacted]										
Tumor/tissue biopsy collection										
Tumor biopsy	X*									*Fresh or archival. Section 8.5.6.
Tumor biopsy quality control evaluation	X*									*Performed as per local laboratory practice. Section 8.5.6.

Table 6: Schedule of Activities for Schedule D (1-Week Intermittent or Step-Down Treatment Schedules in a 21-Day Cycle) (Continued)

	Screening	Treatment				Follow-Up				
		Cycle 1		Cycles 2+		Safety		[redacted]	[redacted]	
Visit Day (Range)	Day −28	Day 1	Day 7	Day 1	EOT	EOT + 30 d	EOT + 90 d	Q8W	Q12W	
Evaluation Window			−1 d	± 3 d	± 7 d	± 7 d	± 14 d	± 7 d	± 14 d	Notes
Tumor/tissue biopsy collection (continued)										
[redacted]										

2. INTRODUCTION

This open-label, global, nonrandomized multicohort trial is designed to provide a benchmark of efficacy for INCB086550 in key indications in which other PD-(L)1 inhibitors have already demonstrated efficacy.

2.1. Background

INCB086550 is a small molecule inhibitor of PD-L1 (also known as CD274). PD-1, also known as CD279, is a cell surface receptor expressed on activated T cells, natural killer T cells, B cells, and macrophages (Greenwald et al 2005, Okazaki and Honjo 2006). PD-1 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 such as cancer and viral infection (Postow et al 2015, Sharpe et al 2007). 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 alternate approach for the treatment of some types of cancer.

In the clinical setting, therapeutic use of blocking antibodies to either PD-L1 or PD-1 has been validated as an effective cancer treatment. Durable clinical responses in a wide variety of solid and hematologic malignancies has led to marketing approvals of the anti–PD-1 antibodies pembrolizumab, cemiplimab, and nivolumab, as well as the anti–PD-L1 antibodies atezolizumab, durvalumab, and avelumab.

2.2. Study Rationale

2.2.1. Scientific Rationale for Study Design

This open-label, nonrandomized study will evaluate the efficacy and safety of INCB086550, a first-in-class oral inhibitor of PD-L1, as initial immune checkpoint inhibitor therapy in participants with select solid tumors (ie, HCC, melanoma, NSCLC, RCC, and urothelial carcinoma) in which the efficacy of PD-(L)1 inhibitors has previously been established. INCB086550 selectively binds to PD-L1 with high affinity, thereby inhibiting the interaction of PD-L1 with PD-1. INCB086550 also reduces surface PD-L1 expression by inducing PD-L1 dimerization and subsequent internalization. Treatment with INCB086550 results in immune activation as evidenced in preclinical and/or clinical studies by increased nuclear factor of activated T cells activity and cytokine production. The primary endpoint of this study is ORR assessed by RECIST v1.1 as determined by the investigator. Secondary [redacted] endpoints include safety and tolerability, [redacted] changes observed with INCB086550 treatment.

2.2.2. Justification for Dose

INCB086550 will be administered orally in 21-day or 28-day cycles at a dose of 400 mg BID or lower.

The dose was selected based on clinical and safety data from the Phase 1 first in human dose escalation trial (INCB 86550-102). As of 30 OCT 2020, INCB086550 has been evaluated in

48 participants with advanced cancer in the Phase 1 study. Participants have been treated at 100 mg QD (n = 6), 200 mg QD (n = 3), 200 mg BID (n = 10), 400 mg QD (n = 4), 400 mg BID (n = 18), 800 mg QD (n = 1), and 800 mg BID (n = 6). INCB086550 has been generally well-tolerated, and no dose-limiting toxicities have been observed to date. The most frequently occurring TEAEs regardless of causality were decreased appetite (22.9%), fatigue (22.9%), nausea (22.9%), increased blood creatinine (20.8%), constipation (18.8%), diarrhea (18.8%), and increased lipase (16.7%). The most frequently occurring TEAEs assessed as related to INCB086550 by the investigator were nausea (16.7% each) and increased lipase (10.4%). Most TEAEs were Grade 1 or 2 in severity. Serious TEAEs occurred in 16 participants (33.3%). Serious TEAEs that occurred in more than 1 participant were asthenia (n = 2, 4.2%), immune-related peripheral neuropathy (n = 2, 4.2%), and pneumonia (n = 2, 4.2%). Serious TEAEs with a fatal outcome were dyspnea, intracranial hemorrhage, and cerebrovascular accident, each in 1 participant (2.1%). All serious TEAEs with a fatal outcome were assessed as not related to INCB086550 by the investigator. Refer to the INCB086550 IB for more detailed information.

Immune activation has been observed in participants who received doses of INCB086550 at 200 mg QD and higher. Participants whose drug exposure correlated with ≥ 80% inhibition of PD-L1 in an ex vivo whole blood assay had increases in immune markers of T-cell activation or exhaustion (Ki-67, PD-1, ICOS, and/or TIM3) and interferon-related cytokines in plasma (CXCL9, CXCL10, IFNγ). These findings align with those seen with anti–PD-(L)1 monoclonal antibodies.

As of 01 MAR 2021, 6 participants in Study INCB 86550-102 have had investigator-assessed objective responses per RECIST v1.1. The following responses have been observed: confirmed CR in a participant with squamous cell anal carcinoma (400 mg BID), unconfirmed PR in a participant with squamous cell anal carcinoma (800 mg BID), confirmed PR in a participant with MSI-H colorectal carcinoma (400 mg BID), confirmed PR in a participant with ovarian cancer (400 mg BID), unconfirmed PR in a participant with MSI-H colorectal carcinoma with neuroendocrine histology (400 mg BID), and confirmed PR in a participant with MSI-H colorectal carcinoma (400 mg BID).

The short half-life of INCB086550 ($t_{½}$ = 8.62 hours) facilitates the investigation of alternative study dosing schedules to optimize benefit/risk. Therefore, intermittent and/or step-down dosing schedules of INCB086550 may be investigated in specified cohorts. These alternative schedules will consist of INCB086550 administered at or below 400 mg BID daily, followed by a period of either no treatment (intermittent dosing) or lower dosing (step-down dosing). These cycles will then be repeated.

2.3. Benefit/Risk Assessment

Antibodies against PD-L1 or PD-1 can enhance or restore T-cell effector function, including cytokine production and cytolytic activity against tumor cells, as well as increase proliferation and/or infiltration of tumor-reactive CD8 T cells into established tumors. To date, immune checkpoint inhibitors have shown that they are generally well-tolerated in patients with many different types of solid tumors. Common treatment-related AEs that are related to the mechanism of action have occurred in several organ systems. Although many different types of serious irAEs have uniformly occurred with different immune checkpoint inhibitors, most irAEs

are successfully managed by following irAE management guidelines (Brahmer et al 2018, Haanen et al 2017), an adapted version of which is incorporated in the current study.

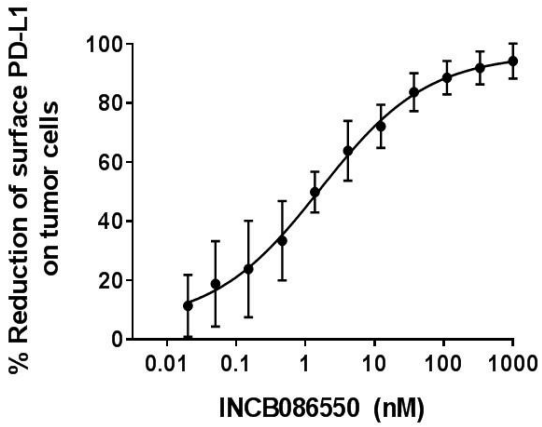
INCB086550 has a short half-life (8.62 hours after a single 100-mg dose) in comparison to monoclonal antibodies such as nivolumab, which has a terminal half-life of 26 days and receptor occupancy of 72% after 57 days (Fessas et al 2017). Thus, blockage of PD-(L)1 signaling is maintained for extended periods after interruption of monoclonal antibodies for irAEs. In this regard, the ability to more rapidly interrupt immune checkpoint blockade with INCB086550 along with the option to utilize standard therapy such as corticosteroids may improve irAE management options compared with immune checkpoint monoclonal antibodies.

Treatment with PD-(L)1 therapies causes irAEs in all organ systems evaluated. In fact, development of irAEs predicts clinical benefit for patients, and appropriate management of irAEs may provide maximum clinical benefit (Ricciuti et al 2019, Toi et al 2018, Xing et al 2019). Therefore, the assessment of outcomes for participants who experience AEs including the frequency and overall CTCAE grade will be key safety objectives in INCB086550 studies.

2.3.1. INCB086550 Preclinical Background

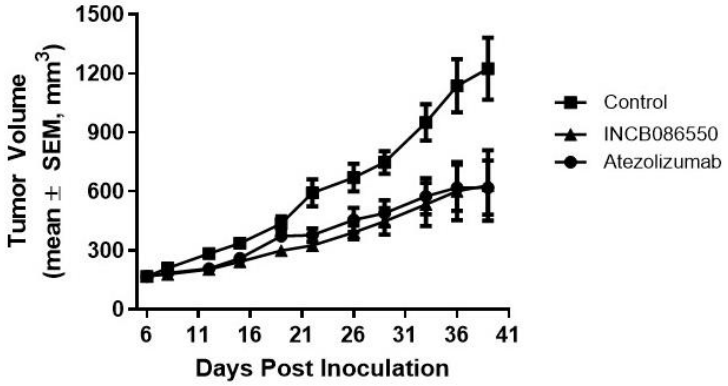
INCB086550 binds to, and reduces the cellular surface expression of PD-L1 with high affinity. For example, PD-L1 expression was decreased following treatment with INCB086550 in MDA-MB-231 breast cancer cells (which express high levels of PD-L1) with an IC_{50} of 2 nM. Similarly, INCB086550 reduced PD-L1 expression on IFNγ-stimulated human peripheral blood monocytes with an IC_{50} value of 12.2 nM (see Figure 2).

Figure 2: INCB086550 Reduces Tumor PD-L1 Expression



INCB086550 also appears as efficacious as atezolizumab in preclinical humanized mouse model studies. Figure 3 shows that INCB086550 and atezolizumab produce a similar reduction of tumor volume in humanized mice bearing MDA-MB-231 tumors.

Figure 3: MDA-MB-231 Humanized Mouse Model



More detailed information about the preclinical activity of INCB086550 may be found in the IB.

2.3.2. INCB086550 Nonclinical Safety Summary

In vitro studies were conducted to characterize the potential risks of inhibiting the PD-(L)1 interaction with INCB086550. These studies demonstrated that INCB086550 binds to human PD-L1 and disrupts the PD-L1/PD-1 interaction at nanomolar concentrations. Clinical studies with blocking antibodies to either PD-1 or PD-L1 have shown an induction of autoimmune responses. Given the mechanism of action of INCB086550, autoimmune AEs may be seen upon administration. Nonclinical pharmacology and toxicology studies have shown no adverse effects or target organ toxicity.

In the pivotal 28-day studies, INCB086550 was well tolerated at all tested doses up to 1000 mg/kg in rats and 715 mg/kg per day in monkeys. Findings associated with INCB086550 in rats were observed only at 1000 mg/kg per day and included decreased red blood cell mass (red blood cells, hemoglobin, and hematocrit), higher reticulocyte counts and red cell distribution, higher neutrophil and monocyte counts, and histiocytic infiltrates in the duodenum, jejunum, and/or ileum, and increased apoptosis/necrosis in the ileum in both males and females. The severity of these findings was limited to minimal to mild, and they were thus considered nonadverse. Treatment-related findings in monkeys were limited to emesis at doses ≥ 200 mg/kg per day with no evidence of target organ toxicity.

Consistent with pharmacodynamic data, INCB086550 reduced the growth of MDA-MB-231 in humanized NSG mice and increased the number of CD4 T cells after 28 days of treatment. INCB086550 induced statistically significant TGI compared to vehicle control. The dose levels of INCB086550 0.2, 2, and 20 mg/kg induced TGI of 40%, 49%, and 52%, respectively. A similar study was conducted using immunocompromised Balb/C nu/nu mice as the host, and no TGI was found. These results indicate that an intact immune system is required for the efficacy of INCB086550. Similar data were obtained using MC38 tumor cells that genetically overexpressed human PD-L1. INCB086550 induced statistically significant TGI compared with the vehicle control. The dose levels of INCB086550 2, 20, and 200 mg/kg induced TGI of 37%, 60%, and 71%, respectively. Consistent with the MDA-MB-231 xenograft data, INCB086550 did not inhibit MC38-hPD-L1 tumor growth in immunocompromised NSG mice. This indicates that an intact immune system is required for the efficacy of INCB086550. Dose-dependent tumor growth inhibition and PD-L1 reduction were observed. Accordingly, increasing numbers

of infiltrating CD8 T cells were observed after INCB086550 administration. Antitumor activity was abolished in immunocompromised animals for both preclinical mouse models, suggesting an immune-mediated mode of action.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of INCB086550 may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Table 7 presents the objectives and endpoints.

Table 7: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the ORR of participants treated with INCB086550.	ORR, defined as the percentage of participants with a best overall response of CR or PR confirmed by at least 1 repeat assessment ≥ 28 days later according to RECIST v1.1 as determined by the investigator.
Secondary	
To determine the efficacy of INCB086550 in participants with advanced solid tumors in respect to DCR.	DCR, defined as the percentage of participants with a best overall response of CR or PR confirmed by at least 1 repeat assessment ≥ 28 days later, or SD for ≥ 12 weeks, by investigator assessment per RECIST v1.1.
To determine the efficacy of INCB086550 in participants with advanced solid tumors in respect to DOR.	DOR, defined as the time from the earliest date of CR or PR confirmed by at least 1 repeat assessment ≥ 28 days later until the earliest date of disease progression by investigator assessment per RECIST v1.1, or death due to any cause, if occurring sooner than progression.
To evaluate the safety of INCB086550 in participants with advanced solid tumors.	Safety is determined by monitoring the frequency and severity of AEs, including the evaluation of laboratory tests, vital signs, and ECGs
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase 2, open-label, global, multicenter study designed to assess the clinical activity and safety of INCB086550 as initial immune checkpoint inhibitor therapy in participants with advanced selected solid tumors in which the efficacy of PD-(L)1 inhibitors has previously been established. Participants will be enrolled at 1 or more dose levels into disease-specific cohorts as indicated in Figure 1 and Section 5.1, with a safety/efficacy run-in analysis in up to 15 participants and a nonbinding interim futility analysis planned after approximately 50% of the participants in each cohort are evaluable for response using the RECIST evaluable population.

The primary endpoint is confirmed ORR as determined by the investigator using RECIST v1.1.

The study consists of 3 periods: screening, study drug treatment, and follow-up.

Eligible participants in a given dose level will receive INCB086550 either in continuous, intermittent, or step-down treatment schedules at or below 400 mg BID daily. For participants on BID treatment, study drug will be administered orally in the morning and evening, approximately 12 hours apart. For participants on QD treatment, study drug will be administered orally in the morning. Treatment cycles may be 28 days (see Table 3 and Table 4) or 21 days (see Table 5 and Table 6), and this will be specified for each dose level.

Treatment may be delayed for up to 28 days to allow for resolution of toxicity. The treating investigator should contact the medical monitor to discuss the case of any participant whose treatment has been interrupted for more than 28 days before restarting treatment with INCB086550. See Section 6 for additional details.

A maximum study treatment duration of 2 years is allowed. Participants who achieve a CR may discontinue INCB086550 after 4 additional cycles (with a minimum of 1 year of treatment) upon consultation with the medical monitor.

The follow-up period will begin once a participant has completed 2 years of study treatment or has met criteria for discontinuation from study drug. Participants will be evaluated for AEs (including irAEs) for 90 days after the last dose of study drug.

Once participants discontinue treatment, they will enter the follow-up period [redacted]. Participants who discontinue study treatment without experiencing disease progression will enter the follow-up period and continue to undergo tumor assessments according to the SoA (see Table 3, Table 4, Table 5, and Table 6) until they experience disease progression, the start of a new anticancer treatment, withdrawal of consent, lost to follow-up, the end of the study, or death.

[redacted] The analytes to be evaluated in the safety laboratory analyses are found in Table 17.

4.2. Overall Study Duration

The study begins when the first participant signs the ICF. The end of the study is defined as the date of the last visit of the last participant in the study. Participants completing treatment or prematurely discontinuing the study drug will be followed [redacted]

A participant is considered to have completed the study if he/she has completed all periods of the study [redacted]

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. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination, 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 or upon advice of the DMC. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study. The DMC will recommend termination of the study if warranted, as described in Section 5.6.

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 the 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. Men and women 18 years of age or older.
3. Measurable disease per RECIST v1.1.
4. ECOG performance status of 0 to 1 for all tumor types. Urothelial carcinoma allows ECOG of 0 to 2.
5. Histologically or cytologically confirmed disease-specific diagnosis as follows:
    a. Treatment-naïve, stage IV NSCLC (AJCC v8) in participants whose tumors express PD-L1 TPS $\geq$ 50% using the Dako PD-L1 IHC 22C3 assay and who have no known activating genomic aberrations that require targeted therapy (eg, EGFR, ALK, ROS, BRAF).

b. Locally advanced, and unresectable or metastatic UC of the renal pelvis, ureter, bladder, or urethra (including transitional cell and mixed transitional or nontransitional cell histologies) in participants who are cisplatin-ineligible, who are immune checkpoint inhibitor–naïve, and whose tumors express high PD-L1 (CPS ≥ 10) using the Dako PD-L1 IHC 22C3 assay.
Exception for UC: Previous systemic therapy for locally advanced and unresectable or metastatic UC is not allowed except for neoadjuvant or adjuvant chemotherapy if more than 12 months before disease recurrence.

c. Advanced HCC that is not amenable to curative surgery or local treatment in participants who have received at least 1 previous line of systemic therapy (ie, sorafenib or lenvatinib) or who were intolerant of sorafenib/lenvatinib treatment, have a Child-Pugh score of ≤ 6 (Child-Pugh A), and who are immune checkpoint inhibitor–naïve. Participants with HBV infection are required to be receiving effective antiviral therapy and have a viral load < 100 IU/mL at screening; participants with HCV must have no detectable HCV RNA after curative therapy. Participants with fibrolamellar and mixed hepatocellular/cholangiocarcinoma subtypes are not eligible.
Exception for HCC: Participants without access to prior systemic therapy (ie, sorafenib or lenvatinib).

d. Advanced or metastatic RCC with a clear cell component with or without sarcomatoid features in participants who have received prior systemic therapy for their disease (up to 2 previous regimens of a VEGF or mTOR inhibitor) and who are immune checkpoint inhibitor–naïve.
Exception for RCC: Participants without access to prior systemic therapy (ie, VEGF or mTOR inhibitors).

e. Unresectable stage III or IV melanoma (excluding ocular/uveal melanoma) in participants who are immune checkpoint inhibitor–naïve. BRAF V600 mutation status must be known.
Exception for melanoma: Participants may have received 1 prior line of therapy. This therapy could include previous treatment with BRAF/MEK inhibitors in participants with known BRAF V600 mutation or chemotherapy.

6. Willingness to avoid pregnancy or fathering children based on the criteria below (CTFG 2020).

   a. Men must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 190 days after the last dose of study drug (or longer as appropriate based on country-specific requirements) and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.

b. Women of childbearing potential must:

- have a negative serum pregnancy test at screening and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through 190 days after the last dose of study treatment. Additionally, monthly telephone visits should take place to check pregnancy status (which may include home pregnancy tests) during the period when contraception is mandatory (190 days after the last dose of study drug). Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
- refrain from donating oocytes from 30 days before the first dose of study drug until 190 days after the last dose.

c. Women of nonchildbearing potential (as defined in Appendix A) are eligible.

7. Participants must have radiologic documentation of disease progression after treatment with available therapies except for participants with NSCLC, who are required to be treatment-naïve.

5.2. Exclusion Criteria

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

1. Prior receipt of an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent, or treatment with an immune modulator (eg, CTLA-4, GITR, LAG3, TIM3, OX40, ICOS, IL2, 4-1BB, CAR-T).
2. Receipt of any anticancer therapy or participation in another interventional clinical study.

   Note: For RCC and HCC, the participant must not have received treatment within 21 days or 5 half-lives (whichever is longer) before the first administration of study drug.
3. Radiotherapy within 14 days of first dose of study treatment (28 days for pelvic radiotherapy or 6 months for thoracic region radiotherapy that is > 30 Gy).
4. Concomitant treatment with moderate and potent CYP3A4/CYP3A5 inhibitors or inducers (see Appendix E).

   Note: A washout period ≥ 5 half-lives before the first dose of INCB086550 is required for enrollment into the study for prior treatment with CYP3A4/CYP3A5 inhibitors/inducers.
5. Toxicity of prior therapy that has not recovered to ≤ Grade 1 or baseline (with the exception of anemia not requiring transfusion support and any grade of alopecia). Endocrinopathy, if well-managed, is not exclusionary and should be discussed with the medical monitor.
6. Participant has not recovered adequately from toxicities and/or complications from surgical intervention before starting study drug.
7. Participants with laboratory values at screening defined in Table 8.

Table 8: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	≤ 100 × 10^9/L
b	Hemoglobin	≤ 9 g/dL or < 5.6 mmol/L (transfusion is acceptable to meet this criterion)
c	ANC	≤ 1.5 × 10^9/L
Hepatic		
d	ALT	> 2.5 × institutional ULN For participants with HCC or liver metastases: > 5 × ULN
e	AST	> 2.5 × institutional ULN For participants with HCC or liver metastases: > 5 × ULN
f	Total bilirubin	≥ 1.5 × institutional ULN unless conjugated bilirubin ≤ ULN (conjugated bilirubin only needs to be tested if total bilirubin exceeds ULN). If there is no institutional ULN, then direct bilirubin must be < 40% of total bilirubin.
g	Alkaline phosphatase	≥ 2.5 × ULN. Note: Participants with 1) bone metastases and 2) no hepatic parenchymal metastases on screening radiographic examinations may enroll if the alkaline phosphatase is < 5 × ULN. Participants with 1) bone metastases and 2) hepatic parenchymal metastases on screening radiographic examinations may enroll if the alkaline phosphatase is < 5 × ULN only with medical monitor approval.
Renal		
h	Serum creatinine; or calculated CrCl[a]	Serum creatinine > 1.5 × institutional ULN; or CrCl < 50 mL/min for participants with creatinine levels < 1.5 × institutional ULN. For participants with UC or RCC, CrCl < 40 mL/min with creatinine levels < 1.5 × institutional ULN.
Coagulation		
i	INR or PT	> 1.5 × institutional ULN for participants not receiving anticoagulant therapy. For participants with HCC: > 2.3 × institutional ULN.
j	aPTT or PTT	> 1.5 × institutional ULN for participants not receiving anticoagulant therapy
k	Albumin	< 3 g/dL For participants with HCC or liver metastases: < 2.5 g/dL

[a] The Cockcroft and Gault equation (1976): CrCl = {([140–age] × weight in kg) / (72 × serum creatinine)} × 0.85 (if female).

8. Active malignancy of a type not included in the study population requiring treatment.

   Note: Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, in situ cervical cancer, or early-stage endometrial cancer.

9. Active autoimmune disease requiring systemic immunosuppression in excess of physiologic maintenance doses of corticosteroids (> 10 mg of prednisone or equivalent).

10. Evidence of interstitial lung disease or active, noninfectious pneumonitis.

11. Untreated or known active CNS metastases and/or carcinomatous meningitis.

    Note: Participants with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 28 days before the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases or CNS edema, and have not required steroids for at least 7 days before the first dose of study drug.

12. With the exception of participants with HCC, known active HAV, HBV, or HCV infection, as defined by elevated transaminases with the following serology: positivity for HAV IgM antibody, anti-HCV, anti-HBc IgG or IgM, or HBsAg (in the absence of prior immunization).

    Note: For participants with cleared prior HBV infection: HBV prophylaxis should be considered per investigator discretion. Monitor for HBV reactivation every 3 cycles by performing HBV viral load and HBsAg serology test. Additional viral serologic testing may be performed at the investigator's discretion.

    Note: Participants with no prior history of HBV infection who have been vaccinated against HBV and who have a positive antibody against HBsAg as the only evidence of prior exposure may participate in the study.

    Note: Hepatitis C antibody–positive participants who received and completed treatment for hepatitis C that was intended to eradicate the virus may participate if HCV RNA levels are undetectable.

13. Active infection requiring systemic therapy.

14. Receipt of systemic antibiotics within 28 days of first dose of study treatment.

15. Probiotic usage during screening and throughout the study treatment period.

16. Participants who are known to be HIV-positive.

17. Participants with impaired cardiac function or clinically significant cardiac disease:

    a. New York Heart Association Class III or IV cardiac disease, including preexisting clinically significant ventricular arrhythmia, congestive heart failure, or cardiomyopathy.
    b. Unstable angina pectoris ≤ 6 months before study participation.
    c. Acute myocardial infarction ≤ 6 months before study participation.
    d. Other clinically significant heart disease (ie, ≥ Grade 3 hypertension, history of labile hypertension, or poor compliance with an antihypertensive regimen) must have recovered (to baseline or ≤ Grade 1) from toxicity associated with prior treatment.

18. History or presence of an ECG finding that, in the investigator's opinion, is clinically meaningful. Screening QTcF interval > 450 milliseconds is excluded; in the event that a single QTc is > 450 milliseconds, the participant may enroll if the average QTc for the 3 ECGs is ≤ 450 milliseconds. For participants with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be ≤ 340 milliseconds if JTc is used in place of the QTc. Participants with left bundle branch block are excluded.

Note: Participants with QTc prolongation due to pacemaker may enroll if the JTc is normal (≤ 340 milliseconds) and medical monitor approval is granted.

19. Female participant is pregnant or breastfeeding within the projected duration of the study, starting with the screening visit through the 90-day safety follow-up, or male participant is expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 100 days after the last dose of study treatment.
20. Has received a live vaccine within 90 days of the planned start of study drug.

    Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, some zoster, yellow fever, rabies, BCG, and typhoid vaccines. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live-attenuated vaccines and are not allowed.
21. Current use of a prohibited medication as described in Section 6.6.3.
22. Life expectancy < 3 months.
23. Known hypersensitivity or severe reaction to any component of study drug or formulation components.
24. History of organ transplant, including allogeneic stem cell transplantation.
25. Presence of a gastrointestinal condition that may affect drug absorption.
26. 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.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants will refrain from consuming Seville oranges, pomegranates, grapefruit, pomelos, exotic citrus fruits, grapefruit hybrids, and juice containing these restricted fruits from 72 hours before the first dose of study drug and throughout the study.

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. This could be because the participant does not meet the eligibility criteria as described in Section 5.1 and Section 5.2 or for any other reason. At a minimum, the following information must be collected and entered into the eCRF: demography, screen failure details, and eligibility criteria. Information on SAEs that occur after consent should be submitted to the sponsor.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time.

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error. Additionally, a participant who fails screening may

repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Replacement of Participants

No participants will be replaced at any time during this study.

5.6. Data Monitoring Committee

This study will use a DMC to monitor safety at the planned analyses. The DMC will make recommendations to the Sponsor clinical team regarding steps to ensure both participant safety and the continued ethical integrity of the trial. Also, the DMC may review interim trial results (see Section 10.5), consider the overall risk and benefit to trial participants, and recommend if the trial should continue in accordance with the Protocol. Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the members are described in the DMC charter. Requirements for and proper documentation of DMC reports, minutes, and recommendations are also described in the DMC charter. The DMC charter will be reviewed and approved by all the DMC members.

6. STUDY TREATMENT

6.1. Study Treatment Administered

Table 9 presents the study treatment information. See Appendix C for instructions for participant handling of study drug.

Table 9: Study Treatment Information

Study treatment name:	INCB086550
Mechanism of action:	PD-L1 inhibitor
Dosage formulation:	Tablet
Unit dose strength/ dosage level:	100 mg and 400 mg
Route of administration:	Oral
Administration instructions	• Administered orally in 100 mg or 400 mg tablets. • Study drug may be taken QD or BID on the days specified of a 21-day or 28 day cycle for a given dose level. – QD doses are taken in the morning – BID doses are taken in the morning and evening approximately 12 hours apart. If the morning or evening dose is missed by more than 4 hours, then that dose should be skipped, and the next scheduled dose should be taken at the usual time. • INCB086550 should be administered with water. • Participants should fast for at least 2 hours before and at least 1 hour after each dose. [redacted] • INCB086550 tablets may be crushed and administered with water, apple juice, applesauce, or yogurt. Instructions for this administration are detailed in the Pharmacy Manual.
Packaging and labeling:	INCB086550 will be provided as 35 tablets per bottle. Each container will be labeled as required per country requirements.
Storage:	Must be refrigerated and protected from light. Store at 2°C-8°C (36°F-46°F).
Status of treatment in participating countries:	Investigational

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:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Participant use of the study drug including tablet counts from each supply dispensed.
- Return of study drug to the investigator or designee by participants.

The investigational product must be used only in accordance with the Protocol. The investigator 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 shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional SOPs. If local procedures mandate on-site destruction of investigational supply, 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.

Further guidance and information for the final disposition of unused study treatments are provided in the Study Reference Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to open-label study treatment using IRT. Full details will be provided in the IRT Study Reference Manual. Study drug will be dispensed at the study visits summarized in the SoA (see Table 3, Table 4, Table 5, and Table 6). Returned study drug should not be redispensed to the participants.

6.4. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with INCB086550 will be calculated by the sponsor based on the drug accountability (eg, tablet counts) documented by the site staff and monitored by the sponsor/designee. Participants will be instructed to bring all unused study drug with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

6.5. Dose Modifications

Interruptions and modifications to the study treatment regimen are allowed per Protocol. The occurrence of toxicities (related or unrelated to study drug) will guide decisions for treatment interruptions, modifications, or discontinuation for individual participants.

Investigators should contact and discuss dose modifications with the medical monitor.

Intraparticipant dose escalations will not be permitted during the course of the study.

6.5.1. Management of Immune-Related Adverse Events

An AE of a potential immunologic etiology or an irAE may be defined as an AE consistent with an immune phenomenon associated with drug exposure after all other etiologies have been eliminated. Immune-related AEs may be expected based on the nature of INCB086550, its mechanism of action, and reported experience with other immunotherapies. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, autoimmune, toxic, or other etiologic causes before categorizing an AE as an irAE. The investigator should promptly notify the sponsor (or designee) about participants who develop an irAE ≥ Grade 2.

Participants, who have irAEs that resolve to ≤ Grade 1 within 14 days, may be rechallenged at the starting dose or with a dose reduction. Continuation, withholding, dose modification, or discontinuation of INCB086550 will depend on severity of the irAE and affected organ/organ system and should be discussed with the medical monitor. Any irAEs ≥ Grade 3 that require permanent discontinuation of INCB086550 per Table 10 may only be rechallenged with approval of the medical monitor. Elevations in amylase or lipase that are ≥ Grade 3 do not require dose interruption or reduction if the participant is asymptomatic or if the elevation is clinically insignificant and has been discussed with the medical monitor.

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested measures for the management of irAEs are outlined in Table 10. For each AE, attempts should be made to rule out other causes, including but not limited to metastatic disease, bacterial infection, or viral infection that might require specific supportive care.

Management guidance for irAEs not detailed elsewhere in the Protocol should follow the ASCO Clinical Practice Guideline or ESMO Clinical Practice Guidelines (Brahmer et al 2018, Haanen et al 2017).

Table 10: Immune-Related Adverse Events Management Guidelines for INCB086550

irAE	CTCAE v5 Grade	Guidance for Restarting INCB086550	Monitoring and/or Supportive Care
Pneumonitis	Grade 1	Continue INCB086550 if asymptomatic. Withhold INCB086550 given radiographic evidence of pneumonitis progression. May resume with radiographic evidence of improvement or resolution.	• Monitor as appropriate (CT, spirometry/DLCO, history and physical examination, pulse oximetry, chest x-ray). • If no improvement, treat as Grade 2.
	Grade 2	Withhold INCB086550 until resolution to ≤ Grade 1.	• Administer systemic corticosteroid (prednisone 1-2 mg/kg or equivalent) with taper. • May consider empiric antibiotics. • Consider bronchoscopy with bronchoalveolar lavage. • Monitor as appropriate (history and physical examination, pulse oximetry, chest x-ray). • If no improvement within 2-3 days, treat as Grade 3.
	Grade 3, Grade 4, or recurrent Grade 2	Permanently discontinue INCB086550.	• Administer IV methylprednisolone 1-2 mg/kg or equivalent with taper. • Administer empiric antibiotics. • If no improvement after 2 days, may add infliximab 5 mg/kg, mycophenolate mofetil IV 1 g twice daily, IV immunoglobulin for 5 days, or cyclophosphamide. • Pulmonary and infectious disease consults, if necessary. • Bronchoscopy with bronchoalveolar lavage ± transbronchial biopsy. *Note:* If clinical presentation is consistent with pneumonitis, transbronchial biopsy is not needed.

Table 10: Immune-Related Adverse Events Management Guidelines for INCB086550 (Continued)

irAE	CTCAE v5 Grade	Guidance for Restarting INCB086550	Monitoring and/or Supportive Care
Diarrhea/colitis	Grade 1	Continue INCB086550.	• Monitor as appropriate. • Provide supportive care (hydration, electrolyte replacement, dietary changes). • Consider gastroenterology consult for prolonged event.
	Grade 2 or Grade 3	Withhold INCB086550 until resolution to ≤ Grade 1.	Grade 2: • If clinically indicated, administer systemic corticosteroids (prednisone 1 mg/kg or equivalent) with taper. • Consider symptomatic treatment with antidiarrheal if infection has been ruled out. Grade 3: • Administer systemic corticosteroids (prednisone 1-2 mg/kg or equivalent) with taper. • If no improvement after 3-5 days, IV corticosteroid with taper or infliximab. • Gastroenterology consult for additional workup as appropriate.
	Grade 4	Permanently discontinue INCB086550.	• Administer IV methylprednisolone 1-2 mg/kg or equivalent with taper. • If no improvement after 2-3 days, consider infliximab 5-10 mg/kg. • Gastroenterology consult for additional workup as appropriate.

Table 10: Immune-Related Adverse Events Management Guidelines for INCB086550 (Continued)

irAE	CTCAE v5 Grade	Guidance for Restarting INCB086550	Monitoring and/or Supportive Care
Hepatitis (AST/ALT increased and/or total bilirubin increased)	Grade 1	Continue INCB086550.	• Repeat laboratory measurements 1-2 times/week until return to baseline. • Provide supportive care for symptoms.
	Grade 2 or Grade 3 lasting ≤ 10 days	Withhold INCB086550 until resolution to ≤ Grade 1.	• Repeat laboratory measurements every 3 days until return to baseline. • If elevations persist after 3 days or symptomatic, administer systemic corticosteroids (prednisone 0.5-1 mg/kg or equivalent) with taper. • **Infliximab should NOT be used.**
	Grade 3 lasting > 10 days or Grade 4	Permanently discontinue INCB086550.	• Repeat laboratory measurements every 1-2 days until return to baseline. • Administer IV methylprednisolone 1-2 mg/kg or equivalent with taper. • If corticosteroid refractory or elevations persist after 3 days, consider mycophenolate mofetil or azathioprine. • **Infliximab should NOT be used.** • Hepatology consult for additional workup, as appropriate.
Dermatitis	Grade 1 or Grade 2	Continue INCB086550.	• Consider dermatology consult. • Supportive care with topical emollients, oral antihistamines. • Administer topical corticosteroid as needed. • If no improvement with topical corticosteroid, consider systemic (oral) corticosteroid.
	Grade 3	Withhold INCB086550 until resolution to ≤ Grade 1.	• Dermatology consult. • Administer IV methylprednisolone 1-2 mg/kg or equivalent with taper. • Monitor for progression to severe cutaneous adverse reaction (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and system symptoms/drug-induced hypersensitivity syndrome).
	Grade 4	Permanently discontinue INCB086550.	
Nephritis or renal dysfunction (creatinine increased)	See Table 12 for immune-related nephritis and renal dysfunction AE management guidelines.		

Table 10: Immune-Related Adverse Events Management Guidelines for INCB086550 (Continued)

irAE	CTCAE v5 Grade	Guidance for Restarting INCB086550	Monitoring and/or Supportive Care
Diabetes mellitus	Grade 1 or Grade 2	Continue INCB086550.	• Endocrine consult, especially for Type 1 diabetes mellitus. • Oral antihyperglycemic therapy ± insulin for new onset Type 2 diabetes mellitus, as appropriate. • Insulin for Type 1 diabetes mellitus. • Titrate therapy to achieve glucose control.
	Grade 3 or Grade 4	Withhold INCB086550 until glucose control is achieved and ≤ Grade 1.	
Hypothyroidism	Grade 1	Continue INCB086550.	• Monitor TSH, FT4 as appropriate.
	Grade 2	Consider withholding until resolution to ≤ Grade 1.	• Endocrine consult for Grade 3 or Grade 4, consider for Grade 2. • Thyroid hormone replacement as appropriate. • Monitor TSH, FT4 while titrating hormone replacement and once adequately resolved.
	Grade 3 or Grade 4	Withhold INCB086550 until resolution to ≤ Grade 1 with appropriate thyroid hormone supplementation.	
Hyperthyroidism	Grade 1	Continue INCB086550.	• Monitor TSH, FT4 as appropriate.
	Grade 2	Consider withholding until resolution to ≤ Grade 1.	• Consider endocrine consult. • Beta-blocker (eg, atenolol, propranolol) for symptomatic relief.
	Grade 3 or Grade 4	Withhold INCB086550 until resolution to ≤ Grade 1 with appropriate therapy.	• Endocrine consult. • Prednisone 1-2 mg/kg or equivalent with taper only for severe symptoms of concern for thyroid storm. • Beta-blocker (eg, atenolol, propranolol) for symptomatic relief. • Consider potassium iodide or thionamide (methimazole or propylthiouracil).
Myocarditis	Any Grade	Permanently discontinue INCB086550.	• Administer high-dose corticosteroids initiated rapidly (oral or IV depending on symptoms). • Manage cardiac symptoms according to American College of Cardiology/American Heart Association. • Cardiology consult. • May offer immediate transfer to a coronary care unit for participants with elevated troponin or conduction abnormalities. • In participants without an immediate response to high-dose corticosteroids, may offer early institution of cardiac transplant rejection doses of corticosteroids (eg, methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin.

Table 10: Immune-Related Adverse Events Management Guidelines for INCB086550 (Continued)

irAE	CTCAE v5 Grade	Guidance for Restarting INCB086550	Monitoring and/or Supportive Care
Hypophysitis or adrenal insufficiency	Grade 1 or Grade 2	Consider withholding until resolution to ≤ Grade 1.	• Endocrine consult. • Administer systemic corticosteroids (with taper) and hormone replacement as clinically indicated.
	Grade 3 or Grade 4	Withhold INCB086550 until resolution to ≤ Grade 1.	
Nervous system disorders	Grade 1	Continue INCB086550.	• Neurologic consult • Monitor closely for any symptom progression.
	Grade 2	Withhold INCB086550 until resolution to ≤ Grade 1.	• Neurologic consult and workup including MRI. Consider EMG, lumbar puncture, and CSF analysis. • Administer supportive care and corticosteroids. • Monitor closely for any symptom progression.
	Grade 3	Withhold INCB086550 until resolution to ≤ Grade 1 ***OR*** Permanently discontinue INCB086550.	• Neurologic consult and workup including MRI. Consider EMG, lumbar puncture, and CSF analysis. • Administer supportive care and corticosteroids. • Continuation, withholding, or discontinuation of INCB086550 will depend on severity of irAE and affected organ/organ system. Restarting participants after Grade 3 nervous system AEs requires medical monitor approval.
	Grade 4	Permanently discontinue INCB086550.	• Neurologic consult and workup including MRI. Consider EMG, lumbar puncture, and CSF analysis. • Administer supportive care and/or corticosteroids.
Other irAEs	Grade 1	Continue INCB086550.	• Administer supportive care and/or corticosteroid for symptoms. • Continuation, withholding, or discontinuation of INCB086550 will depend on severity of irAE and affected organ/organ system. **Investigator must discuss with medical monitor**. • Consider relevant consults, as appropriate.
	Grade 2	Continue INCB086550 ***OR*** withhold INCB086550 until resolution to ≤ Grade 1	
	Grade 3	Withhold INCB086550 until resolution to ≤ Grade 1	
	Grade 4	Permanently discontinue INCB086550.	

CSF = cerebrospinal fluid; EMG = electromyography; FT4 = free thyroxine; TSH = thyroid-stimulating hormone.

6.5.2. Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug

Dose interruptions and modifications of INCB086550 may occur for participants during the study treatment period. The short half-life of INCB086550 (8.62 hours after a single 100 mg dose) may improve management options for participants who experience irAEs, unobtainable with immune checkpoint monoclonal antibodies, which possess long half-lives. Management guidelines for AEs requiring dose modifications are described for general hematologic and nonhematologic toxicities that are not thought to be immune-related in Table 11. Decisions regarding dose interruptions of INCB086550 should be made using clinical judgment of the investigator, taking into account the possible relatedness of the AE to the study drug and the participant's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-interruption/discontinuation rules. Participants may resume treatment as per management guidelines if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further treatment and participation in the study. Treatment with INCB086550 may be delayed for up to 28 days to allow for resolution of toxicity. The treating investigator should contact the medical monitor to discuss the case of any participant whose treatment has been interrupted for more than 28 days before restarting treatment with INCB086550.

Dose interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, subject vacation, holidays). Participants should be placed back on study therapy within 4 weeks (ie, 28 days) of the scheduled interruption, unless otherwise discussed with the medical monitor. The reason for interruption should be documented accordingly.

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment. Additional unscheduled visits with CBC may be performed.

Table 11: Non–Immune-Related Adverse Events Dose Modification Guidelines

CTCAE Severity	Suggested Modification
Hematological toxicities	
CTCAE Grade 1 or Grade 2	Continue INCB086550 treatment at the discretion of the investigator.
CTCAE Grade 3	• Restart when toxicity resolves to baseline or ≤ Grade 1. • **First occurrence:** Restart at same dose or reduce dose by 1 dose level at the discretion of the investigator after discussion with the medical monitor. • **Second occurrence:** Restart at reduced dose (if not already).
CTCAE Grade 4	Permanently discontinue study drug or discuss with medical monitor if treatment algorithm for CTCAE Grade 3 events (above) is appropriate.
Nonhematological toxicities	
All Grades	• For irAEs, follow the guidelines in Table 10. Permanently discontinue treatment for: • Any liver function abnormalities that meet the definition of Hy's law. • Encephalopathy of any grade.
CTCAE Grade 1 or 2	Continue treatment and initiate supportive care at the discretion of the investigator EXCEPT: • Permanently discontinue treatment for ≥ Grade 2 ocular toxicity.
CTCAE ≥ Grade 3	Permanently discontinue study treatment for any ≥ Grade 3 nonhematologic toxicity EXCEPT: • Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. • Laboratory abnormalities ≥ Grade 3 without associated clinically significant signs or symptoms. • Nondesquamating rash ≥ Grade 3 that resolves within 48 hours with standard treatment. Grade 3 rash in the absence of desquamation, without mucosal involvement, and not requiring systemic steroids that resolves to ≤ Grade 1 in ≤ 14 days. • Grade 3 fatigue < 1 week. • Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours. – For ≥ Grade 3 events that do not require permanent discontinuation, the following guidelines should be used: • Restart when toxicity resolves to baseline or ≤ Grade 1. • **First occurrence:** Restart at same dose or reduce dose by 1 dose level at the discretion of the investigator after discussion with the medical monitor. • **Second occurrence:** Restart at reduced dose (if not already). • **Third occurrence:** Permanently discontinue study drug.

INCB086550 is an inhibitor of the creatinine transporter OCT2 (in vitro IC_{50} of 2.6 µM). Creatinine increases observed during treatment with INCB086550 may be due to immune-mediated nephritis, inhibition of the OCT2 transporter, or may be unrelated to drug administration. Work-up should begin early and a nephrology consult considered. Assessment and management of INCB086550 should consider the relative increase in creatinine from baseline, and timing of the increase. Guidelines for continuing or withholding INCB086550 treatment and the timing for repeat chemistry laboratory studies are presented in Table 12.

Table 12: Management and Evaluation of Increased Creatinine

CTCAE v5.0 Grade	Guidance for Restarting INCB086550	Monitoring and/or Supportive Care
Relative increase of 1 CTCAE Grade in Cycle 1 (If baseline was within normal range, a change to Grade 1, or if Grade 1 at baseline, a change to Grade 2).	Continue INCB086550 and recheck chemistry labs in 48 hours. If creatinine is stable and there is no further increase in 48 hours, INCB086550 may be continued and labs checked in 48-72 hours. If creatinine increases within 48 hours, withhold INCB086550 and recheck chemistry labs in 48 hours. INCB086550 treatment may resume when creatinine returns to Grade 1 or baseline.	• Evaluate for alternative etiologies (eg, IV contrast, fluid status) and recheck labs in 48 hours.
Grade 1 (> ULN – 1.5 × ULN)	Continue INCB086550.	• Evaluate for alternative etiologies (eg, IV contrast, fluid status).
Grade 2 (> 1.5 × ULN – 3.0 × ULN)	If creatinine was Grade 1 at baseline, INCB086550 may be continued and labs checked in 48 hours. If creatinine is stable and there is no further increase in 48 hours, INCB086550 may be continued and labs checked in 48-72 hours. If creatinine increases within 48 hours, withhold INCB086550 and recheck chemistry labs in 48 hours. INCB086550 treatment may resume when creatinine returns to Grade 1 or baseline. If creatinine was within normal range at baseline, withhold INCB086550 until resolution to ≤ Grade 1.	• Consult nephrology. • Evaluate for alternative etiologies (eg, IV contrast, fluid status). • Administer prednisone 0.5-1 mg/kg or equivalent with appropriate taper.
Grade 3 (> 3.0 × ULN – 6.0 × ULN), Grade 4 (> 6.0 × ULN), or persistent Grade 2	Permanently discontinue INCB086550.	• Consult nephrology. • Evaluate for alternative etiologies (eg, IV contrast, fluid status). • Administer prednisone 1-2 mg/kg or equivalent with appropriate taper. • If elevations persist for > 3 days, consider mycophenolate.

6.5.3. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable toxicity not caused by the underlying disease will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- The occurrence of an AE that is related to study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.

  - Adverse events requiring treatment discontinuation are found in Table 10 and Table 11.

- A persistent AE requiring a delay of therapy for more than 4 weeks (ie, 28 days) unless a greater delay has been approved by the sponsor.

See Section 7 for discontinuation procedures.

6.5.4. Treatment After Initial Evidence of Radiologic Evidence of Disease Progression

Immunotherapeutic agents such as INCB086550 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows PD, tumor assessment should be repeated ≥ 4 weeks later to confirm PD, with the option of continuing treatment as described in the following text while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared with the initial scan demonstrating PD, treatment may be continued according to the treatment calendar. If repeat imaging confirms PD, participants will be discontinued from study treatment. In determining whether the tumor burden has increased or decreased, investigators should consider all target lesions as well as nontarget lesions.

When feasible, participants should not be discontinued until progression is confirmed; however, the decision to continue study treatment after the first evidence of disease progression is at the investigator's discretion based on the clinical status of the participant as described in Table 13.

Participants may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.
- Absence of rapid PD.
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

Table 13: Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments every 8 weeks	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments every 8 weeks	May restart study treatment if condition has improved and/or is clinically stable per investigator's discretion

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 28 days before the first dose of study drug and 30 days after the last dose of study drug, or until the participant begins a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered more than 30 days after the last dose of study drug should be recorded for SAEs as defined in Section 9.3. 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.

6.6.1. Permitted Medications and Procedures

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator, in keeping with the community standards of medical care, except those specifically defined as prohibited (see Section 6.6.3). All concomitant medications will be recorded in the eCRF, including all prescription and over-the-counter medications, herbal supplements, and IV medications and fluids. If changes occur during the study, documentation of drug regimen, frequency, route, and date may also be included in the eCRF.

Use of prophylactic growth factors should be based on ASCO or ESMO guidelines for the use of WBC growth factors (Crawford et al 2010, Smith et al 2015) and the investigator's clinical judgment. Bisphosphonates are allowed while participants are receiving study treatment.

6.6.2. Restricted Medications and Procedures

6.6.2.1. P-glycoprotein Substrates

INCB086550 is an inhibitor of P-gp and BCRP. Concomitant medications that are P-gp substrates with a narrow therapeutic index (eg, apixaban, colchicine, cyclosporine, dabigatran, digoxin, edoxaban, rivaroxaban, and tacrolimus) should be administered with caution and INCB086550 administration should be separated by a least 6 hours before or after the administration of the P-gp substrate.

6.6.2.2. Metformin

INCB086550 is an inhibitor of the creatinine transporter OCT2. Metformin is an OCT2 substrate and should be administered with caution. Careful monitoring of blood glucose levels should be performed when metformin is administered as a concomitant medication.

6.6.2.3. Stomach Acid–Reducing Medications

Since the impact on INCB086550 absorption is unknown, stomach acid–reducing medications such as proton pump inhibitors and H_2-receptor blockers should be used with caution. For participants who have a requirement for stomach acid–reducing medication, H_2-receptor blockers should be considered rather than proton pump inhibitors. H_2-receptor blockers should be administered > 2 hours after INCB086550 administration.

6.6.2.4. Systemic Steroids

Systemic steroids may be used at doses ≤ 10 mg/day prednisone or equivalent with medical monitor approval. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.3. Prohibited Medications and Procedures

Medications or vaccinations specifically prohibited in the exclusion criteria (see Section 5.2) are not allowed during the study. If there is a clinical indication for one of these medications or vaccinations specifically prohibited during the study, discontinuation from study treatment may be required. The investigator should discuss any questions regarding this with the medical monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the sponsor, and the participant.

Participants are prohibited from receiving the following therapies during the screening and treatment periods of this study, unless otherwise indicated:

- Any anticancer medications, including chemotherapy or biologic therapy other than study treatment.
- Moderate and potent CYP3A4/CYP3A5 inducers and inhibitors.
  - A washout period ≥ 5 half-lives before the first dose of INCB086550 is required for enrollment into the study for prior treatment with CYP3A4/CYP3A5 inhibitors/inducers.

- Any immunological-based treatment for any reason from screening through the 30-day follow-up visit.

  Note: Completed adjuvant therapy (eg, vaccines) with medical monitor approval, inhaled or topical steroids, systemic steroids (eg, prednisone or equivalents) at doses ≤ 10 mg/day, and immunosuppressants are allowed for the treatment of irAEs as described in Table 10 or as prophylaxis for contrast allergy for imaging procedures.

  Note: Allergy shots may be permitted after consultation with the medical monitor.
- Investigational agents other than study treatment. Use of such medications from screening through the follow-up period is strictly prohibited.
- Concomitant radiation therapy. A washout period of 14 days is required before the first dose of INCB086550.

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with the medical monitor. The participant must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression.
- Live vaccines within 90 days of the first dose of study treatment and while participating in the study through 90 days after the last dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, some zoster, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.
- A 28-day washout period before the first dose of INCB086550 is required for systemic antibiotics.
- Probiotic usage during screening and while receiving study treatment.
- Participants may receive other medications that the investigator deems to be medically necessary.

6.6.4. COVID-19

Information on COVID-19 pandemic mitigation strategies and instructions can be found in Appendix F.

6.7. Treatment After the End of the Study

Following treatment discontinuation, participants will not be eligible to receive further study drug treatment as part of this study. Participants should remain on the study and continue in follow-up accordingly, as outlined in Sections 8.8 and 8.9.

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:

- The participant becomes pregnant.
- Disease progression (see Section 8.2).
- 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. Participants may choose to discontinue study treatment and remain in the study [redacted].
- 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 6.5.3.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- If, during the course of the study, a 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 drug/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 EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 3, Table 4, Table 5, and Table 6. The last date of the last dose of study drug and the reason for discontinuation of study drug will be recorded in the eCRF.

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 EOT visit should be performed.

- The status of the participant should be updated to EOT in the IRT.
- After the EOT visit, participants will remain in the study [redacted] and will be followed for safety and AEs per Sections 8.9 and 9.

Discontinuation from study drug does not mean withdrawal from the study, and remaining study procedures should be completed as indicated by the study Protocol.

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), 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/efficacy assessments according to Table 3, Table 4, Table 5, and Table 6.

7.2. Participant Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

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.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See Table 3, Table 4, Table 5, and Table 6 for data to be collected at the time of study discontinuation 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 he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- 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, he/she 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 his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A 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. 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 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 or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. 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 or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is enrolled in the study (Cycle 1 Day 1). 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.

Procedures conducted as part of the participant's routine clinical management (eg, blood count, imaging study) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 28 days of Cycle 1 Day 1). For participants who are enrolled in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before enrollment into the study will be used to determine eligibility. Treatment should start as soon as possible but within 7 days after the date of enrollment registration.

See Sections 5.4 and 5.5 for information regarding screen failures and replacement of participants, respectively.

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site staff should contact the IRT to obtain the participant ID number during screening. Upon determining that the participant is eligible to participate in the study, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted on Day 1 of each cycle to update the study drug supply. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Dosing Diary and Patient Information Cards

Participants will be provided with a reminder card and dosing diary at each visit, as specified in Table 3, Table 4, Table 5, and Table 6. The reminder card and dosing diary will indicate the date/time of the next visit and will also remind the participants when they should not take their morning dose of study drug and when they should arrive for their visit on days of blood draws for [redacted] safety evaluation. The dosing diary will have an area on which the date and time of the last dose taken (from the previous evening) and the time and contents of their last meal before the visit should be recorded. Participants will receive a participant information card that lists common irAE symptoms and reminds them to report any symptoms to their study physician immediately.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include year of birth/age, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment within the last 5 years that are considered to be clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's malignancy under study, including date of diagnosis, initial and current cancer stage, tumor histology, relevant disease characteristics, and prior treatments, including systemic treatments, radiation, and surgical procedures, will be recorded.

8.1.5.3. Baseline Biomarker Documentation

Information regarding microsatellite instability and/or DNA mismatch repair deficiency, PD-L1 expression, HPV status, KRAS, NRAS, ALK, EBV, EGFR, ER/PR, HER2, ROS1, BRAF, and other tumor markers should be recorded in the eCRF.

8.2. Efficacy Assessments

Objective assessment of disease status is required, using the evaluations by RECIST v1.1 (Eisenhauer et al 2009). The investigator's assessment will be used to determine responses and will be recorded in the eCRF.

Efficacy baseline assessments will be performed at screening, and further efficacy assessments will be performed throughout the study at the intervals defined in Table 3, Table 4, Table 5, and Table 6. Cycle delays should not interrupt the 8-week scan interval; thus, tumor assessments and cycles may become out of sync. Participants who discontinue treatment for reasons other than disease progression should continue to have disease assessments performed and recorded every 8 weeks until they have experienced disease progression or started a subsequent anticancer treatment.

8.2.1. Tumor Imaging by RECIST v1.1

A local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for participant management; radiological and clinical assessments (including photographs) will be collected for retrospective analysis by a central vendor. The same imaging technique should be used for a participant throughout the study. The baseline scan must be a contrast CT or MRI, except in circumstances in which there is a contrast allergy or with medical monitor approval. The CT component of a positron emission tomography/CT scan may use higher energy and thinner slices. This allowance must recorded accordingly in the eCRF and the same method must be used for all subsequent scans. Images of the chest, abdomen, and pelvis are required for all participants. Additional imaging of anatomical sites (eg, head, neck, brain) should be performed as applicable for the malignancy under study. Based on the methods of assessment guidelines from the RECIST Working Group, participants with skin lesions should have documentation of their skin lesions by color photography, which would include a ruler to

estimate the size of the lesion. Therefore, per RECIST guidance, participants with target lesions in the skin that cannot be followed by standard imaging (CT/MRI) should have a photograph taken (with caliper measurement) to follow their disease. If a participant does not have other target lesions that can be followed by CT/MRI, photography is required.

A CT or MRI scan of the brain will be performed at screening if there are signs or symptoms suggesting that the participant has disease involvement in the CNS.

Bone scans will be performed at baseline for all participants. Participants with positive bone scans at baseline will be followed with additional scans performed at the same schedule and interval as CT/MRI. For participants with new symptoms suggestive of osseous metastasis, a bone scan should be obtained. Additionally, a plain x-ray evaluation should be obtained for symptomatic sites with negative bone scan evaluations.

8.2.1.1. Baseline Assessment During Screening

Initial tumor imaging must be performed within 28 days before the first dose of study treatment. The site study team must review prestudy reports and images to confirm that the participant has measurable disease per RECIST v1.1. Participants with a single target lesion that has been previously irradiated or subjected to other local-regional therapy may be enrolled if the target lesion is considered measureable per RECIST v1.1 and has demonstrated at least a 10-mm increase in the shortest diameter of the lesion. Additionally, it is recommended that tumor lesions selected for biopsy not be selected as target lesions.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before the first dose of study treatment.

8.2.1.2. Assessment of Disease Response During Treatment

The first imaging assessment should be performed 8 weeks (56 ± 7 days) after the first dose of INCB086550 and then every 8 weeks (56 ± 7 days) for the first 6 months. After 6 months of study treatment, imaging frequency may be reduced to every 12 weeks (84 ± 14 days). Participants who discontinue study treatment for a reason other than disease progression should continue to have efficacy assessments performed according to the original schedule following their final on-study treatment scan until disease progression as determined by RECIST, new anticancer therapy is started, death, withdrawal of consent, or end of study. Imaging assessments may be performed more frequently if clinically indicated.

Complete response or PR should be confirmed by imaging at least 4 weeks after the initial documentation.

Imaging should follow calendar days and should not be delayed for delays in cycle starts.

8.2.1.3. Assessment of Disease Response After Treatment

If the participant discontinues study treatment for reasons other than disease progression, imaging assessments should continue at the Protocol-specified interval until documented disease progression, the start of new anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

8.2.2. Health Economics

Not applicable.

8.3. Safety Assessments

See Section 6.5 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 90 days after the last dose of study drug or until the start of new anticancer therapy, whichever occurs first. Adverse events 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 drug. 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, surrogate, or the participant's legally authorized representative). 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, considered related to the study drug/procedures, or that caused the participant to discontinue the study drug. 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 recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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).

Participants who discontinue treatment due to an AE should continue to have disease assessments performed and recorded every 8 weeks until they experience disease progression or start a subsequent anticancer treatment (see Section 7.1).

8.3.1.1. Telephone Adverse Event Assessments

Adverse event assessments will be performed by telephone as per Table 3, Table 4, Table 5, and Table 6. Participants may be directed to report to the clinic for further assessment. At least 3 attempts should be made to contact the participant for these telephone AE assessments and documented if unsuccessful.

8.3.2. Physical Examinations

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

At the screening visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include height and body weight, and 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 thorough neurological examination.

During the study, a targeted examination of the participants will be conducted 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 AE eCRF.

8.3.2.1. Neurologic Examination

At baseline and throughout the study, including the 30-day safety follow-up visit, neurologic examinations should be performed as part of the physical examination. The neurologic examination should include assessment of motor system, muscle reflexes, sensory system, coordination, and gait and stance.

8.3.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests), include blood pressure, pulse, respiratory rate, and body temperature. If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Abnormal vital sign results identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug.

8.3.4. Eastern Cooperative Group Performance Status

The ECOG performance status score will be assessed according to the criteria in Table 14.

Table 14: Eastern Cooperative Group Performance Status Scoring

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: Oken et al 1982.

8.3.5. Electrocardiograms

Twelve-lead ECGs will be obtained as outlined in the SoA (see Table 3, Table 4, Table 5, and Table 6), Table 15, and Table 16 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. On days of timed blood collections, ECGs are to be collected before any blood draws. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest. The 12-lead ECGs (screening and during study treatment period) will be collected from a single measurement. In the event that a single QTc is > 450 milliseconds, 2 additional ECGs will be measured and the average ECG from the triplicates will be reported for the occasion (ie, visit and/or timepoint if applicable). For participants with an intraventricular conduction delay (QRS interval > 120 milliseconds) at screening, the JTc interval may be used in place of the QTc. The JTc must be ≤ 340 milliseconds if JTc is used in place of the QTc. In addition, the JTc interval should be used for all subsequent assessments.

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate participant management. Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. The decision to include or exclude a participant or discontinue study treatment 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.

Table 15: Electrocardiogram Collection Schedule (≥ 2-Week Treatment Schedules)

Visit	Any Time	Before the Morning Dose of INCB086550[a]	2 and 4 Hours After the Morning Dose of INCB086550[a,b]
Screening	X		
Cycle 1 Day 1		X	X
Cycle 1 Day 14		X	X
Every 2 cycles thereafter (eg, C3, C5, C7)		X	
EOT	X		

[a] INCB086550 is administered in the clinic on days of timed ECGs.
[b] To be collected within 15 minutes before blood draws.

The ECG schedule in Table 15 applies to participants who are assigned to continuous, 2-week and 3-week intermittent, or 2-week and 3-week step-down treatment schedules in a 21-day or 28-day cycle.

Table 16: Electrocardiogram Collection Schedule (1 Week Intermittent/Step-Down Treatment Schedule)

Visit	Any Time	Before the Morning Dose of INCB086550[a]	2 and 4 Hours After the Morning Dose of INCB086550[a,b]
Screening	X		
Cycle 1 Day 1		X	X
Cycle 1 Day 7		X	X
Every 2 cycles thereafter (eg, C3, C5, C7)		X	
EOT	X		

[a] INCB086550 is administered in the clinic on days of timed ECGs.
[b] To be collected within 15 minutes before blood draws.

The ECG schedule in Table 16 applies to participants who are assigned to 1-week intermittent step-down treatment schedules in a 21-day or 28-day cycle.

8.3.6. Laboratory Assessments

See Table 17 for the list of clinical laboratory tests to be performed and the SoA (see Table 3, Table 4, Table 5, and Table 6) for the timing and frequency. A certified laboratory local to the investigative site will perform all clinical laboratory assessments for safety (eg, blood chemistries, hematology assessments, coagulation tests, endocrine function, and urinalysis). The investigative site will enter the laboratory results and laboratory normal ranges into the eCRF. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Clinically significant abnormal laboratory findings are those that are not associated with the 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 30 days after the last 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 the 28-day screening window and the tests must be repeated and eligibility confirmed before the first dose of study treatment is administered on Cycle 1 Day 1. A 48-hour window before first dose is permitted for safety laboratory assessments before Cycle 1 Day 1. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study treatment administration (within the 3-day study window), and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

Table 17: Required Laboratory Analytes

<table>
<tr><th>Blood Chemistries</th><th>Hematology</th><th>Urinalysis With Microscopic Examination</th><th>Serology</th><th>Coagulation</th></tr>
<tr><td rowspan="3">Albumin (screening only)
Alkaline phosphatase
ALT
AST
Amylase
Bicarbonate or CO_2[a]
Blood urea nitrogen or urea[a]
Calcium
Chloride
Creatinine
C reactive protein (low sensitivity assay)
Glucose
Lactate dehydrogenase
Lipase
Phosphate
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Total protein
Uric acid</td><td rowspan="3">Complete blood count, including:
• Hemoglobin
• Hematocrit
• Platelet count
• Red blood cell count
• WBC count

Differential count, including:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils

Absolute values must be provided for:
• WBC differential laboratory results</td><td>Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein</td><td>HBsAg
HBsAg antibody
Hepatitis B core antibody
HAV-IgM
HBV-DNA
HCV antibody
HCV-RNA
HIV</td><td>PT
PTT or aPTT
INR</td></tr>
<tr><th>Lipid Panel</th><th>Endocrine Function</th><th>Pregnancy Testing</th></tr>
<tr><td>Total cholesterol
Triglycerides
LDL
HDL</td><td>Thyroid-stimulating hormone
Free T4
Total T3 (free T3 only if total T3 is not performed locally)</td><td>Women of childbearing potential require a serum test at screening and EOT.
Urine or serum pregnancy tests may be used for other scheduled assessments.
Additionally, monthly telephone visits should take place to check pregnancy status (via testing, including home pregnancy tests) during the period when contraception is mandatory (190 days after the last dose of study drug).</td></tr>
</table>

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data.
[a] If considered standard by the region.

8.3.6.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening and at the EOT visit. Urine pregnancy tests will be performed locally as outlined in Table 3, Table 4, Table 5, and Table 6, as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement (note that country-required urine pregnancy testing will be outlined and communicated to investigational sites under separate cover). Additionally, monthly telephone visits should take place to check pregnancy status (which may include home pregnancy tests) during the period when contraception is mandatory (190 days after the last dose of study drug).

If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

If the serum pregnancy test is negative after a urine test was positive, the investigator will assess the potential benefit/risk to the participant and determine whether it is in the participant's best interest to resume study drug and continue participation in the study.

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.6 for reporting requirements.

8.3.6.2. Serology

Hepatitis screening assessments will be performed at the screening visit to rule out hepatitis infection; required analytes are shown in Table 17. 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.

[redacted]

[redacted]

[redacted]

8.5.6. Tumor Biopsy

Tumor biopsies are required for all participants at screening (fresh or archival tissue, after any prior systemic or targeted therapy, including radiation therapy). The tumor tissue will be assessed for PD-L1 expression [redacted]

Note: As a quality control step, a hematoxylin and eosin stain will be performed and reviewed by a local pathologist to verify the adequacy of the tumor biopsy. Additionally, a quality control form will be signed and dated by the reviewing pathologist. For the screening biopsy, this form should be completed prior to participant enrollment. Refer to the Laboratory Manual for further information.

[redacted]

8.6. Tumor Tissue Collection for Testing PD-L1 Expression

For participants with NSCLC and UC, PD-L1 expression must be tested by a local or central laboratory as part of the screening process using the Dako PD-L1 IHC 22C3 pharmDx companion diagnostic. The PD-L1 status (TPS $\geq$ 50% for NSCLC; CPS $\geq$ 10 for UC) must be obtained during the screening period before enrollment as outlined in Section 5.1. If submitting unstained cut slides, 3 unstained, consecutive formalin-fixed paraffin-embedded, newly cut slides should be submitted to the testing laboratory within 30 days from the date they are cut.

Details for sample collection, processing, and shipping will be provided in the Laboratory Manual.

8.7. Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed at those visits should be recorded in the eCRF.

8.8. End of Treatment and/or Early Termination

When the participant permanently discontinues study drug, whether the participant is terminating the study early or the participant has completed the study, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The participant should be encouraged to return for the follow-up visit.

8.9. Follow-Up

Participants who discontinue study treatment are to continue in the follow-up period for up to 90 days (± 14 days) for collection of post-treatment evaluations. The assessment schedule following treatment discontinuation is described in Table 3, Table 4, Table 5, and Table 6.

8.9.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 and 90 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until 1) at least 90 days after the last dose of study drug, or the start of a new anticancer therapy or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period. If the participant cannot return to the site for the safety follow-up visit (eg, lives far away), the participant should be contacted by telephone for assessment of AEs and SAEs, which should be appropriately documented in the source documents and eCRF.

If a participant is scheduled to begin a new anticancer therapy before the end of the 90-day safety follow-up period, the safety follow-up visit should be performed before a new anticancer therapy is started. Once a new anticancer therapy has been initiated, the participant will move into the [redacted].

8.9.2. Post-Treatment [redacted] Follow-Up

Participants who discontinue study treatment for a reason other than disease progression will move into the [redacted] follow-up period and should be assessed as follows to monitor [redacted]:

- If before 6 months from first dose of study treatment - every 8 weeks (56 ± 7 days).
- If after 6 months from first dose of study treatment - every 12 weeks (84 ± 14 days).

Every effort should be made to collect information [redacted] until:

- The start of new anticancer therapy.
- Disease progression.
- Death.
- The end of the study.

8.9.3. [redacted] Follow-Up

Once a participant has received the last dose of study drug, has confirmed disease progression, or starts a new anticancer therapy, the participant moves into the [redacted] and should be contacted by telephone, email, or visit at least every 12 weeks to assess for [redacted], withdrawal of consent, or the end of the study, whichever occurs first, for maximum of 2 years after EOT.

For participants having entered the [redacted] of the study, the site will use continuing participant records to supply data on subsequent treatment regimens, tumor assessments (if discontinued treatment for a reason other than progression), [redacted] in the eCRF. For participants who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, patient records, and public records/databases at intervals of no longer than 12 weeks.

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 considered drug-related. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
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 progression of underlying disease). • Abnormal laboratory test results constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal lab result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the Adverse Event Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or considered to be treatment-related by the investigator. • Efficacy endpoints as outlined in Section 3 will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the cancer under study. Unblinded aggregated efficacy endpoint events and safety data will be monitored to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Incyte Pharmacovigilance as a SAE within 24 hours of determination that the event is not progression of the cancer under study. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing informed consent. If present before entering the study, the condition should be captured as medical history. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.2. Definition of Serious Adverse Event

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

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 occurred. 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 detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

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. Other situations (Important Medical Event)

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 invasive or malignant cancers (excluding the disease[s] under study), 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. Secondary malignancies should always be considered SAEs.

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 Event Form in the eCRF. Conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator (or delegate) 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 AE eCRF page.
- There may be 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 on the copies of the medical records before submission.
- 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 severity grade (CTCAE v5 Grade 1 to 5). 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 final follow-up.
- The action taken with regard to study drug 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 Event 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 CTCAE v5 Grades 1 through 5. If an event is not classified by CTCAE, 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.
- **Grade 5:** Fatal.

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 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 relationship.
- The investigator will also consult the Reference Safety Information in the IB and/or Product Information, for marketed products, in his/her assessment.
- Alternative causes, such as underlying 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 he/she has reviewed the AE/SAE and has 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 for every event before the initial transmission of the SAE.**
  - The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up SAE report with 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. • 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. • New or updated information will be recorded in the originally completed eCRF. • Any updated SAE data will be submitted to the sponsor (or designee) within 24 hours of receipt of the information. • Once an AE is detected, it should be followed 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 drug, 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 until the event resolves.

See Appendix D for the management of potential Hy's law cases.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug or study procedure[s]), all SAEs occurring after the participant has signed the ICF through 90 days after the last dose of study treatment ***or*** until the participant starts a new anticancer therapy, whichever occurs earlier) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must notify the sponsor (or designee) within 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 of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for 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 and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

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, IRB/IEC, and investigators.

Investigator safety reports must be prepared for suspected unexpected 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 a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Serious Adverse Event Reporting

- Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF.
- The investigator must also complete the Incyte Serious Adverse Event Report Form, in English. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- Facsimile or email transmission of the Serious Adverse Event Report Form is the preferred method to transmit this information to Incyte Pharmacovigilance/designee. The contact information of the sponsor's study-specific representatives is listed in the Study Reference Manual provided to each site. The original copy of the Serious Adverse Event Report Form and the confirmation sheet must be kept at the study site.
- Follow-up information is recorded on an amended or new Serious Adverse Event Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous Serious Adverse Event Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug 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.
- In rare circumstances and in the absence of facsimile or computer equipment, notification by telephone is acceptable with a copy of the Incyte Serious Adverse Event Report Form sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.
- Contacts for SAE reporting can be found in Study Reference Manual.

9.5. Emergency Unblinding of Treatment Assignment

Not applicable.

9.6. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a participant during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure safety:

- The study treatment must be interrupted immediately (female participants only).
- If the female participant is no longer pregnant and meets the treatment continuation criteria within 28 days of the scheduled start of a cycle, study treatment may be resumed after approval has been received from the sponsor medical monitor.
- 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 evaluation. 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 drug 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.

Any SAE occurring during pregnancy of a study participant must be recorded on the Serious Adverse Event Report Form and submitted to the sponsor or designee.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs (if occurring in the study participant) and must be reported as described in Section 9.4. If an abnormal pregnancy outcome is reported in a study participant's partner, the event should be reported to the sponsor on the Clinical Trial Pregnancy Form.

9.7. Warnings and Precautions

Special warnings or precautions for the study drug, 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.

9.8. 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 his/her 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, he/she will return a copy of the product complaint communication with the product.

9.9. Treatment of Overdose

For this study, any dose of INCB086550 greater than the dose prescribed within a 24-hour time period will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose; therefore, treatment of overdose should be managed as clinically indicated.

In the event of an overdose, the investigator/treating physician should:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until INCB086550 can no longer be detected systemically (at least 30 days).
- [redacted]
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

10. STATISTICS

10.1. Sample Size Determination

The number of participants has been determined independently for each disease-specific cohort (irrespective of dose level) and can be found in Table 20. The target ORR (p_1) for each cohort is based on published clinical experience with a reference PD-1 inhibitor (El-Khoueiry et al 2017, Keytruda 2018, Mok et al 2019, Motzer et al 2015, Reck et al 2016, Robert et al 2015). The target ORR (p_1) for the NSCLC cohort was calculated by combining 2 different studies (Mok et al 2019, Reck et al 2016). The null ORR (p_0) for the melanoma and RCC cohorts is based on the control arm ORRs in the reference studies. For the NSCLC, UC, and HCC cohorts, the null ORR (p_0) was selected to be the p_0 that creates a test with a rejection region that begins with the lower CI bound of the reference PD-1 inhibitors. The sample size for each cohort provides approximately 80% power and 5% 1-sided Type I error.

Table 20: Sample Size per Cohort

Tumor Type (Cohort)	ORR		Sample Size
	p_0	p_1	
NSCLC	18.0%	41.1%	32
UC	20.0%	47.0%	25
HCC	6.0%	20.0%	42
RCC	5.0%	25.0%	23
Melanoma	11.9%	32.9%	30

10.2. Populations for Analysis

The populations for analysis are provided in Table 21.

Table 21: Populations for Analysis

Population	Description
FAS	The FAS includes all study participants who have received at least 1 dose of study drug. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, [redacted]. Participants will be analyzed according to the treatment group/dose to which they have been assigned.
Safety evaluable	The safety evaluable population includes all participants who received at least 1 dose of study drug. All safety analyses will be conducted using the safety evaluable population. Treatment groups for this population will be determined according to the actual treatment group/dose the participant received regardless of assigned study drug treatment.
RECIST evaluable	The RECIST evaluable population includes all participants who have received at least 1 dose of study drug, completed a baseline scan, and met at least 1 of the following criteria: • ≥ 1 postbaseline efficacy assessments. • The participant has been on the study for a minimum of 63 days (9 weeks) of follow-up. • The participant has discontinued from treatment. The RECIST evaluable population will be used for all ORR, DCR, and DOR efficacy analyses. Participants will be analyzed according to the treatment group/dose to which they have been assigned.
[redacted]	[redacted].

10.3. Level of Significance

Formal statistical tests for the primary endpoint will be performed for each cohort that control Type I error at ≤ 1-sided 5% for each cohort. Parameters for other secondary [redacted] endpoints will be estimated using 95% CIs.

10.4. Statistical Analyses

10.4.1. Primary Efficacy Analysis

All efficacy analyses will be performed independently for each disease cohort.

10.4.1.1. Overall Response Rate

The primary endpoint ORR is defined as the percentage of participants with best overall response of CR or PR confirmed by at least 1 repeat assessment ≥ 28 days later by investigator assessment per RECIST v1.1 (Eisenhauer et al 2009). Overall response rate and its exact 95% CI will be calculated separately for each cohort. The exact binomial test will be used to test the null hypotheses in Table 20.

10.4.2. Secondary Efficacy Analysis

10.4.2.1. Duration of Response

Duration of response is defined as the time from the earliest date of CR or PR confirmed by at least 1 repeat assessment ≥ 28 days later, until the earliest date of disease progression according to RECIST v1.1 or death due to any cause, if occurring sooner than progression. For participants who have not progressed and are still alive at the time of the analysis, DOR will be censored on the day of last evaluable disease assessment. For participants who have discontinued study or have started other anticancer treatment, DOR will be censored on the day of last evaluable disease assessment documenting absence of PD before the discontinuation or the start of the new anticancer treatment. The total number of objective responders, number of participants who progressed or died, and number of participants censored will be summarized for each cohort. The Kaplan-Meier estimate of median DOR and its 95% CI will be provided separately for each cohort.

10.4.2.2. Disease Control Rate

Disease control rate is defined as the percentage of participants with best overall response of CR or PR confirmed by at least 1 repeat assessment ≥ 28 days later, or SD for ≥ 12 weeks, by investigator assessment per RECIST v1.1. The DCR and its exact 95% CI will be summarized separately for each cohort.

[redacted]

10.4.4. Safety Analyses

The clinical safety data (eg, vital signs, ECGs, routine laboratory tests, physical examinations, AEs) will be summarized using descriptive statistics (eg, mean, frequency) for the FAS.

10.4.4.1. Adverse Events

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after the first dose of study drug up to 90 days after the last dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be tabulated by MedDRA system organ class and preferred term. Severity of AEs will be based on the NCI CTCAE v5 using Grades 1 through 5.

The subset of AEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered treatment-related.

Number (%) of participants reporting any TEAEs, any SAEs, any Grade 3 or higher TEAEs, irAEs, any treatment-related TEAEs, any treatment-related serious TEAEs, any treatment-related Grade 3 or higher TEAEs, any fatal TEAEs, and any TEAEs leading to treatment interruption/discontinuation will be tabulated by MedDRA system organ class and preferred term.

10.4.4.2. Clinical Laboratory Tests

Laboratory data will be classified into Grades 1 through 4 using CTCAE v5 when applicable. The following summaries will be produced for the laboratory data:

- Descriptive statistics of the value and change from baseline at each assessment time will be provided.
- For laboratory parameters that have CTC grading, shift tables will be provided showing change in CTC grade from baseline to the worst postbaseline grade.

Categorical laboratory data will be tabulated by visit at baseline and postbaseline visits when necessary. Possible Hy's law events will be listed. The criteria for determining possible Hy's law events will be provided in the Statistical Analysis Plan.

10.4.4.3. Vital Signs

Descriptive statistics for the value at each assessment and change from baseline will be provided for vital signs (ie, blood pressure, pulse, respiratory rate, and body temperature). Vital sign results will be reviewed for clinically notable abnormalities (see Table 22), and the abnormal values for participants exhibiting clinically notable vital sign abnormalities will be listed. Alert vital sign values are defined as an absolute value outside the defined range and an absolute percentage change of > 25% from baseline. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 22: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 160 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 120 bpm	< 45 bpm
Temperature	> 38°C	< 35°C
Respiratory rate	> 24 breaths/min	< 8 breaths/min

10.4.4.4. Electrocardiograms

Descriptive statistics for the value at each assessment and change from baseline will be provided for each ECG parameter. The ECG results will be reviewed for clinically notable abnormalities according to predefined criteria (see Table 23). Participants exhibiting clinically notable ECG abnormalities will be listed.

Normal ranges for ECG values are defined in Table 23. Electrocardiogram values will also be considered abnormal if the absolute percentage change from baseline is more than 25% (30% for QRS interval). Participants exhibiting ECG values outside the normal ranges will be listed. Abnormal values for participants with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed. Outliers of QT and QTcF values, defined as absolute values > 450 milliseconds for QTcF and > 500 milliseconds for QT or change from baseline > 30 milliseconds, will be summarized.

Table 23: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 450 ms	< 295 ms
PR	> 220 ms	< 75 ms
QRS	> 120 ms	< 50 ms
QT	> 500 ms	< 300 ms
RR	> 1330 ms	< 600 ms

10.4.4.5. Dose Intensity

Measures of exposure (eg, days of exposure, dose intensity) of study drug will be summarized by means of summary statistics.

[redacted]

[redacted]

10.5. Interim Analysis

A safety/efficacy run-in analysis is planned when up to 15 participants in select disease-specific cohorts of each dose level are evaluable for response using the RECIST evaluable population. The Type I error inflation would only require at most a 1-participant increase to the sample size for each cohort shown in Table 20 in order to maintain the level at 0.05; therefore, the impact of this run-in is minimal. Safety and efficacy will be assessed to determine whether to continue with the study or stop after the run-in analysis. With 15 participants, there is approximately 91.3% probability of observing at least an objective response if the underlying response rate is 15%.

After passing the run-in, the study will proceed according to the group sequential rules in Table 24. Nonbinding interim futility analyses are planned after approximately 50% of the participants in each disease-specific cohort of each dose level are evaluable for response using the RECIST evaluable population. Information from all cohorts and other emerging data will determine whether to pause or stop recruitment in any single cohort. The Hwang-Shih-DeCani (Hwang et al 1990) beta-spending function with parameter -1 will be used to determine the futility bound for all cohorts, and alpha-spending function with parameter -4 will be used to determine the efficacy bound for all cohorts except for melanoma, which used parameter -1 because lower values did not achieve at least 80% power. Table 24 presents the planned nonbinding futility and efficacy boundaries for the interim and final analyses.

Table 24: Group Sequential Rules for Interim and Final Analysis

Tumor Type (Cohort)	Futility Boundary for ORR at Planned Interim Analysis	Efficacy Boundary for ORR at Planned Interim Analysis	Efficacy Boundary for ORR at Final Analysis
NSCLC	< 4/16 = 25%	≥ 8/16 = 50%	≥ 11/32 = 34%
UC	< 3/12 = 25%	≥ 7/12 = 58%	≥ 10/25 = 40%
HCC	< 2/21 = 10%	≥ 6/21 = 29%	≥ 6/42 = 14%
RCC	< 1/11 = 9%	≥ 4/11 = 36%	≥ 4/23 = 17%
Melanoma	< 2/15 = 13%	≥ 6/15 = 40%	≥ 8/30 = 27%

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 IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- 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 IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both Health Authorities and IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- Adhering to the Protocol as described in this document and agreeing 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 IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of 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 the termination of the test article for investigation 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 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.

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the Sponsor Medical Monitor before the end of the study. As part of his or her responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

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, or study charters, [redacted], as applicable.

The sponsor (or designee) will be responsible for:

- 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:

- 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, [redacted], photographs, diary data), or as otherwise specified in the Protocol.
- 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, or 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 at the investigator's site.
  - 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. Also, current applicable medical records must be available.
- May have responsibility for sending participants' data, either as unique samples, or 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, IRB/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 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 sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable. Appropriate consent for collection, use and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

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.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations require otherwise. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.4. 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 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.

11.5. Publication Policy

By signing the study Protocol, the investigator and his/her institution agree that the results of the study may be used by the sponsor, Incyte Corporation, 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.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of

multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined in line with International Committee of Medical Journal Editors authorship requirements.

11.6. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. 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.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

Definitions

WOCBP

A woman 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:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- 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 HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Female participants on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For male participants of reproductive potential[a]

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[b]
- Abstinence from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agreement to remain abstinent.

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.

For female participants who are WOCBP
The following methods during the Protocol-defined timeframe in Section 5.1 that can achieve a failure rate of < 1% per year when used consistently and correctly are considered as highly effective birth control methods: • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation. – oral – intravaginal – transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation – oral – injectable – implantable • Intrauterine device[c] • Intrauterine hormone-releasing system[c] • Bilateral tubal occlusion[c] • Vasectomized partner[d] • Sexual abstinence[b]

FSH = follicle-stimulating hormone; HRT = hormone replacement therapy; WOCBP = woman of childbearing potential.

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

[b] 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 treatments. 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.

[c] Contraception methods that in the context of this guidance are considered to have low user dependency.

[d] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.

Source: Clinical Trials Facilitation and Coordination Group 2014 and Clinical Trials Facilitation and Coordination Group 2020.

[redacted]

APPENDIX C. INSTRUCTION TO PARTICIPANTS FOR HANDLING STUDY DRUG (INCB086550)

The participant must be instructed in the handling of study drug as follows:

- INCB086550 must be refrigerated and protected from light. Store the study drug in a refrigerator at 2°C to 8°C (36°F-46°F).
- Only remove the number of tablets needed at the time of administration.
- Do not remove doses in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed doses/lost tablets.
- Take study drug with a full glass of water and fast at least 2 hours before and at least 1 hour after each dose. [redacted]
- Study drug may be taken QD or BID on the days specified of a 21-day or 28 day cycle for a given dose level.
  - QD doses are taken in the morning.
  - BID doses are taken in the morning and evening approximately 12 hours apart. If the morning or evening dose is missed by more than 4 hours, then that dose should be skipped, and the next scheduled dose should be taken at the usual time.
- If vomiting occurs after taking study drug, do not take another dose.
- Keep study drug in a safe place and out of reach of children.
- Bring all used and unused study drug bottles/kits to the site at each visit.

APPENDIX D. MANAGEMENT OF POTENTIAL HY'S LAW CASES

INTRODUCTION

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets PHL criteria at any point during the study.

The investigator participates, in conjunction with Incyte clinical project and pharmacovigilance representatives, in the review and assessment of cases fulfilling PHL criteria to ascertain whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug.

The investigator fulfils requirements for the recording of data pertaining to PHL or Hy's law cases and AE/SAE reporting according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

For the purpose of this process definitions are as follows

Potential Hy's Law

An increase in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN at any point during the study. The elevations do not have to be at the same time or within a specified timeframe.

Hy's Law

An increase in AST or ALT ≥ 3 × ULN and total bilirubin > 2 × ULN, where no other reason can be found to explain the combination of increases (eg, elevated serum ALP indicating cholestasis, viral hepatitis, another drug).

ACTIONS REQUIRED IN CASES OF AST OR ALT > 3 × ULN OR TOTAL BILIRUBIN ≥ 2 × ULN

Identification and Determination of Potential Hy's Law

To identify cases of AST or ALT > 3 × ULN or total bilirubin > 2 × ULN and consequently determine whether the participant meets PHL criteria, please follow the instructions below:

- Review the laboratory report and if a participant has AST or ALT > 3 × ULN OR total bilirubin > 2 × ULN at any visit:
  - Determine without delay whether the participant meets PHL criteria by reviewing laboratory reports from all previous visits.
  - Enter the laboratory data into the laboratory eCRF as soon as possible.

Potential Hy's Law Criteria Not Met

If the participant has NOT had AST or ALT ≥ 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instruction below:

- Perform follow-up on subsequent laboratory results according to the guidance provided in Section 8.3.6.

Potential Hy's Law Criteria Met

If the participant has had AST or ALT ≥ 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instruction below:

- Have participant interrupt study drug.
- Notify Incyte study team without delay.
  - The investigator, or designee, should contact the medical monitor to discuss and agree upon an approach for the study participant's follow-up and the continuous review of data.
- Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as medically indicated.
- Investigate the etiology of the event and perform any relevant diagnostic investigations as discussed with the medical monitor.
- Enter the laboratory data into the laboratory CRF as soon as possible.
- If at any time (in consultation with the medical monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

REVIEW AND ASSESSMENT

No later than 3 weeks after the biochemistry abnormality is initially detected and the criteria for PHL is met, the medical monitor, Incyte pharmacovigilance physician, and investigator will discuss and review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug. Participant matter experts will be included in the review as appropriate.

Evaluation of Alternative Causes

In order to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, the following alternative etiologies should be considered, including but not limited to,

- Active viral hepatitis
- Alcoholic and autoimmune hepatitis
- Hepatobiliary disorders
  - Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if alkaline phosphatase is increased. Malignant interruption of the biliary tract also should be considered.
- Concomitant treatment

- Other causes such as systemic infections (bacterial, fungal, viral), nonalcoholic steatohepatitis, and cardiovascular diseases

Actions After Review and Assessment

According to outcome of the review and assessment, please follow the instructions below:

If there **is** an agreed alternative explanation for the AST or ALT **and** total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE.

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF if possible.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the standard study processes.
- Have participant resume study drug as per Protocol guidelines.

If it is agreed that there is no explanation that would explain the AST or ALT and total bilirubin elevations:

- Have participant permanently discontinue study drug and perform end-of-treatment procedures.
- Report an SAE (report term "Hy's Law").
  - The 'medically important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the Hy's law case, a causality assessment of related should be assigned.
- If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for a Hy's law case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made. Report an SAE (report term "Potential Hy's Law") applying serious criteria and causality assessment as per above.

ACTIONS REQUIRED FOR REPEAT EPISODES OF AST OR ALT > 3 × ULN AND/OR TOTAL BILIRUBIN > 2 × ULN

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

If the alternative cause for the previous occurrence of PHL was not chronic or progressing malignant disease, please follow the process for PHL review and assessment as described in this appendix.

If the alternative cause for the previous occurrence of PHL was chronic or progressing malignant disease, please follow the instructions below:

- Determine whether there has been a significant change* in the participant's condition.
  - If there is no significant change, no action is required.

- If there is a significant change, follow the process described for PHL review and assessment as described in this appendix.

[*] A 'significant' change in the participant's condition refers to a clinically relevant change in ALT, AST, or total bilirubin, or associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty.

APPENDIX E. CYTOCHROME P450 INHIBITORS/INDUCERS

Concomitant treatment with moderate and potent CYP3A4/CYP3A5 inhibitors or inducers are prohibited in this study.

Below is a list of potent and moderate inhibitors and inducers. This list is not exhaustive. For a comprehensive list, please check with your pharmacy personnel for the most current list of potent CYP3A4/CYP3A5 inhibitors or inducers.

Additional references include:

- Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.
- EMA (2013) Guideline on the Investigation of Drug Interactions.
- NPS Australia.

Potent and Moderate CYP3A4/CYP3A5 Inhibitors

Aprepitant	Grapefruit	Posaconazole
Atazanavir	Grapefruit juice	Ritonavir
Cannabidiol (CBD)	Indinavir	Saquinavir
Casopitant	Itraconazole	Telithromycin
Clarithromycin	Ketoconazole[a]	Troleandomycin
Diltiazem	Mibefradil	Verapamil
Erythromycin	Nefazodone	Voriconazole
Fluconazole	Nelfinavir	

[a] Note topical use of 2% ketoconazole cream is allowed.

Potent CYP3A4/CYP3A5 Inducers

Apalutamide	Enzalutamide	Phenytoin
Bosentan	Etravirine	Primidone
Carbamazepine	Mitotane	Rifampicin
Efavirenz	Phenobarbital	St. John's wort

APPENDIX F. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

The COVID-19 global pandemic presents challenges to the ongoing conduct of clinical trials. In line with regulatory guidance regarding clinical trial execution during the pandemic, the sponsor has issued the following Protocol considerations to ensure participant safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain. Recognizing the dynamic nature and flexibility required to manage the impact of the pandemic on this clinical trial, additional details will be incorporated into respective study manuals and site-specific monitoring plans as applicable, with institutional requirements as warranted, and communicated to the investigative sites as needed. Relevant test results will be documented in the eCRF, and applicable changes to the ICF will be made and monitored.

Study Site Visits

If local travel restrictions, isolation requirements, or the investigator's benefit/risk assessment determines it to be unsafe for participants to attend study visits at the investigational site, the site staff may elect to pursue the following:

- In order to minimize participant risk, study visits may be conducted via telemedicine modalities (phone or video) or as per site institutional guidelines. At a minimum, a review of AEs and concomitant medications must be completed. On-site visits should be conducted whenever feasible and are required for administration of study treatment. The participant may also be asked to undergo additional safety laboratory assessments.
- In order to support investigator oversight of participant safety and disease management, the participant may be asked to undergo some laboratory tests or study procedures at a local laboratory or facility closer to the participant's residence rather than at the investigational site. In this case, the study physician will provide the participant with the list of parameters to be checked. These tests should be performed in certified laboratories.
- Some tests, such as ECG or CT scan assessments, may require longer windows due to the COVID-19 pandemic and may be performed outside the regularly scheduled visit window or may be conducted at the next scheduled visit. It is the investigator's responsibility to check with the facility (if performed at a different facility) that the data will be obtained and available for evaluation. General procedures performed outside of protocol parameters will be captured as protocol deviations due to COVID-19 in the eCRF.

Participant SARS-CoV-2 Infection and Study Treatment

An event of active SARS-CoV-2 infection by a participant in the study should be reported as an AE or SAE and appropriate medical intervention provided. For participants with active SARS-CoV-2 infection, study treatment should be delayed until the resolution of symptoms and until it is allowable for the participant to return to the clinic per institutional guidelines. Prior to restarting treatment, the participant should be afebrile for 72 hours and the treating physician should determine that the participant's condition is stable enough to resume study treatment. The

study physician should also consider if the participant is SARS-CoV-2 negative (by test) before restarting study treatment if COVID-19 was diagnosed during the trial. The study team should be notified when the study treatment is restarted. Safety monitoring following COVID-19 should be implemented as per institutional guidance or clinical judgment (eg, coagulation factors).

COVID-19 Vaccination

Participants may receive the COVID-19 vaccine as long as it is not a live vaccine, which is prohibited per the Protocol (see Section 5.2). COVID-19 vaccination will be captured in the eCRF as a concomitant medication. Administration of study treatment may be delayed to ensure vaccination is completed. The medical monitor may be consulted if needed.

Clinical Trial Monitoring

Study monitoring visits could be postponed; however, the site monitor and sponsor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, emails, video visits) with the sites to get information on trial progress, participant status, and information on issue resolution. The study monitor may remotely review data entered into the EDC for accuracy and completeness if allowed by the national regulatory body, investigational site, and/or in compliance with local authorities.

Reimbursement of Additional Expenses

The sponsor will reimburse for any extraordinary expenses, keeping appropriate documentation as evidence (eg, travel expenses for the local laboratory visit[s], the costs of local [proximate] laboratory tests).

APPENDIX G. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1 (Version 2):	08 MAR 2021

Amendment 1 (08 MAR 2021)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to incorporate additional dose levels to evaluate the safety and preliminary activity of INCB086550 with intermittent and/or step-down dose administration schedules. The changes are summarized below.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema; Table 3: Schedule of Activities for 28-Day Cycle [Schedule A]; Table 4: Schedule of Activities for 28-Day Cycle [Schedule B]; Table 5: Schedule of Activities for 21-Day Cycle [Schedule C]; Table 6: Schedule of Activities for 21-Day Cycle [Schedule D]); Section 2.2.1, Scientific Rationale for Study Design; Section 2.2.2, Justification for Dose; Section 4.1, Overall Design; Section 6.1, Study Treatment Administered (Table 9: Study Treatment Administered)**

   Description of change: Removed initial treatment regimen of 400 mg BID as the pharmacologically active dose that will be used initially and provided updated safety language from the Phase 1 study. Updated INCB086550 treatment administration to incorporate evaluation of intermittent and/or step-down dose administration regimens. Added a 21-day schedule of assessments as an option and added new SoA to accommodate the additional schedules (Tables 4-6).

   Rationale for change: To enable the evaluation of safety and tolerability and preliminary efficacy of intermittent and/or step-down dose administration in 21-day or 28-day treatment cycles.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements)**

   Description of change: The number of participants planned to receive INCB086550 has been clarified as up to approximately 304 participants, rather than 152 participants, given that more than 1 level may be tested.

   Rationale for change: Ability to add dose levels.

3. **Section 1, Protocol Summary (Figure 1: Study Design Schema); Section 4.1, Overall Design; Section 10.5, Interim Analysis**

   Description of change: Added nonbinding safety and efficacy run-in analysis in up to 15 participants in select disease-specific cohorts.

   Rationale for change: To enable the early evaluation of safety and efficacy.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities for 28-Day Cycle [Schedule A]; Table 4: Schedule of Activities for 28-Day Cycle [Schedule B]; Table 5: Schedule of Activities for 21-Day Cycle [Schedule C]; Table 6: Schedule of Activities for 21-Day Cycle [Schedule D]); Section 8.5.1, Serum and Plasma for Correlative Assessments**

   Description of change: Added note to hematology panel that additional unscheduled CBCs may be performed. Added note to endocrine panel, plasma and serum for correlative studies, [redacted] that additional assessments may be performed if a participant has an irAE. Added a new collection of serum for correlative studies.

   Rationale for change: To further evaluate immune activation and irAEs.

5. **Section 1, Protocol Summary (Table 3: Schedule of Activities for 28-Day Cycle [Schedule A]; Table 4: Schedule of Activities for 28-Day Cycle [Schedule B]; Table 5: Schedule of Activities for 21-Day Cycle [Schedule C]; Table 6: Schedule of Activities for 21-Day Cycle [Schedule D]); Section 5.1, Inclusion Criteria (Inclusion Criterion 6); Section 8.3.6, Laboratory Assessments (Table 17: Required Laboratory Analytes); Section 8.3.6.1, Pregnancy Testing; Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: Modified requirements for pregnancy testing and contraception based on Clinical Trials Facilitation and Coordination Group 2014 and 2020 guidance.

   Rationale for change: Updated guidance.

6. **Section 3, Objectives and Endpoints (Table 7: Objectives and Endpoints); Section 8.2, Efficacy Assessments; Section 8.2.1.2, Assessment of Disease Response During Treatment; Section 10.4, Statistical Analyses**

   Description of change: Removed evaluation of efficacy per iRECIST and option for treatment beyond progression.

   Rationale for change: Not required.

7. **Section 5.1, Inclusion Criteria**

   Description of change: Modified Inclusion Criterion 5.e to include chemotherapy as an allowable line of prior therapy and added Inclusion Criterion 7 to clarify that participants (except those with NSCLC) must have documented disease progression after treatment with available therapies.

   Rationale for change: Clarification.

8. **Section 6.1, Study Treatment Administered (Table 7: Study Treatment Information); Appendix C, Instruction to Participants for Handling Study Drug (INCB086550)**

   Description of change: Added INCB086550 400 mg tablet strength. Specified that INCB086550 tablets may be crushed and administered with water, apple juice, applesauce, or yogurt. Clarified language pertaining to doses for QD and BID dose schedules.

   Rationale for change: Addition of new tablet strength and treatment administration method and clarification of QD and BID dose schedules.

9. **Section 6.6.2, Restricted Medications and Procedures**

   Description of change: Added examples of P-gp inhibitors with a narrow therapeutic window as well as information pertaining to INCB086550 as an inhibitor of the creatinine transporter OCT2 and use of stomach acid–reducing medications such as proton pump inhibitors and H_2-receptor blockers.

   Rationale for change: To provide examples of P-gp inhibitors and clarification on use of metformin (an OCT2 substrate) and stomach acid–reducing medications. [redacted]

10. **Section 6.6.4, COVID-19; Appendix F, COVID-19 Pandemic Mitigation Strategies and Instructions**

    Description of change: Added information related to management of the study and participants during the COVID-19 pandemic.

    Rationale for change: New information.

11. **Section 1, Protocol Summary (Table 3: Schedule of Activities for 28-Day Cycle [Schedule A]; Table 4: Schedule of Activities for 28-Day Cycle [Schedule B]; Table 5: Schedule of Activities for 21-Day Cycle [Schedule C]; Table 6: Schedule of Activities for 21-Day Cycle [Schedule D]); Section 8.1.4, Distribution of Dosing Diary and Patient Information Cards**

    Description of change: Dosing diaries will also be provided for each patient at each visit.

    Rationale for change: Clarification.

12. **Section 8.2.1, Tumor Imaging by RECIST v1.1; Section 10.2, Populations for Analysis (Table 21: Populations for Analysis)**

    Description of change: Updated information for assessment of skin lesions according to RECIST v1.1 and the evaluable populations.

    Rationale for change: Clarification.

13. **Section 8.3.5, Electrocardiograms**

    Description of change: Revised Table 15 and added Table 16 to clarify the ECG collection schedule based on treatment schedule.

    Rationale for change: Clarification.

14. **Section 8.3.6, Laboratory Assessments (Table 17: Required Laboratory Analytes)**

    Description of change: Specified that free T4 and total T3 should be performed to evaluate endocrine function. Added requirement for IgM for HAV serology testing. Updated requirements for pregnancy testing.

    Rationale for change: Clarification.

15. [redacted]

    Rationale for change: Clarification.

16. **Appendix E, Cytochrome P450 Inhibitors/Inducers**

    Description of change: Added cannabidiol to the list of potent and moderate CYP3A4/CYP3A5 inhibitors.

    Rationale for change: To prohibit use of cannabidiol because there is a potential for a drug-drug interaction.

    Rationale for change: Clarification.

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

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Approval	[redacted] Approver [redacted]
Approval	[redacted] Approver [redacted]
Approval	[redacted] Approver [redacted]
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