Official Title: A Phase 1/2 Open-Label, Multicenter Study of INCB000928 Administered as a Monotherapy or in Combination With Ruxolitinib in Participants With Anemia Due to Myeloproliferative Disorders

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Clinical Study Protocol

INCB 00928-104

A Phase 1/2 Open-Label, Multicenter Study of INCB000928 Administered as a Monotherapy or in Combination With Ruxolitinib in Participants With Anemia Due to Myeloproliferative Disorders

Product:	**INCB000928**
IND Number:	[redacted]
EudraCT Number:	**2020-004029-21**
EU CT Number:	**2023-503625-19-00**
Phase of Study:	**Phase 1/2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol:	**25 FEB 2020**
Protocol Amendment 1:	**25 MAR 2020**
Protocol Amendment 2:	**15 APR 2020**
Protocol Amendment 3:	**27 AUG 2020**
Protocol Amendment 4:	**10 MAY 2021**
Protocol Amendment 5:	**02 SEP 2021**
Protocol Amendment 6:	**22 DEC 2021**
Protocol Amendment 7:	**21 DEC 2022**
Protocol Amendment 8:	**05 DEC 2023**
Protocol Amendment 9:	**20 FEB 2025**

INVESTIGATOR'S AGREEMENT

I have read the INCB 00928-104 Protocol Amendment 9 (dated 20 FEB 2025) 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
ALK	activin receptor-like kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma/urine concentration curve
AUC_{0-24}	area under the plasma concentration-time curve from time 0 to time 24 hours
AUC_{0-t}	area under the plasma concentration-time curve from time 0 to the last quantifiable measurable plasma concentration
AUC_{∞}	observed area under the plasma concentration-time curve from time 0 to infinity
BAP	bone alkaline phosphatase
BCRP	breast cancer resistance protein
BID	twice daily
BM	bone marrow
BMP	bone morphogenetic protein
BOIN	Bayesian optimal interval
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence intervals
C_{max}	maximum concentration
CNS	central nervous system
COMFORT	Controlled MyeloFibrosis Study With ORal JAK Inhibitor Treatment
COVID-19	coronavirus disease of 2019
CR	complete response/remission
CRP	C-reactive protein
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trials Regulation
CYP	cytochrome P450
DDI	drug-drug interactions
DIPSS	Dynamic International Prognostic Scoring System

Abbreviations and Special Terms	Definition
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EOT	end of treatment
EPO	erythropoietin
ESA	erythropoietin-stimulating agent
ET	essential thrombocythemia
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practices
G-CSF	granulocyte colony stimulating factor
GDPR	General Data Protection Regulation
GI	gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte/macrophage colony stimulating factor
HbA1c	glycated hemoglobin
HBV	hepatitis B virus
Hct	hematocrit
HCV	hepatitis C virus
HDL	high-density lipoprotein
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDH	isocitrate dehydrogenase
IEC	independent ethics committee

Abbreviations and Special Terms	Definition
IL	interleukin
INR	international normalized ratio
IPSS-R	Revised International Prognostic Scoring System
IRB	institutional review board
IRT	interactive response technology
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
JAK	Janus-associated kinase
J-GCP	Japanese Good Clinical Practices
LCM	left costal margin
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFS	leukemia-free survival
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MM	multiple myeloma
MMA	methylmalonic acid
MPN	myeloproliferative neoplasm
MPN-SAF	myeloproliferative neoplasms symptom assessment form
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
NRBC	nucleated red blood cell
NTBI	non–transferrin-bound serum iron
PD	pharmacodynamic(s)
PFS	progression-free survival
P-gp	P-glycoprotein
PHL	potential Hy's law
PhV	pharmacovigilance
PK	pharmacokinetic(s)

Abbreviations and Special Terms	Definition
PMDA	Pharmaceuticals and Medical Devices Agency
PMF	primary myelofibrosis
PR	partial response/remission
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
PV	polycythemia vera
QD	once daily
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
RBC-TI	red blood cell-transfusion independency
RC	reticulocyte count
RDE	recommended dose for expansion
RDW	red blood cell distribution width
RNA	ribonucleic acid
RSI	reference safety information
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOP	standard operating procedure
sTfR	soluble transferrin receptor
Study drug	Incyte medicinal investigational product INCB000928
Study treatment	all medications that the participant is required to receive as part of this study
$t_{½}$	half-life
TD	transfusion-dependent (transfusion dependency)
TEAE	treatment-emergent adverse event
TGA	treatment group A
TGB	treatment group B
TGC	treatment group C
TGF-β	transforming growth factor beta
TI	transfusion-independent (transfusion independency)
TIBC	total iron-binding capacity
t_{max}	time to maximum plasma concentration
TRAcP 5b	tartrate-resistant acid phosphatase type 5b
TSAT	transferrin saturation
TSI	total serum iron

Abbreviations and Special Terms	Definition
TSS	total symptom score
UIBC	unsaturated iron-binding capacity
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

Protocol Title:

A Phase 1/2 Open-Label, Multicenter Study of INCB000928 Administered as a Monotherapy or in Combination With Ruxolitinib in Participants With Anemia Due to Myeloproliferative Disorders

Protocol Number: INCB 00928-104

Objectives and Endpoints:

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

Table 1: Primary and Key Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the safety and tolerability of INCB000928 administered as monotherapy (TGA) or in combination with ruxolitinib (TGB and TGC).	• Frequency and severity of AEs and SAEs, including changes in vital signs, ECGs, physical examinations, and clinical blood and urine laboratory parameters. • Identification of the DLTs, MTD, and RDE.
Secondary	
To determine the efficacy of INCB000928 administered as monotherapy (TGA) or in combination with ruxolitinib (TGB and TGC).	• Anemia response, defined as follows (modified from Tefferi et al [2013] definitions): – An Hgb increase of 1.5 g/dL relative to baseline for any "rolling" 12-week period (84 days with each assessment meeting this requirement) during the first 24 weeks of treatment if TI at baseline **OR** – Achieving TI for any "rolling" 12-week period (absence of any RBC transfusion over any 84-day period) during the first 24 weeks of treatment if TD at baseline. • Duration of anemia response, defined as follows: – The interval from the first onset of anemia response to the earliest date of loss of anemia response that persists for at least 4 weeks or death from any cause (for the TI participants at baseline) **OR** – Duration of RBC-TI period for participants achieving RBC-TI for at least 12 consecutive weeks during the first 24 weeks of treatment (for the TD participants at baseline). • Mean change from baseline in the Hgb value over 12-week treatment periods. • Rate of RBC transfusion through Weeks 24 and 48, defined as the average number of RBC units per participant-month during the treatment period.
To evaluate the PK of INCB000928 administered as monotherapy (TGA) or in combination with ruxolitinib (TGB and TGC).	PK parameters: C_{max}, t_{max}, and AUC_{0-t} for INCB000928 alone, for ruxolitinib alone, or for the combination of INCB000928 with ruxolitinib, as applicable.
To evaluate the effect of INCB000928 administered as monotherapy (TGA) or in combination with ruxolitinib (TGB and TGC) on hepcidin level, iron homeostasis, and erythropoiesis.	• Blood levels of hepcidin • Iron homeostasis parameters • Erythropoiesis parameters **Note:** Upon implementation of Amendment 9, further analyses will not be performed.

Overall Design:

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

Table 2: Key Study Design Elements

Study Phase	Phase 1/2
Clinical Indication	Participants with anemia due to PMF, post–PV, or post–ET MF.
Population	Male and female participants at least 18 years of age who have not undergone any stem cell transplantation, who are not candidates for stem cell transplantation, and who are transfusion-dependent or present with symptomatic anemia due to PMF, post–PV, or post–ET MF.
Number of Participants	A dose-escalation stage for each of 3 treatment groups (TGA, TGB and TGC), and an expansion stage for each treatment group (TGA, TGB and TGC); approximately 206 evaluable participants will be included. Upon implementation of Amendment 9, the expansion stage will not be enrolled.
Study Design	Part 1 Dose escalation based on the BOIN method (Liu and Yuan 2015) will proceed first with INCB000928 as monotherapy in TGA (participants previously treated with JAK inhibitors for at least 12 weeks and are resistant, refractory, or lost response to a JAK inhibitor, OR are intolerant, OR are not eligible to receive a JAK inhibitor treatment). Once the monotherapy dose has been evaluated in at least 3 participants, combination therapy with ruxolitinib will start in TGB (participants who have been on a stable dose of ruxolitinib for at least 12 weeks). Based on safety results from Study INCB 000928-102, the dose escalation in TGB will start at 100 mg (50% of the safe and tolerated tested dose in Study INCB 00928-102) and will not exceed the monotherapy MTD if identified in this current study. After the TGB starting dose (combination of INCB00928 with ruxolitinib) is cleared, combination therapy of INCB000928 with ruxolitinib in TGC (participants who are JAK inhibitor treatment naive) may start at the highest dose of INCB000928 that has been shown to be safe and tolerable in the TGB treatment group. Part 2 Upon implementation of Amendment 9, Part 2 will not be conducted. After completion of dose escalations in TGA, TGB and TGC cohorts, and identification of a safe and tolerated dose(s) (RDE(s)) in each treatment group independently, additional TGA, TGB and TGC participants will be included in the expansion stage at the respective RDE(s). For TGA, at least 9 evaluable participants will be included at each RDE dose level. For TGB and TGC, at least 25 evaluable participants will be included in each RDE dose level. Expansion cohorts will be evaluated to further test safety, efficacy, PK, and PD effects of INCB000928 as monotherapy (for TGA) and in combination with ruxolitinib (for TGB and TGC). For each TGB and TGC cohort, this will provide a $\geq$ 90% chance of identifying a toxicity with a true event rate of 9%. Assuming an unacceptable anemia response rate of 0.07 and a target response rate of 0.25, 25 participants per group will provide an actual Type I error of 0.0936 and a power of 0.904 using the exact binomial test.

Table 2: Key Study Design Elements (Continued)

Estimated Duration of Study Participation	Up to 56 days for screening, continuous treatment in consecutive 28-day treatment cycles for up to 12 months, as long as participants are receiving benefit and have not met any criteria for study treatment discontinuation, 30 days for the safety follow-up period, and up to 1 year after the study treatment discontinuation for the post-treatment follow-up period. Upon implementation of Amendment 9, treatment cycles will be every 3 months for participants who have completed Cycle 12 and remain on treatment. Treatment duration is expected to be up to 12 months.
DMC	Yes (external)
Coordinating Principal Investigator	Prithviraj Bose, MD

Treatment Groups and Duration:

The following 3 treatment groups are planned:

- TGA − INCB000928 administered as monotherapy in participants with transfusion-dependent or symptomatic anemia due to PMF, post–PV, or post–ET MF who were previously treated with JAK inhibitors for at least 12 weeks and are resistant, refractory, or lost response to a JAK inhibitor, OR are intolerant, OR are not eligible to receive a JAK inhibitor treatment.
- TGB − INCB000928 administered in a combination regimen with ruxolitinib in participants with transfusion-dependent or symptomatic anemia due to PMF, post–PV, or post–ET MF who have been on a stable dose of ruxolitinib for at least 12 weeks.
- TGC − INCB000928 administered in a combination regimen with ruxolitinib in JAK inhibitor treatment naive MF participants with transfusion-dependent or symptomatic anemia due to PMF, post–PV, or post–ET MF, with an indication for ruxolitinib initiation for MF-related symptoms.

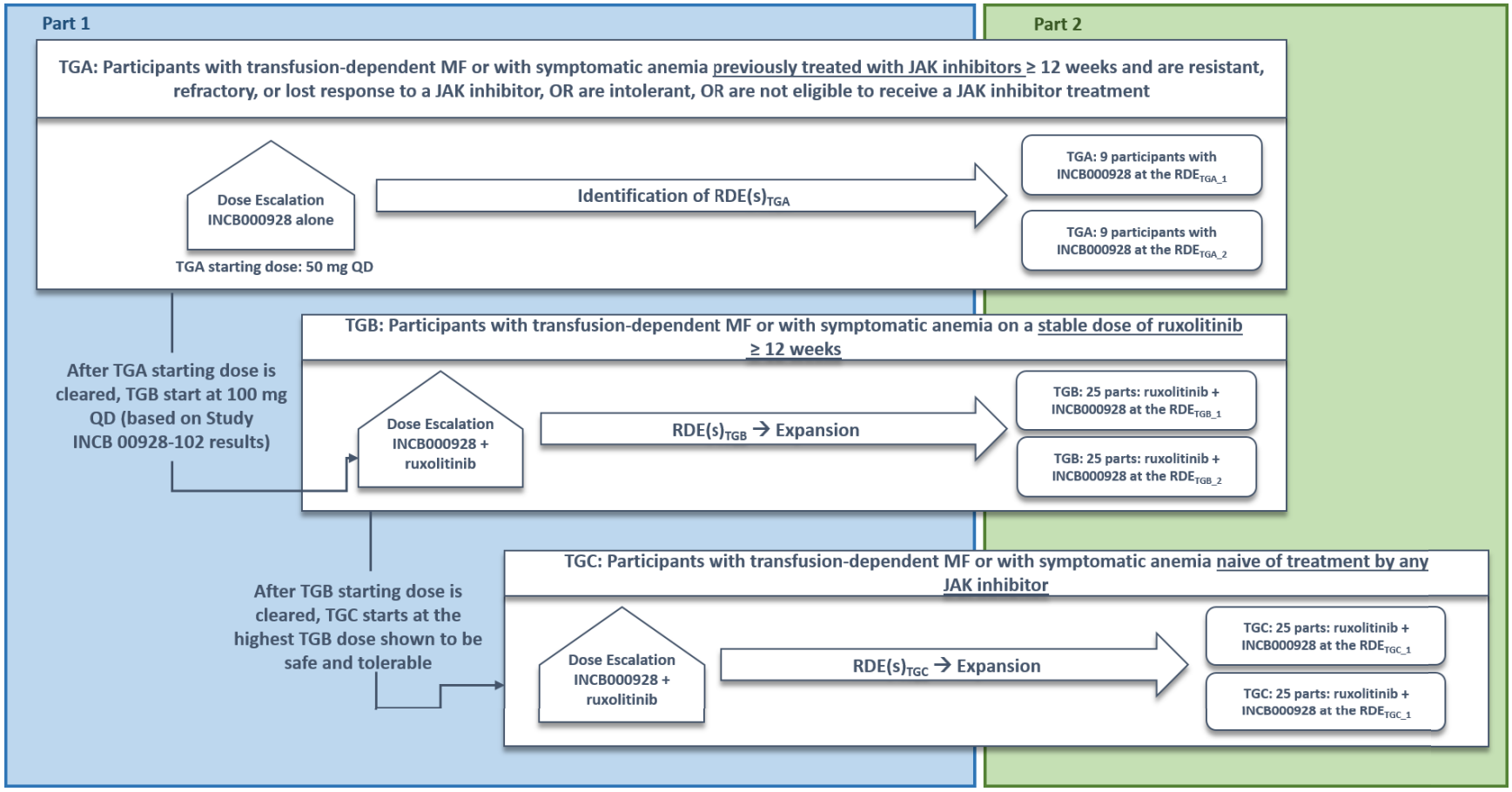
Figure 1 presents a schematic representation of the study design.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. All study assessments will be performed as indicated in the SoA (see Table 3 and Table 4), and all laboratory assessments will be performed as indicated in Table 5 and Table 6.

Day −1 is defined as the day immediately before Day 1.

Further details of study procedures and assessments can be found in the Investigator Site File.

Figure 1: Study Design Schema



Note: Upon implementation of Amendment 9, Part 2 will not be enrolled.

Table 3: Schedule of Activities Prior to Amendment 9

Visit Day (Range)	Screening	Treatment Period									Follow-Up		Notes/Protocol Section
			Cycle 1 (± 1 day)				Cycle 2 (± 1 day)		≥ Cycle 3 (± 3 days)				
	Day −56 to Day −1	Day −1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15	EOT (± 7 days)	Safety (30 + 5 days)	Post-trt (Q6mo ± 14 days)	
Administrative Procedures														
Informed consent signed	X													
Contact IRT	X		X				X		X		X			
Inclusion/exclusion criteria	X		X											Section 5
Demography/general and disease history	X													
Dispense/administer study treatment			X				X		X					Section 6.1
Administer ruxolitinib alone*		X**												*Dose escalation of TGB only. **Within 7 days before Day 1.
Prior/concomitant medications	←From 30 days before Cycle 1 Day 1 until 30 days after the last study treatment dose →													Section 6.7
Safety Assessments														
AE assessment	←From ICF signature to at least 30 days after the last study treatment or start of a new anticancer treatment→													Section 8.3.1 and Section 9
Physical exam/ECOG performance status	X		X	X	X	X	X		X		X	X		Section 8.3.2 and Section 8.3.3
Height	X													
Vital signs/body weight	X		X	X	X	X	X	X	X		X	X		Section 8.3.4
12-lead ECG	X		X				X		X*		X	X		Section 8.3.5 *Will be performed predose on Day 1 of every third cycle (Cycles 3, 6, 9, etc) and postdose on Day 1 of Cycles 3 and 6.

Table 3: Schedule of Activities Prior to Amendment 9 (Continued)

Visit Day (Range)	Screening	Treatment Period									Follow-Up		Notes/Protocol Section
			Cycle 1 (± 1 day)				Cycle 2 (± 1 day)		≥ Cycle 3 (± 3 days)		EOT (± 7 days)	Safety (30 + 5 days)	Post-trt (Q6mo ± 14 days)	
	Day −56 to Day −1	Day −1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15				
Timed triplicate 12-lead ECGs aligned with PK/PD sampling as applicable in TGA participants only	X*		X		X									Section 8.3.5 *At screening and within 7 days prior to Cycle 1 Day 1. ECGs from Cycle 2 and beyond only need to be performed in triplicate if there has been a QT prolongation on-study or the ECG shows a clinically significant abnormality not present at baseline.
Cardiac echography or MUGA scan	X								X*		X			Section 8.3.5.1 *Every sixth cycle.
Liver MRI														
Participants with screening ferritin level of < 1000 ng/mL*									X*		X*			*When on treatment ferritin level is > 1.5 × screening ferritin level AND on treatment ferritin level ≥ 1000 ng/mL; every 3 cycles thereafter and at EOT.
Participants with screening ferritin level of ≥ 1000 ng/mL*	X**								X**		X			*Every 6 cycles. When on treatment, ferritin level > 1.5 × screening level; every 3 cycles, and EOT. **May be performed within 3 months prior to screening.

Table 3: Schedule of Activities Prior to Amendment 9 (Continued)

Visit Day (Range)	Screening	Treatment Period										Follow-Up		Notes/Protocol Section
	Day −56 to Day −1	Day −1	Cycle 1 (± 1 day)				Cycle 2 (± 1 day)		≥ Cycle 3 (± 3 days)		EOT (± 7 days)	Safety (30 + 5 days)	Post-trt (Q6mo ± 14 days)	
			Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15				
Efficacy Assessments														
RBC transfusion record	←During a minimum of 8 weeks before Cycle 1 Day 1, throughout study treatment and until 30 days after the last study dose →													Section 8.2
Hgb (see also the hematology panel)	←During a minimum of 8 weeks before Cycle 1 Day 1, weekly for Cycle 1, every 2 weeks at each cycle thereafter (optional after Cycle 8), at EOT, and safety follow-up →													
BM aspirate and biopsy	X**								X*		X			Section 8.2 *Every sixth cycle (at end of cycle). **May be performed within 3 months prior to screening.
Spleen measurement by palpation*	X		X				X		X		X			Section 8.2 *TGB and TGC only.
MRI/CT scan of the abdomen and the pelvis*	X								X**		X			Section 8.2 *TGB and TGC only. **Every third cycle (at end of cycle).
Symptom burden assessment*			X				X		X		X	X		Section 8.2.1. *TGB and TGC only.
Disease response assessment									X*					Section 8.2 *Every sixth cycle (at end of cycle).
Post-Treatment Assessments														
Disease progression/leukemia transformation/new anticancer treatment													X	Section 7.1 and Section 8.10

Table 4: Schedule of Activities Beginning With Amendment 9

Visit Day (Range)	Treatment Period			Follow-Up	Notes/Protocol Section
	Cycle 3-12 (Q28 days ± 3 days) Day 1	> Cycle 12 (Q3 months ± 14 days) Day 1	EOT (± 7 days)	Safety (30 + 5 days)	
Administrative Procedures					
Contact IRT	X	X	X		
Dispense/administer study treatment	X	X			Section 6.1
Concomitant medications	←From 30 days before Cycle 1 Day 1 until 30 days after the last study treatment dose →				Section 6.7
Safety Assessments					
AE assessment	←From ICF signature to at least 30 days after the last study treatment or start of a new anticancer treatment→				Section 8.3.1 and Section 9
Physical exam/ECOG performance status	X	X	X	X	Section 8.3.2 and Section 8.3.3
Vital signs/body weight	X	X	X	X	Section 8.3.4
12-lead ECG	X*		X*		Section 8.3.5 *Will be performed Day 1 of every third cycle (Cycles 3, 6, 9, 12, and EOT).
Cardiac echography or MUGA scan	X*		X		Section 8.3.5.1 *Every sixth cycle until Cycle 12 (ie, Cycles 6, 12, and EOT)
Liver MRI					
Participants with screening ferritin level of < 1000 ng/mL	X*	X*	X*		*When on-treatment ferritin level is > 1.5 × screening ferritin level AND on-treatment ferritin level is ≥ 1000 ng/mL; every 3 cycles thereafter and at EOT.
Participants with screening ferritin level of ≥ 1000 ng/mL	X*	X*	X*		Every 6 cycles. *When on-treatment ferritin level is > 1.5 × screening level; every 3 cycles, and EOT.
Efficacy Assessments					
RBC transfusion record	←During a minimum of 8 weeks before Cycle 1 Day 1, throughout study treatment, and until 30 days after the last study dose →				Section 8.2
Hgb (see also the hematology panel)	←During a minimum of 8 weeks before Cycle 1 Day 1, weekly for Cycle 1, and every 2 weeks at each cycle thereafter (optional after Cycle 6, at EOT, and safety follow-up→				
BM aspirate and biopsy	X*				Section 8.2 *Every sixth cycle (at end of cycle). Upon implementation of Amendment 9, no longer required after Cycle 6.

Table 5: Schedule of Laboratory Assessments Prior to Amendment 9

Visit Day (Range)	Screening	Treatment Period									Follow-Up		Notes/Protocol Section
	Day −56 to Day −1	Day −1	Cycle 1 (± 1 day for the visits)				Cycle 2 (± 1 day)		≥ Cycle 3 (± 3 days)		EOT (± 7 days)	Safety (30 + 5 days)	Post-trt (Q6mo ± 14 days)	
			Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15				
Safety and Efficacy Assessments														
Pregnancy testing	X						X		X		X	X		Section 8.4.1 Within 3 days of Cycle 1 Day 1 for TGA participants and TGB/TGC participants in the expansion stages and within 3 days of Cycle 1 Day −1 for TGB and TGC participants in the dose-escalation stages) before the first dose of study treatment.
Hematology	X		X	X	X	X	X	X	X		X	X		Section 8.3 and Table 21
Hgb only (in addition to hematological panel above)										X*				Sections 8.2 and Section 8.4 *Optional after Cycle 8
Blood chemistry	X		X	X	X	X	X	X	X		X	X		Section 8.3 and Table 21
HbA1c	X								X*		X			*Every third cycle, from Cycle 3 onward.
Vitamin B12 and MMA	X								X*		X			
Serology screening	X													Section 8.4.2 and Table 21
Lipid panel	X		X				X		X		X	X		Section 8.3 and Table 21 *Cycle 3 Day 1 only.
Coagulation panel	X		X				X		X*		X	X		
Urinalysis	X										X			

Table 5: Schedule of Laboratory Assessments Prior to Amendment 9 (Continued)

Visit Day (Range)	Screening	Treatment Period									Follow-Up		Notes/Protocol Section
	Day −56 to Day −1	Day −1	Cycle 1 (± 1 day for the visits)				Cycle 2 (± 1 day)		≥ Cycle 3 (± 3 days)		EOT (± 7 days)	Safety (30 + 5 days)	Post-trt (Q6mo ± 14 days)	
			Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15				
PD Sampling														
Plasma PD		X*	X		X		X		X**					Section 8.6 *TGA, TGB, and TGC. May be drawn within 7 days prior to Day 1. **Predose on Day 1 of each cycle from Cycle 3 onwards until Cycle 24 Day 1 and additionally 1 sample between 4 and 8 hours postdose on Cycle 3 Day 1 and Cycle 6 Day 1 only. See Table 23 for timing.
Iron homeostasis, erythropoiesis parameters and EPO*	X		X	X	X	X	X	X	X		X	X		Section 8.6 *Included in hematology and chemistry panels. A T2 MRI should be performed in participants as described in Section 6. See Table 23 for timing.
Serum biomarker (predose at Cycles 1, 2, 4, and 7)			X				X		X*		X			Section 8.6 *Cycle 4 Day 1 and Cycle 7 Day 1 only. See Table 23 for timing.
Whole blood correlative DNA*			X						X**					Section 8.6 *May not be collected if local restrictions apply. **Cycle 7 Day 1 only. See Table 23 for timing.
Whole blood correlative RNA*			X											Section 8.6 *May not be collected if local restrictions apply. See Table 23 for timing.

Table 5: Schedule of Laboratory Assessments Prior to Amendment 9 (Continued)

Visit Day (Range)	Screening	Treatment Period									Follow-Up		Notes/Protocol Section
	Day −56 to Day −1	Day −1	Cycle 1 (± 1 day for the visits)				Cycle 2 (± 1 day)		≥ Cycle 3 (± 3 days)		EOT (± 7 days)	Safety (30 + 5 days)	Post-trt (Q6mo ± 14 days)	
			Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15				
PK Sampling														
Blood sampling		X*	X		X				X**					Section 8.5 *TGB dose escalation only, within 7 days before Day 1. **1 sample predose, 1 sample 2 hours postdose, and 1 sample between 4 and 8 hours postdose on Cycle 3 Day 1 and Cycle 6 Day 1. See Table 22 for timing.
Urine sampling					X									Section 8.5.2

Table 6: Schedule of Laboratory Assessments Beginning With Amendment 9

Visit Day (Range)	Treatment Period				Follow-Up	Notes/Protocol Section
	Cycle 3-12 (Q28 days ± 3 days)		> Cycle 12 (Q3 mo ±14 days)	EOT (± 7 days)	Safety (30 + 5 days)	
	Day 1	Day 15	Day 1			
Safety and Efficacy Assessments						
Pregnancy testing	X		X	X	X	Section 8.4.1
Hematology	X		X	X	X	Section 8.3 and Table 21
Hgb only (in addition to hematological panel above)		X*		X	X	Sections 8.2 and Section 8.4 *Optional after Cycle 6
Blood chemistry	X		X	X	X	Section 8.3 and Table 21
Vitamin B12 and MMA	X		X	X		
Lipid panel	X		X			Section 8.3 and Table 21
Iron homeostasis	X		X		X*	Section 8.3.6 *Optional for participants with elevated ferritin.

2. INTRODUCTION

2.1. Background

2.1.1. Overview of Myelofibrosis

The classic MPNs include chronic myelogenous leukemia, PV, ET, and PMF. Myelofibrosis can present as a de novo disorder (PMF) or evolve secondarily from previous PV or ET (post–PV MF or post–ET MF). Regardless of whether MF is a primary or secondary disorder, it is characterized by a clonal stem cell proliferation associated with production of elevated serum levels of multiple inflammatory and proangiogenic cytokines; a characteristic BM stromal pattern that includes varying degrees of collagen fibrosis, osteosclerosis, and angiogenesis; and a peripheral blood smear showing a leukoerythroblastic pattern with varying degrees of circulating progenitor cells. Clinically, MF is characterized by progressive anemia, leukopenia or leukocytosis, thrombocytopenia or thrombocythemia, and multi-organ extramedullary hematopoiesis most prominently involving the liver and spleen. Patients may experience debilitating symptoms (Mesa et al 2013a, Mesa et al 2013b), sequelae of massive splenomegaly (eg, pain, limitations of movement, early satiety and shortness of breath, hepatic obstruction, splenic infarction), a hypermetabolic state with cachexia, progressive hematopoietic failure, progression to leukemia, and premature death.

The median age at diagnosis of MF is approximately 60 to 65 years, and the incidence of PMF has been estimated at 4 to 6 cases per 100,000 people in the US (Stein et al 2015). Survival in MF varies with the presence or absence of specific risk factors. Analysis of risk factors over the last 20 years has resulted in a number of prognostic scoring systems (Bose and Verstovsek 2016). A prognostic scoring system based on a time-dependent risk evaluation has been developed: the Dynamic International Prognostic Scoring System for PMF (Passamonti et al 2010). Age of greater than 65 years, presence of constitutional symptoms, anemia (Hgb < 100 g/L), leukocytosis (WBC count > 25×10^9/L), and a circulating blast percentage of 1% or higher were assessed for their impact on survival when analyzed as time-dependent covariates in a multivariate Cox proportional hazard model. The approach showed that acquisition of anemia over time affects survival with a hazard ratio roughly double that of other parameters, and therefore anemia was assigned a score of 2, while the other 4 factors were assigned scores of 1. Four risk categories with nonoverlapping survival curves have been then described (Passamonti et al 2010).

For the subset of patients who are younger (generally < 65 years), are otherwise healthy, and have a histocompatible donor, allogeneic stem cell transplantation may provide a curative option, although with substantial risks of mortality (10%-20%; Deeg et al 2003). Drug therapies used in MF, including hydroxyurea, busulfan, 6-mercaptopurine, anagrelide, thalidomide, lenalidomide, interferon, corticosteroids, and ESAs or growth factors, have not been shown to improve survival. Some can increase the risk of leukemic transformation and can be poorly tolerated, and all have limited effectiveness in improving splenomegaly and constitutional symptoms. Splenectomy, performed in approximately 10% of the patient cohort reported by Cervantes et al (2009), is associated with significant morbidity and mortality. Splenic irradiation is also employed to reduce symptoms secondary to splenomegaly, but symptomatic improvement is

variable and short-lived; moreover, transient and life-threatening pancytopenia and an approximate 20% treatment-related mortality have been noted.

2.1.2. Anemia in Patients With Myelofibrosis

Myelofibrosis is a progressive disease. In a study with 1000 patients, the percentage of anemia was 38% in patients at the time of diagnosis versus 64% in patients assessed more than 1 year after diagnosis (Tefferi et al 2012).

Anemia is among the cardinal features of MF and represents a therapeutic challenge in patients with primary- or secondary-MF. Between 35% and 54% of patients with MF have Hgb levels < 10 g/dL, and approximately 25% of these patients are already RBC transfusion-dependent at the time of diagnosis (Cervantes et al 2009, Masarova et al 2017, Passamonti et al 2010, Tefferi et al 2012) and nearly all patients with MF will eventually develop anemia. Anemia is associated with poor prognosis in MF (Cervantes et al 2012) and inferior quality of life (Tefferi et al 2014). Hemoglobin levels of less than 10 g/dL at the time of diagnosis and during the course of the disease have a significant negative impact on overall survival (Cervantes et al 2009, Gangat et al 2011, Passamonti et al 2010).

The pathogenesis of anemia in MF can be of multiple etiologies including:

- Displacement of medullary erythropoietic tissue due to BM fibrosis leading to extramedullary erythropoiesis (characterized by inadequate erythropoiesis at extramedullary sites, and in particular in spleen and liver) inducing (hepato) splenomegaly and RBC sequestration and destruction.
- Perturbation of the BM cytokine expression (upregulation of inflammatory cytokines in the BM), leading to a proinflammatory cytokine profile including increased hepcidin levels (resulting in impaired iron metabolism), and impaired erythroid differentiation.
- RBC loss due to bleeding in some patients.

The commonly used treatments for anemia in patients with MF include ESAs, androgens, immunomodulating drugs, corticosteroids, and splenectomy. However, these treatments have the following limitations:

- ESA only benefits RBC-transfusion-independent patients with low levels of endogenous erythropoietin. Even among these patients, less than half will respond to ESA treatment, and the responses are generally short-lived (Birgegård 2014, Cervantes et al 2004, Cervantes et al 2006, Huang and Tefferi 2009, Tsiara et al 2007).
- The use of androgens and corticosteroids is limited due to their low efficacy and potential adverse effects (transaminases increase and potential androgenic promotion of prostate cancer for androgens [Cervantes et al 2015] and long-term side effects of corticosteroids).
- The use of splenectomy is limited by its short-term morbidity including bleeding, infection, and thrombosis and by its mortality (Tefferi et al 2000).

Moreover, anemia in patients with MF can be exacerbated by therapies administered to treat the disease.

Ruxolitinib was the first JAK inhibitor approved for patients with intermediate- and high-risk MF. When administered to patients with MF, it may cause therapy-related anemia due to suppression of residual BM function (Cervantes et al 2013, Mead et al 2015). The most frequent hematological AEs observed in patients with MF receiving ruxolitinib are anemia and thrombocytopenia (Harrison et al 2017).

Two randomized Phase 3 studies have been conducted in patients with PMF, post–PV MF, or post–ET MF comparing ruxolitinib with the best available therapy in the COMFORT-I study and comparing ruxolitinib to placebo in the COMFORT-II study. The following results were observed:

- In the COMFORT-I study, 45.2% of the participants in the ruxolitinib arm experienced Grade 3-4 anemia based on laboratory values and the proportion of those ruxolitinib-treated participants requiring RBC transfusions increased during the first 8-12 weeks and then decreased to levels similar to those in the placebo arm at approximately Week 24 (Verstovsek et al 2012). In the COMFORT-II study, 42% of the participants receiving ruxolitinib experienced Grade 3-4 anemia at some point during the study (Harrison et al 2012).
- The analysis of the 5-year events in participants treated with ruxolitinib in the COMFORT-II trial showed that anemia was the most frequent Grade 3-4 AE, experienced by 22.5% of the participants. Nearly half of the participants (46.1%) who received ruxolitinib (including after crossover from the best available therapy) experienced a new or worsening Grade 3-4 decrease Hgb based on the laboratory values (Harrison et al 2016).
- Hemoglobin dynamics were analyzed for the participants with MF receiving ruxolitinib in the framework of the COMFORT-I (n = 155) and COMFORT-II (n = 146) studies. A total of 301 participants received ruxolitinib across both studies. In this pooled analysis, the mean Hgb levels in participants treated with ruxolitinib decreased from a pretreatment value of 10.88 g/dL to 9.08 g/dL at Week 12. Thereafter, Hgb levels improved to levels close to pretreatment values after 24 weeks. At Week 24, the mean Hgb level in the ruxolitinib group was 10.2 g/dL (Al-Ali et al 2016).
- Of the participants in the ruxolitinib arm from both COMFORT studies not anemic at baseline (defined as Hgb ≥ 10 g/dL), 61% developed postbaseline anemia, and of those with baseline anemia, 69% experienced worsening anemia (Gupta et al 2016).

A potential approach to limit JAK inhibitor-associated exacerbation of MF-related anemia was evaluated in the Phase 2 REALISE study (Cervantes et al 2021). This study investigated a novel ruxolitinib dose administration strategy with a reduced starting dose of 10 mg BID followed by delayed up-titration to a maximum dose of 25 mg BID in participants with anemic MF who were starting on ruxolitinib treatment. A total of 51 participants with either primary MF, post–ET MF, or post–PV MF, and with Hgb < 10 g/dL and palpable splenomegaly were included. Overall, 70% of participants achieved a ≥ 50% reduction in palpable spleen length at any time during the study. Median hemoglobin levels remained stable with transfusion support, and transfusion

requirements did not increase when compared with baseline; as a result, this suggests that this may be a useful approach to limit therapy-related exacerbation of anemia in this population, although improving the underlying MF-related anemia remains a clinical need.

Currently available treatments for MF-related anemia are inadequate, with less than 40% of patients presenting a response among RBC transfusion-independent patients and even less among transfusion-dependent patients, and often short-lasting.

Unfortunately, most patients with MF presenting with anemia either require transfusion or have an inadequate response to the currently available therapies and become transfusion-dependent. For the majority of patients with MF, the management of anemia remains an unmet need (Barraco et al 2019, Naymagon and Mascarenhas 2017).

Management of anemia in patients with MF and in patients with MF receiving ruxolitinib includes blood transfusions and/or ruxolitinib dose modifications. Repeated transfusions carry the risk of alloimmunization as well as morbidity and mortality due to iron overload.

2.1.3. Role of Janus Kinase Pathway in Myelofibrosis

Ruxolitinib, a potent and selective inhibitor of JAKs 1 and 2, is approved for use in patients with intermediate- or high-risk MF, including PMF, post–ET MF, and post–PV MF, in all participating countries. Registration studies showed improvement in spleen size, symptom burden, and overall survival with ruxolitinib use in this patient population (Cervantes et al 2013, Harrison et al 2012, Mesa et al 2013a, Mesa et al 2013b, Verstovsek et al 2012, Verstovsek et al 2015, Vannucchi et al 2015).

2.2. Overview of INCB000928

2.2.1. INCB000928 Mechanism of Action

INCB000928 represents a novel and selective inhibitor of ALK2. Cell-based profiling indicated that INCB000928 inhibited ALK2, with a 12-fold selectivity over ALK1 and an 18-fold selectivity against ALK3 in cell-based assays. INCB000928 demonstrated weak IC_{50} potency against ALK5 and ALK6 biochemically. In human liver cells, INCB000928 inhibited the BMP-induced production of hepcidin in both Huh7 cells and human primary hepatocytes (refer to the INCB000928 IB for further details).

2.2.2. INCB000928 Safety Pharmacology

INCB000928 had no effect on CNS or respiration in rats after a single dose; the no-observed-effect level was 100 mg/kg, the highest dose evaluated. The IC_{50} for hERG inhibition was estimated to be > 100 µM, and administration of INCB000928 to dogs as a single oral dose of 15 and 50 mg/kg resulted in dose-dependent increases in mean heart rate (mean differences of up to 17 and 70 BPM, respectively, over time-matched controls), with concomitant decreases in PR, RR, and QTc (Van de Water) intervals and blood pressure at 50 mg/kg per day. The NOAEL was 15 mg/kg based on the small magnitude of the effects at this dose. The cause of the increased heart rate is uncertain.

Given the ability to monitor vital signs in clinical studies, the risk associated with INCB000928 administration is expected to be low.

2.2.3. INCB000928 Pharmacology Summary

In anemia mouse models, the liver-specific deletion of either ALK2 or ALK3 can block the induction of hepcidin production and induce iron overload (Steinbicker et al 2011a). BMP signaling plays a central role in driving hepcidin transcriptional induction by activating SMAD signaling.

In studies using naive C57BL/6 mice, INCB000928 exhibited consistent PK with exposures that were in line with the doses used. Target engagement of INCB000928 was proven by studies showing dose-dependent decreases in the direct targets of ALK2 and pSMAD1/5, and these decreases corresponded to plasma concentrations exceeding the in vivo pSMAD IC_{50}. Likewise, hepcidin, the downstream target of pSMAD signaling, was also suppressed in a dose-dependent manner by INCB000928.

INCB000928 is efficacious in 2 mouse models of hepcidin driven anemia. In the B16F10-induced anemia model, INCB000928 was able to reduce the anemia brought on by intraperitoneal growth of B16F10 cells in a dose dependent manner, as indicated by improved RBC counts, Hgb levels, and Hct levels. Doses of INCB000928 that give IC_{50} exposure for approximately 9 hours are likely to result in improvement in symptoms of anemia. Likewise, INCB000928 also was efficacious in the turpentine induced anemia model where mice dosed with INCB000928 had RBC, Hgb, and Hct levels similar to those of nonanemic mice.

The results from the in vitro and in vivo pharmacology studies (refer to the IB) indicate that INCB000928 is a potent, orally bioavailable and highly selective small molecule inhibitor of ALK2. Dysregulation of the iron homeostasis regulator hepcidin can result in iron deficiency and anemia. Hepcidin levels have been found to be elevated in patients suffering from anemias brought on by numerous primary diseases including cancer. Activin receptor-like kinase-2 signaling through the SMAD pathway leads to transcriptional activation of hepatic hepcidin (HAMP gene), making ALK2 inhibition a potential therapeutic intervention point for hepcidin induced anemia.

Therefore, ALK2 inhibition could be a good strategy for treatment of anemia associated with ruxolitinib treatment in MF patients, as inhibition of hepcidin expression in the liver leads to increased mobilization of sequestered iron from cellular stores and subsequent stimulation of erythropoiesis, which does not require the action of JAK2 (Asshoff et al 2017, Ross et al 2012).

2.3. Study Rationale

2.3.1. Role of Activin Receptor-Like Kinase-2 Regulating the Bone Morphogenetic Protein Pathway

Bone morphogenetic protein belongs to the TGF-β superfamily, and the binding of BMP ligands to BMP receptors leads to the assembly of tetrameric receptor complexes composed of Type II receptors (BMPRII, ACTRIIA, or ACTRIIB) and Type I receptors (ALK1, ALK2, ALK3, or ALK6). The activated BMP receptor complex phosphorylates SMAD proteins, such as SMAD1/5/8, which then associate with co-SMADs and translocate to the nucleus to regulate gene transcription (Blobe et al 2000, Ross et al 2012).

Activin receptor-like kinase-2 has been reported to mediate multiple human diseases including fibrodysplasia ossicans progressive, diffuse intrinsic pontine glioma, and cancer (Massagué and Wotton 2000, Taylor et al 2014). Importantly, ALK2 has been shown to play an essential role in regulating hepcidin levels and may contribute to anemia of chronic diseases and anemia due to hematological malignancies where hepcidin elevation has been observed (Andriopoulos et al 2009, Gallitz et al 2018, Meynard et al 2009, Steinbicker et al 2011a, Steinbicker et al 2011b).

2.3.2. Role of Hepcidin in Myelofibrosis-Related Anemia

Hepcidin is a small peptide hormone primarily synthesized in hepatocytes that reduces both duodenal iron absorption and iron export from monocytes and macrophages by binding to and inducing the internalization and degradation of the iron exporter ferroportin (Nemeth et al 2004, Theurl et al 2011, Weiss and Goodnough 2005, Zhao et al 2013). The elevated serum hepcidin levels enhance storage of iron within the reticuloendothelial system and result in reduced iron availability and iron restricted erythropoiesis. Inappropriately increased hepcidin expression causes severe functional iron deficiency anemia in humans and is central to the pathophysiology of anemia of chronic disease (Weiss and Goodnough 2005).

In vivo, target engagement of INCB000928 was shown by dose dependent pSMAD1/5 reduction in the mouse liver, with a corresponding decrease in plasma hepcidin levels ($IC_{50} \approx 200$ nM at 4 hours post–single oral dose).

Elevated serum hepcidin levels in patients with MF have been shown to be associated with reduced Hgb levels, increased requirement for RBC transfusions, and reduced overall survival (Pardanani et al 2013). A study on 99 participants with MF (49 with PMF and 50 with secondary-MF) showed that the serum hepcidin level was not different between participants with primary- and secondary-MF (103.3 vs 80.8 ng/mL, $p = 0.380$) and was positively correlated with IL-2Rα and IL-6. Serum hepcidin levels were also elevated in participants treated with ruxolitinib (Zhou et al 2018). A significant proportion of patients develop anemia and become dependent on frequent RBC transfusions (Tefferi et al 2012).

2.3.3. Scientific Rationale for Study Design

This is an open-label, nonrandomized, Phase 1/2 study to evaluate the safety and tolerability, the PK, the PD, and the efficacy (antianemic activity) of INCB000928 administered alone or in combination with ruxolitinib in participants with MF who are transfusion-dependent or presenting with symptomatic anemia (see Section 5.1 for the definitions of the populations).

As noted in Section 2.3.2, elevated hepcidin levels have been observed in both MF participants who are not on JAK inhibitor therapy, as well as in MF participants who are being treated with JAK inhibitor. It is unclear which patient population may derive the greatest benefit from ALK2 inhibition and hepcidin reduction, when considering participants who are post-JAK inhibitor treatment (TGA) versus those on active ruxolitinib therapy (TGB) versus those who are JAK inhibitor naive and newly starting ruxolitinib (TGC). Early hepcidin control by concurrent initiation of INCB000928 with ruxolitinib may lead to improved erythropoiesis and prevention or reduction of transfusion dependence, which can be observed in participants newly starting JAK inhibitor therapy. Of note, early initiation and long-term continuation of ruxolitinib therapy have been shown to contribute to improved MF outcomes, including an overall survival benefit

(Verstovsek et al 2012a, Verstovsek et al 2017). Given that anemia is a common reason to discontinue ruxolitinib early or delay ruxolitinib initiation, it is plausible that hepcidin control may yield the greatest benefit in participants receiving frontline treatment. With these considerations, evaluation of ALK2 inhibition on anemia will be evaluated independently in these 3 populations.

INCB000928 tablets will be administered orally at a starting dose of 50 mg QD in the TGA participant population (monotherapy). Based on safety results from Study INCB 00928-102, the dose escalation in TGB will start at 100 mg (50% of the safe and tolerated tested dose in Study INCB 00928-102) and will not exceed the monotherapy MTD if identified in this current study. One cycle will be defined as 28 consecutive days; treatment will consist of repeating 28-day cycles.

The dose-escalation stages will be performed in each treatment group to determine the MTD. The INCB000928 dose will be escalated using an open-label BOIN design in each defined population, and a safe and tolerable dose(s) RDE(s) will be determined. The RDE(s) will be further explored in the expansion stages. Dose escalation and de-escalation will follow the BOIN design algorithm (see Section 4.1).

For TGA, the recommended dose(s) for expansion of INCB000928 monotherapy will be determined based on the TGA dose-escalation stage results. For TGB and TGC, the recommended dose(s) for expansion of INCB000928 when administered in combination with ruxolitinib will be determined based on the TGB and TGC dose-escalation stage results, independently.

The expansion stages will aim at further assessing the safety and tolerability of INCB000928, the PK and PD, and determining its antianemic activity as monotherapy and when combined with ruxolitinib in participants with transfusion-dependent or symptomatic anemia due to myeloproliferative disorders.

2.3.4. Justification for Dose

A Phase 1a, double-blind, randomized, placebo-controlled, single-dose, dose-escalation and food-effect study has been conducted with INCB000928 in order to assess the safety, tolerability, and PK of INCB000928 when administered orally as a single dose to healthy adult participants (refer to Study INCB 00928-101 and the IB).

Following single oral dose administration, INCB000928 was rapidly absorbed, with median t_{max} observed at 2.0 to 4.1 hours postdose in plasma and across the dose range of 10 to 500 mg. A high-fat meal delayed INCB000928 median t_{max} by 1 hour; however, it did not statistically significantly change C_{max} or AUC ($p = 0.2788$). The geometric mean ratios (90% CIs) for C_{max} and AUC_{∞} were 0.977 (0.905, 1.055) and 1.031 (0.968, 1.098), respectively; both 90% CIs were within the "no effect limits" of 0.80 to 1.25, suggesting INCB000928 can be administered without regard to food (refer to the IB).

Study INCB 00928-102 is a single-center, randomized, double-blind, placebo-controlled, sponsor-unblinded, multiple-dose, Phase 1 study designed to evaluate the safety, tolerability, PK, and PD of escalating oral doses of INCB000928 in healthy adult participants (refer to the IB).

Preliminary PK data and analysis from this multiple ascending dose study are available for 44 healthy participants who have received 50-, 100-, 150-, 200-, or 400-mg INCB000928 QD orally for 10 days. INCB000928 achieved C_{max} at a median t_{max} of 2- to 4-hours postdose and was eliminated in a biexponential fashion, with a mean $t_{½}$ ranging from 24.2 to 26.7 hours (see Table 7). The mean accumulation ratio was 2.01- to 2.16-fold across the dose range. INCB000928 reached steady-state around Day 5 to Day 7. Supraproportionality was observed from 50 to 400 mg QD; however, INCB000928 plasma exposures seemed to increase proportional to dose as the dose increased from 150 to 400 mg QD.

Table 7: Summary of Preliminary Steady-State Pharmacokinetic Parameters for INCB000928 on Day 10 (Study INCB 00928-102)

Parameter	Dose (mg)				
	50 (N = 9)	**100 (N = 8[a])**	**150 (N = 9)**	**200 (N = 9)**	**400 (N = 9)**
C_{max} (nM)	391 ± 116 (375, 31.0%)	635 ± 189 (605, 36.0%)	1470 ± 288 (1450, 18.5%)	1850 ± 393 (1810, 24.4%)	4400 ± 1170 (4270, 25.6%)
T_{max} (h)	2.0 (2.0, 4.0)	4.0 (2.0, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	4.0 (2.0, 4.0)
C_{min} (nM)	141 ± 26.4 (139, 18.8%)	241 ± 89.9 (221, 53.2%)	477 ± 90.9 (468, 20.3%)	686 ± 208 (659, 30.5%)	1890 ± 655 (1800, 32.5%)
AUC_{τ} (h·nM)	5540 ± 1150 (5430, 21.3%)	9330 ± 2940 (8880, 35.9%)	19,600 ± 2260 (19,500, 12.0%)	27,200 ± 6560 (26,500, 25.3%)	70,200 ± 19,700 (68,100, 25.9%)
$t_{½}$ (h)	26.7 ± 2.88 (26.6, 10.7%)	26.4 ± 2.84 (26.3, 11.3%)	24.2 ± 2.56 (24.0, 10.6%)	25.9 ± 4.00 (25.6, 15.4%)	26.2 ± 2.96 (26.1, 10.9%)
CL_{ss}/F (L/h)	18.7 ± 3.95 (18.3, 21.3%)	23.7 ± 9.58 (22.4, 35.9%)	15.4 ± 1.91 (15.3, 12.0%)	15.5 ± 4.00 (15.0, 25.3%)	12.0 ± 2.79 (11.7, 25.9%)
V_z/F (L)	721 ± 175 (702, 24.0%)	920 ± 445 (849, 42.8%)	538 ± 95.2 (530, 18.5%)	567 ± 122 (556, 20.9%)	455 ± 123 (440, 28.6%)
Accumulation index	2.16 ± 0.168 (2.15, 7.73%)	2.14 ± 0.165 (2.13, 7.95%)	2.01 ± 0.148 (2.00, 7.37%)	2.11 ± 0.233 (2.10, 10.9%)	2.13 ± 0.172 (2.12, 7.86%)

Note: Values are presented as mean ± STD (geometric mean, geometric percent coefficient of variation), except for t_{max}, which is reported as median (min, max).

[a] One participant was excluded from the summary due to significantly low exposure levels on Day 10 that await further investigation.

The proposed starting dose for the INCB 00928-104 study is 50 mg QD as monotherapy (TGA). In agreement with the principles outlined in ICH S9 (2010) for selecting the starting dose for clinical trials in cancer patients and FDA Guidance for Industry Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals (2019), the proposed starting dose for INCB 00928-104 is 50 mg QD. Based on available clinical exposure data from INCB 00928-101, 50 mg QD is anticipated to be both pharmacologically active and reasonably safe for use. Based on Day 10 PK data from the healthy human participant Phase I study, INCB 00928-102, the AUC_t (total) at 50 mg QD is 5.54 µM·h and 0.391 µM for C_{max} (total). This C_{max} value exceeds the in vivo IC_{50} obtained in a cancer-induced mouse anemia model (200 nM) and is thus anticipated to be pharmacologically active. The AUC and C_{max} values at 50 mg QD are ≥ 4.2-fold and ≥ 5.1-fold lower, respectively, than exposures associated with the NOAELs in 3-month toxicology studies in rats and dogs; thus, this dose is anticipated to be reasonably safe for use.

The initial dose for participants enrolled in Japan is described in Section 4.1.4.

Dose escalation will proceed following review of safety information and PK data collected as the study progresses as described in Section 4.1 and Section 6.5.

The decision on the RDE and future development will incorporate safety, PK, and PD data, as available, obtained during this study (see Section 4.1 and Section 6.5.4).

Based on safety results from Study INCB 00928-102, the dose escalation in TGB will start at 100 mg (50% of the safe and tolerated tested dose in Study INCB 00928-102) and will not exceed the monotherapy MTD if identified in this current study.

After the TGB starting dose (combination of INCB00928 with ruxolitinib) is cleared, the combination therapy of INCB000928 with ruxolitinib in TGC (participants who are JAK inhibitor treatment naive) may start at the highest dose of INCB000928 that has been shown to be safe and tolerable in the TGB treatment group.

Currently, there is favorable safety data for INCB000928 monotherapy and INCB000928 in combination with ruxolitinib, with no overlapping toxicities observed with combination treatment (refer to Study INCB 00928-104). As of 03 OCT 2022 (unaudited data), 18 participants are enrolled in TGA at doses of 50 mg QD (4 participants), 100 mg QD (4 participants), 200 mg QD (6 participants), and 400 mg QD (4 participants). In TGB, 9 participants are enrolled at INCB000928 doses of 100 mg QD (4 participants) and 200 mg QD (5 participants).

The median age of the participants was 73 years (range 53 to 84 years) in TGA and 74 years (range 64 to 85 years) in TGB. In TGA and TGB, respectively, 66.7% and 55.6% of the participants were male. Participants in TGA and TGB were intermediate-2 or high DIPSS risk score, presented with primary or secondary myelofibrosis, and 61.1% of the participants in TGA were transfusion-dependent.

The safety profile of INCB000928 monotherapy and INCB000928 in combination with ruxolitinib was favorable, with mainly low-grade TEAEs. As of 29 OCT 2024, 53 participants with anemia due to MF or MDS received INCB000928 monotherapy at doses up to 600 mg QD in 2 ongoing studies (INCB 00928-104 and INCB 00928-105) or in combination with ruxolitinib (N = 48) in study INCB 00928-104.

Most participants receiving monotherapy (52 participants [98.1%]) had at least 1 TEAE. No event of tachycardia or heart rate increased was reported. Three participants (5.7%) had a TEAE with a fatal outcome (death, pneumonia pseudomonal, and sepsis). Serious TEAEs, including those with a fatal outcome, occurred in 18 participants (34.0%); those occurring in ≥ 2 participants included COVID-19 (4 participants [7.5%]) and anemia (2 participants [3.8%]). Two participants (3.8%) had serious TEAEs considered related to the study drug by the investigator: rash maculo-papular was reported in 1 participant and atrial fibrillation and generalized edema were reported in 1 participant.

Nine participants (17.0%) had a TEAE leading to discontinuation of INCB000928: anemia, cardiac failure acute, hemorrhage intracranial, pneumonia, pneumonia pseudomonal, pruritus, rash maculo-papular, transformation to acute myeloid leukemia, and urinary tract infection in 1 participant (1.9%) each. Anemia, pruritus, and rash maculo-papular were considered related to the study drug by the investigator.

One participant who received INCB000928 600 mg QD (Study INCB 00928-105) had a DLT of thrombocytopenia (Grade 4).

Of the 48 participants with anemia due to MF who received INCB000928 at doses up to 600 mg QD in combination with ruxolitinib (study INCB 00928-104), 47 (97.9%) had at least 1 TEAE. No event of tachycardia or heart rate increased was reported. One participant (2.1%) had a TEAE with a fatal outcome (sepsis). Serious TEAEs, including the event with a fatal outcome, occurred in 22 participants (45.8%); those occurring in ≥ 2 participants included pneumonia (5 participants [10.4%]), squamous cell carcinoma of the skin (3 participants [6.3%]), and acute kidney injury, atrial fibrillation, pneumonia bacterial, sepsis, and urinary tract infection (2 participants [4.2%] each). No serious TEAEs were considered related to INCB000928 by the investigator except for the event of pulmonary alveolar hemorrhage in a participant on INCB000928 400 mg QD and ruxolitinib; this participant had post–essential thrombocythemia MF, was on concomitant aspirin, and had findings of bilateral pneumonia by CT scan. The pulmonary alveolar hemorrhage in this participant was a DLT. Two other participants who received INCB000928 400 mg QD + ruxolitinib also had DLTs (mouth hemorrhage and epistaxis in 1 participant, and diarrhea in 1 participant). The MTD was not established. Seven participants (14.6%) had a TEAE leading to discontinuation of INCB000928: acute kidney injury, hyperferritinemia, pneumonia, sepsis, thrombocytopenia, transformation to acute myeloid leukemia, and urinary tract infection in 1 participant (2.1%) each. Except for the event of hyperferritinemia, no TEAEs leading to study drug discontinuation were considered related to INCB000928 by the investigator.

There have been no treatment-related deaths. The safety laboratory parameters and vital signs did not show any significant change or any indication of toxicity in either TGA or TGB (study INCB 00928-104). In TGA, after clearing the 100 mg and 200 mg QD doses, those participants still on-study were enrolled at lower doses and had their dose of INCB000928 increased without experiencing increased toxicity. As of 29 OCT 2024 among the 32 participants enrolled in TGA of Study INCB 00928-104, 27 discontinued study treatment: 7 due to lack of efficacy, 6 because of investigator decision, 6 due to AEs, 3 withdrew consent to further participate, 2 due to death, 1 met protocol discontinuation criteria, 1 was lost to follow-up, and 1 for other reason. Among the 48 participants enrolled in TGB and TGC (ruxolitinib combination cohorts of study INCB 00928-104), 32 discontinued study treatment: 7 due to lack of efficacy, 8 because of investigator decision, 6 due to AEs, 5 withdrew consent, 3 met Protocol discontinuation criteria, 2 for other reasons, and 1 for progressive disease.

2.4. Benefit/Risk Assessment

2.4.1. Potential Risks of INCB000928 Based on Preclinical Toxicology

The toxicologic and toxicokinetic profiles of INCB000928 were characterized in a single-dose dog study and in repeat oral dose studies of up to 3-months in duration in rats and dogs. Potential genetic toxicity was evaluated in a bacterial mutagenicity assay, an in vitro micronucleus assay, an in vivo micronucleus and comet assay, and a micronuclei assessment in the 28-day GLP rat study. Phototoxicity was evaluated in vitro and in vivo.

For complete details of toxicology studies and results, refer to the IB.

Target tissues identified in 28-day toxicity studies in both rats and dogs include the GI tract, liver, spleen, skin (hair follicles), and BM. Effects on the liver included increased iron levels and inflammatory changes and at high doses, secondary hepatocellular effects and increased ALT/AST levels. Increased hematopoiesis was observed in the BM in both species, and extramedullary hematopoiesis was observed in the spleen and liver of rats. Effects on the GI tract were primarily mucosal hypertrophy/hyperplasia, with secondary inflammatory findings and changes in the draining mesenteric lymph node. Skin changes were related to effects on hair follicles (arrest in the anagen phase).

These findings were consistent with INCB000928 inhibition of ALK2 at lower doses and ALK3 at higher doses. Activin receptor-like kinase-2, a Type I receptor for BMPs, plays an important role in the downstream signaling of multiple BMPs. Bone morphogenetic protein signaling through ALK2 has been demonstrated to play a crucial role in iron regulation (Steinbicker et al 2011b). Additionally, BMP signaling through ALK3, a related BMP Type I receptor, is also involved in iron regulation (Steinbicker et al 2011a), but is also involved in the proliferation of the intestinal mucosa (Vanuytsel et al 2013) and hair follicle growth and differentiation (Andl et al 2004, Ming Kwan et al 2004), amongst other effects. INCB000928 is a potent inhibitor of ALK2 (IC_{50} = 20 nM) with 58-fold selectivity over ALK3 in biochemical assays. Therefore, alterations in iron metabolism are likely related to ALK2 inhibition at lower doses and both ALK2 and ALK3 at higher doses, while findings related to hair and GI tract are likely related to ALK3 inhibition at higher doses.

In the dog studies, dose-related increases in heart rate, decreases in lymphoid cellularity in the lymphoreticular system, hypertrophy/hyperplasia in the gall bladder, and in 1 animal, decreased red cell mass were also observed. In the 14-day study at high doses, pathologic effects in the heart and vasculature were considered potentially secondary to the effects on heart rate (Jones et al 2013). In the 28-day study in dogs, the NOAEL was 5 mg/kg per day based on an increase in inflammatory changes in the liver at 15 mg/kg per day. These findings were not observed in the 3-month study at the same dose.

In rats, additional findings included decreased red cell mass, decreased cellularity of the lymphoreticular system, adrenal cortical hypertrophy, increased heart weights without microscopic correlates, minimal to slight alveolar inflammation and minimal alveolar macrophages in the lung, and changes in the upper and lower incisors. The incisor findings were likely a result of inhibition of ALK2 and ALK3, both of which are important in development and growth of teeth (Andl et al 2004, Wang et al 2012). In rats, incisors grow and differentiate throughout the life of the animal and are renewed every 40 to 50 days (Kuijpers et al 1996). The findings observed in the rat incisors were specific to actively growing teeth, and no findings were observed in the rat molar, which are permanent nongrowing structures. Given that adult human teeth are fully formed by the mid-teen years, rat incisor findings are not considered relevant to adult human risk assessment.

In the rat, most of the treatment-related findings were reversible, although effects on iron storage in the liver and spleen persisted while changes in the incisor teeth incompletely reversed or had progressed at the end of the recovery phase. In the dog, most of these findings also reversed with the exception of the skin and liver findings, including AST and ALT activities, which remained generally the same or progressed during the recovery phase.

In the 3-month studies, findings were similar in nature to those observed in the 28-day toxicology studies and were generally reversible or showed signs of reversibility. Target tissues identified included liver, spleen, skin (hair follicles), teeth (rat only), and bone. No increase in heart rate was observed in the dog at any dose level. The NOAEL in rats was 10 mg/kg per day for males and 30 mg/kg per day for females, and the NOAEL was 15 mg/kg per day in dogs. At doses producing similar exposure between the 28-day and 3-month studies, findings did not increase or only minimally increased in incidence or severity when dosing was extended to 3 months.

INCB000928 is not mutagenic based on the results of a bacterial mutagenicity assay.

Although INCB000928 induced micronuclei in an in vitro human lymphocyte micronucleus assay, the in vivo rat micronucleus and comet assay demonstrated INCB000928 is not clastogenic or aneugenic. Additionally, no induction of micronuclei were observed in the 28-day oral toxicity study in rats. Based on these collective findings, INCB000928 is not considered to be genotoxic.

Developmental and reproductive toxicity studies have not been performed with INCB000928.

INCB000928 is weakly phototoxic in the 3T3 mouse fibroblast assay, and in vivo, 300 mg/kg per day was the phototoxic NOAEL in Balb/c mice.

All adverse findings in nonclinical toxicology studies were associated with exposures that exceed the anticipated exposures in participants over the planned dose range. More detailed information about the known and expected benefits and risks and reasonably expected AEs of INCB000928 may be found in the IB.

INCB000928 is not yet approved in any of the participating countries.

2.4.2. Potential Risks of Ruxolitinib Based on Clinical Safety Results

In the 2 pivotal, Phase 3 studies of ruxolitinib in MF, INCB 18424-351 and CINC424A2352, 301 participants had a median duration of exposure to ruxolitinib of 9.6 months (range: 2 weeks to 17 months). The most frequently reported AEs were thrombocytopenia and anemia. Hematologic AEs (any CTCAE grade) included anemia (81.7%), thrombocytopenia (67.4%), and neutropenia (15.3%). Anemia, thrombocytopenia, and neutropenia are reversible and dose-related effects. The 3 most frequently reported nonhematologic laboratory abnormalities were elevated ALT (26.2%), elevated AST (18.6%), and hypercholesterolemia (16.6%).

The primary clinical risks with ruxolitinib treatment are the potential sequelae of decreased hematopoietic proliferation attributable to the inhibition of growth factor pathways associated with JAK inhibition. Increased rates of infection and anemia are potential risks of myelosuppression, and there are multiple sequelae of anemia, including the burden and risks of transfusion.

A complete discussion about the known, expected benefits and risks associated with ruxolitinib can be found in the current locally approved label for ruxolitinib.

2.4.3. Potential Risks Related to the Combination of INCB000928 and Ruxolitinib

The present study will evaluate escalating doses of INCB000928 administered as a single agent first before initiating combination with ruxolitinib. The study design will maximize participant safety while important PK and safety information is collected. Dose escalation in combination will proceed with safety information and available PK data collected as the study progresses and will start at a dose of INCB000928 which has been safely administered.

The effects of the combination of INCB000928 with ruxolitinib are being assessed in this study. INCB000928 has not been combined with ruxolitinib in the clinic previously. Therefore, the safety profile of the combination is unknown. The most common AE associated with the ruxolitinib is myelosuppression. There is not an expected overlap in toxicity profiles or DDIs between INCB000928 and ruxolitinib.

All AEs, including hematology, blood chemistry, and LFT abnormalities, will be monitored in all participants to identify occurrences of any safety concerns or potentiation of any ruxolitinib-related adverse effects.

Ruxolitinib is cleared by metabolism and is predominantly metabolized by CYP3A4. Ruxolitinib is not an inhibitor of any of the major CYPs (IC_{50} > 25 μM) nor does it cause induction of the 3 inducible CYPs, including CYP3A4.

INCB000928 has a similar profile in that it is predominantly metabolized by CYP3A4 and does not inhibit or induce CYPs. Because of the lack of induction or inhibition potential of both drugs, neither is expected to be a perpetrator of CYP-mediated DDIs. Therefore, a clinically significant DDI is not expected when these 2 drugs are administered together.

2.4.4. Potential Benefit

Serum hepcidin levels are significantly increased in patients with MF at the time of referral and when receiving ruxolitinib treatment. Inhibition of ALK2, an upstream regulator of hepcidin should increase circulating iron levels and improve anemia. INCB000928 has potent activity against the ALK2 kinase and inhibits BMP-induced hepcidin production.

In summary, INCB000928 should reduce hepcidin levels, increase iron availability, and improve anemia in patients with MF as a monotherapy and in combination with ruxolitinib.

Therefore, INCB000928 is proposed to be a potential combination therapy with ruxolitinib treatment in patients with MF since it may block the negative effect of hepcidin on iron metabolism and improve anemia in these patients (Asshoff et al 2017).

2.5. Exposure Margins

The C_{max} and AUC values obtained at the NOAEL in the 3-month rat and dog studies are presented in Table 8, and exposure margins for a 50 mg and 100 mg QD dose relative to the NOAELs in the 3-month studies are summarized in Table 9.

Table 8: C_{max} and AUC Values (for Total) INCB000928 Associated With Doses That Do Not Cause Adverse Effects in 3-Month Studies in Rats and Dogs

	Rats		Dogs
	10 mg/kg/day (males) and 30 mg/kg/day (female)		15 mg/kg/day
NOAEL	**Male**	**Female**	**Male and Female (Average)**
AUC (μM·h)	23.3	27.3	52.9
C_{max} (μM)	2.0	4.7	6.3

Table 9: Exposure Margins for 50 and 100 mg QD Relative to Doses That Do Not Cause Adverse Effects in 3-Month Studies in Rats and Dogs

	Rats		Dogs
	10 mg/kg/day (males) and 30 mg/kg/day (female)		15 mg/kg/day
NOAEL	**Male**	**Female**	**Male and Female (Average)**
50 mg QD[a]			
AUC	4.2	4.9	9.6
C_{max}	5.1	12.0	16.1
100 mg QD[b]			
AUC	2.5	2.9	5.6
C_{max}	3.1	7.4	9.9

Note: AUC and C_{max} from Day 10 PK data obtained from healthy participants (INCB 00928-102).
[a] AUC (total) = 5.54 μM·h, C_{max} (total) = 0.391 μM.
[b] AUC (total) = 9.33 μM·h, C_{max} (total) = 0.635 μM.

3. OBJECTIVES AND ENDPOINTS

Table 10 presents the detailed objectives and endpoints.

Table 10: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the safety and tolerability of INCB000928 administered as monotherapy (TGA) or in combination with ruxolitinib (TGB and TGC).	• Frequency and severity of AEs and SAEs, including changes in vital signs, ECGs, physical examinations, and clinical blood and urine laboratory parameters. • Identification of the DLTs, MTD, and RDE.
Secondary	
To determine the efficacy of INCB000928 administered as monotherapy (TGA) or in combination with ruxolitinib (TGB and TGC).	• Anemia response, defined as follows (modified from Tefferi et al [2013] definitions): – An Hgb increase of 1.5 g/dL relative to baseline for any "rolling" 12-week period (84 days with each assessment meeting this requirement) during the first 24 weeks of treatment if TI at baseline **OR** – Achieving TI for any "rolling" 12-week period (absence of any RBC-transfusion over any 84-day period) during the first 24 weeks of treatment if TD at baseline. • Duration of anemia response, defined as follows: – The interval from the first onset of anemia response to the earliest date of loss of anemia response that persists for at least 4 weeks or death from any cause (for the TI participants at baseline) **OR** – Duration of RBC-TI period for participants achieving RBC-TI for at least 12 consecutive weeks during the first 24 weeks of treatment (for the TD participants at baseline). • Mean change from baseline in the Hgb value over 12-week treatment periods. • Rate of RBC transfusion through Weeks 24 and 48, defined as the average number of RBC units per participant-month during the treatment period.

Table 10: Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary (continued)	
To determine the efficacy of INCB000928 administered as monotherapy (TGA) or in combination with ruxolitinib (TGB and TGC). (continued)	**The following endpoints were intended for Part 2 only and will not be analyzed**. **For TGB and TGC participants only:** • Splenic volume response rate at Week 24, defined as the proportion of participants achieving a ≥ 35% reduction in spleen volume at Week 24 relative to baseline as measured by MRI or CT scan. • Spleen length response, defined as the proportion of participants achieving a ≥ 50% reduction in spleen length at any visit relative to baseline as measured by palpation. • ORR, defined as the proportion of participants with CR or PR (including the morphologic effects of the combination of INCB000928 with ruxolitinib on BM) according to Tefferi et al (2013) definitions. • PFS, defined as the interval from the first dose of study treatment until the first documented progression or death according to Tefferi et al (2013) definitions. • LFS, defined as the interval from the first dose of study treatment until the first documented leukemia transformation or death from any cause.
To evaluate the PK of INCB000928 administered as monotherapy (TGA) or in combination with ruxolitinib (TGB and TGC).	PK parameters: C_{max}, t_{max}, and AUC_{0-t} for INCB000928 alone, for ruxolitinib alone, or for the combination of INCB000928 with ruxolitinib, as applicable.
To evaluate the effect of INCB000928 administered as monotherapy (TGA) or in combination with ruxolitinib (TGB and TGC) on hepcidin level, iron homeostasis, and erythropoiesis.	• Blood levels of hepcidin • Iron homeostasis parameters • Erythropoiesis parameters
Exploratory	
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This Phase 1/2, open-label, dose-finding study is intended to evaluate the safety and tolerability, PK, PD, and efficacy of INCB000928 administered as monotherapy or in combination with ruxolitinib in participants with MF who are transfusion-dependent or presenting with symptomatic anemia. This study will consist of 2 parts (upon implementation of Amendment 9, Part 2 will not be conducted).

4.1.1. Part 1 – Starting Dose, Dose-Escalation, and De-Escalation Schema

The initial dose level in the monotherapy dose-escalation group (TGA) will be 50 mg QD.

The dose level of the next subsequent cohort will be based on the type and severity of the toxicity and on the available PK data observed during at least the first cycle (ie, 28 days, from Cycle 1 Day 1 to Cycle 1 Day 28) in the 3 participants included in the previous cohort; the dose increase will never exceed 100% (2-fold increase). Additional participants may be enrolled to ensure the minimum of 3 evaluable participants per cohort is achieved.

Dose increases will be performed not more than 2-fold until a ≥ Grade 2 toxicity that has a reasonable possibility of being related to the study treatment is observed in that treatment group (not including toxicities with a clear alternative explanation or transient abnormal laboratory values without clinically significant signs or symptoms). Planned dose levels to be tested are 50 mg, 100 mg, 200 mg, and so on. Once toxicity is observed, subsequent increases in INCB000928 doses will be limited to no more than 50% in successive cohorts (eg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg). If the first dose level is not tolerable, the reduced dose level will be tested (25 mg). Further dose de-escalations will be performed as needed with at least 25% reductions of the dose and based on available tablet strengths. Dose escalation will continue until the MTD is reached and/or the RDE(s) is (are) determined (see Section 6).

Once monotherapy dose has been evaluated in at least 3 participants, combination with ruxolitinib will start (TGB).

Based on the safety results from Study INCB 000928-102, the dose escalation in TGB will start at 100 mg (50% of the safe and tolerated tested dose in Study INCB 00928-102) and will not exceed the monotherapy MTD if identified in this current study. Exposures (AUC) observed at doses up to 200 mg QD in Study INCB 00928-102 are below exposures associated with the NOAEL in the 3-month rat and dog toxicology studies.

Estimated exposures at 400 mg QD will likely exceed the NOAEL of the 3-month rat study but will be lower than the NOAEL of the 3-month dog study. The NOAEL of the 3-month rat study was based on adverse bone growth findings (delayed growth/development and alterations in bone maintenance and shaping) observed at the next highest dose level of 30 mg/kg per day in males and 100 mg/kg per day in females. All other findings at 30 mg/kg/day in males and 100 mg/kg/day in females were considered nonadverse. In rats, the growth plate remains open throughout adulthood; therefore, changes to bone in rats are of uncertain relevance to adult humans. Based on 3-month nonclinical toxicology data, 400 mg QD is considered an acceptable dose for the INCB 00928-104 study.

Dose escalation/de-escalation in TGB will continue with the same rules as for TGA and will not exceed the MTD determined in TGA.

After the TGB starting dose is cleared, TGC may start at the highest dose of INCB000928 that has been shown to be safe and tolerable in TGB. The dose escalation/de-escalation in TGC will continue with the same rules applied to TGA and TGB. The dose escalation and expansion stages will be conducted in an independent and parallel fashion in TGA (as applicable), TGB, and TGC; different RDE(s) may be defined in the different treatment groups.

In TGC:

- INCB000928 and ruxolitinib will be started concurrently on Cycle 1 Day 1,
- The starting dose of ruxolitinib will be 10 mg BID or guided by the country-specific label as applicable (for Canada, refer to the Canadian Product Monograph) for all participants with platelet counts between 50 and 75 × 10^9/L, and
- The ruxolitinib dose may be up-titrated after completion of at least 1 study drug treatment cycle, per investigator decision. Ruxolitinib dose increase should be guided by the country-specific label as applicable (for Canada, refer to the Canadian Product Monograph) and as per Section 6.6.6.4 and can be considered if the following are met:
  - Absence of DLT during the first study drug treatment cycle, and
  - Absence of worsening of the participant's anemia (ie, at least 1.5 g/dL decrease as compared with the baseline value).

The rationale for the ruxolitinib starting dose of 10 mg BID in dose escalation for TGC participants is supported by findings from the REALISE study (Cervantes et al 2021), which is outlined in Section 2.1.2. This ruxolitinib dose administration strategy was shown to be effective in limiting JAK inhibitor-related anemia in participants with baseline MF-associated anemia, while maintaining efficacy in reducing MF-associated splenomegaly and symptoms; as a result, this approach may allow for better assessment of INCB000928 impact on MF-associated anemia without the confounding effect of additional therapy-related anemia in JAK inhibitor naive participants.

In each of the dose-escalation stages (TGA, TGB, and TGC), a BOIN design (Liu and Yuan 2015) will be used to determine the MTD. The cohort size will be 3. In each treatment group, up to approximately 40 evaluable participants will be treated in the dose-escalation stage, and the dose-escalation procedure may be stopped if the number of evaluable participants treated at any dose level is greater than 9. The value of 0.6·0.28 is the highest DLT rate that is deemed subtherapeutic. The lowest DLT rate deemed overly toxic is 1.4·0.28, meaning that if the participants have a DLT(s) rate of ≤ 0.6·0.28, dose escalation is required; if the participants have a DLT(s) rate of ≥ 1.4·0.28, dose de-escalation is required. An equal prior probability of hypothesis being true is assigned to each of the hypotheses. The value of 0.95 is selected for the cutoff to eliminate an overly toxic dose for safety.

Table 11 will be used to guide dose escalation/de-escalation decisions.

Table 11: Decision Boundaries

Number of Participants Treated at Current Dose	1	2	3	4	5	6	7	8	9
Escalate if Number of Participants With a DLT is ≤	0	0	0	0	1	1	1	1	1
De-Escalate if Number of Participants With a DLT is ≥	1	1	2	2	2	3	3	3	4
Unacceptable Toxicity if Number of Participants With a DLT is ≥	NA	NA	3	3	4	4	4	5	5

Note: If the number of participants with a DLT specified in the last row is reached, that dose level and any higher dose levels will be eliminated. If the number of participants with a DLT is between the escalation and de-escalation boundaries specified in the second and third rows, another 3 evaluable participants will be enrolled in the current dose-level cohort. The exact number of participants treated in each dose-escalation stage will depend upon the number of participants required per dose level and upon the number of dose levels studied.

One or more RDE may be defined in each of the treatment groups (ie, TGA, TGB, and TGC). The definition of an RDE is, as follows:

- RDE doses are pharmacodynamically active.
- RDE doses will not exceed the MTD defined in each treatment group.

4.1.2. Exploration of Alternative Administration Schedules

The sponsor, in consultation with participating investigators, may elect to explore alternative administration schedules or expand dose cohorts deemed tolerable, in order to obtain supplemental PK, pharmacodynamic, and safety data.

Alternative dose levels or administration schedules (such as BID) may be explored. In that situation, the total daily dose of the alternative administration schedule(s) explored will not exceed 2-fold of the prior total daily dose or the MTD, as applicable. Alternative dose schedules for dose-escalation cohorts will be communicated to sites prior to cohort enrollment.

4.1.3. Part 2 – Expansion Stages of Treatment Groups A, B, and C

Upon implementation of Amendment 9, Part 2 will not be conducted.

Each of the respective RDE identified in the dose-escalation stages will be evaluated as follows:

- Independently between treatment groups
- At least 9 evaluable participants at each RDE in TGA
- At least 25 evaluable participants at each RDE in TGB
- At least 25 evaluable participants at each RDE in TGC
- In the event that more than 1 RDE is explored in a treatment group, the participants in that treatment group will be randomly allocated to 1 of the RDEs
- Further evaluation of the safety, efficacy, PK, and PD of the RDE will be performed

For TGB and TGC, 25 participants per cohort will provide a ≥ 90% chance of identifying a toxicity with a true event rate of 9%. In the expansion stage, assuming an unacceptable anemia response rate of 0.07 (H_0: $p \leq 0.07$ vs H_a: $p > 0.07$) and a target response rate of 0.25, twenty-five participants per cohort will provide an actual Type I error of 0.0936 and a power of 0.904 using the exact binomial test (null hypothesis will be rejected if at least 4 of 25 responses are observed).

Additional participants may be included at the sponsor's discretion in TGB and TGC to ensure that at least 30%, or 10 transfusion-dependent participants, are included in each of the TGB and TGC Dose expansion cohorts.

If an RDE cohort in TGA, TGB, or TGC does not include any Japanese participants, 1 Japanese participant will be enrolled in the cohort.

In TGC:

- INCB000928 and ruxolitinib will be started concurrently on Cycle 1 Day 1.
- The starting dose of ruxolitinib will be at least 10 mg BID or guided by the country-specific label as applicable (for Canada, refer to the Canadian Product Monograph) for all participants with platelet counts between 50 and 75 × 10^9/L.
- The ruxolitinib dose may be up-titrated after completion of at least 1 study drug treatment cycle, per investigator decision and the criteria defined in Section 4.1.1 and as per Section 6.6.6.4.

4.1.4. Integration of Japan and Japanese Safety Run-In Cohort

Since Japan will join the study later than the US and Europe, the first 3 participants in Japan will be enrolled in a Japanese safety run-in cohort in TGA, and the initial dose level for these participants will be the highest dose level already demonstrated to be safe and tolerable in TGA in the US and Europe.

The management of the Japanese safety run-in cohort will be performed as follows:

- In the absence of any DLT in these 3 participants, and if the PK parameters are comparable between Japanese and Western sites, the next participants enrolled in Japan will be enrolled in the same cohort as in the US/Europe. Dose-escalation algorithm as described in Section 4.1.1 and Section 4.1.3 will apply globally.
- If at least 1 of the 3 participants enrolled in the Japanese safety run-in cohort presents a DLT, or if the PK parameters between Japanese and Western sites are determined to be different by the study team, then the BOIN design will apply for Japan, and an independent dose finding will be conducted in this country as described in Section 4.1.1 and Section 4.1.3.

4.2. Overall Study Duration

The study begins when the first participant signs the ICF. The end of the study is defined as when all participants have completed at least 6 months of treatment or have discontinued treatment earlier and completed applicable safety follow-up assessments (as described below) or when the sponsor terminates the study or individual cohort(s) (see Section 4.3). The participants

who have completed at least 6 months of treatment, have not met study discontinuation criteria, and are still receiving INCB000928 and deriving clinical benefit at time of study closure may have the option to continue receiving treatment with INCB000928.

Upon study closure, a database lock will occur to allow analysis of the study data. Any remaining participants may continue to receive study treatment and be seen by the investigator until they meet criteria for discontinuation or alternate access to INCB000928 is available. While a participant is receiving INCB000928, the investigator is expected to monitor and report any SAEs or pregnancies as detailed in Section 9.

A participant is considered to have completed the study if they have completed all stages of the study including the safety follow-up visit.

For each participant, the study will comprise the following:

- Up to 56 days for screening.
- Continuous study treatment in consecutive 28-day treatment cycles as long as participants are deriving benefit from study treatment and have not met any criteria for study treatment discontinuation (see Section 7.1). Upon implementation of Amendment 9, treatment cycles will be every 3 months after Cycle 12.
- An additional 30 days for the safety follow-up period.

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/head of the study site (Japan) 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.

After enrollment has begun in the expansion cohorts at the RDE(s), further enrollment of participants will be suspended if 1) more than 1 participant in the first 5 participants enrolled in a specific dose level group have an AE ≥ Grade 3 that is attributable to the investigational agent, or 2) at least 40% of 5 or more participants enrolled in a specific dose level group have an AE ≥ Grade 3 that is attributable to the investigational agent. Enrollment of participants will be suspended in the specific dose level until the sponsor, investigators, and DMC have determined the appropriate course of action and only after regulatory authority approval of the restart, as applicable.

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/head of the study site (Japan), the IRBs/IECs, and regulatory bodies of the decision and reason for termination of the study. The DMC may recommend termination of the study if warranted, as described in Section 5.6. For Japan, the decision from the sponsor will be via the head of the study site(s) who will notify the investigators and the IRBs of the decision and reason for termination of the study. Based on emerging data, the sponsor may also decide to close individual cohort(s), which will be communicated the same way as above.

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. Male and female participants aged 18 years or older at the time of signing the ICF.
3. ECOG performance status score of the following:
   a. 0 or 1 for the dose-escalation stages.
   b. 0, 1, or 2 for the dose-expansion stage.
4. Life expectancy is greater than 6 months.
5. Agreement to undergo a pretreatment and regular on-study BM biopsies and aspirates (as appropriate to disease). If a biopsy and aspirate are not possible or contraindicated, or the tissue requirement cannot be satisfied, this requirement may be waived with approval from the sponsor's medical monitor.
6. Agreement to avoid pregnancy or fathering children based on the criteria below:
   a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 90 days (a spermatogenesis cycle) after the last study treatment dose and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   b. Female participants who are WOCBP must have a negative serum pregnancy test at screening before the first dose (within 3 days of the first study treatment dose) and must agree to take appropriate precautions to avoid pregnancy from screening through the safety follow-up visit and must not donate oocytes during this period (see Section 8.10.1 and Table 5 and Table 6). Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed,
   c. Female participants not considered to be of childbearing potential as defined in Appendix A are eligible.

Inclusion Criteria Defining the Disease Characteristics:

7. Participants with MF who are transfusion-dependent or present with symptomatic anemia, define as follows:
    a. Anemia: An Hgb value < 10 g/dL recorded on 3 separate occasions with at least 7 days between measurements during the 12 weeks immediately prior to Cycle 1 Day 1. The most recent measurement must have occurred during the 56-day screening period immediately prior to Cycle 1 Day 1
    (Note: RBC transfusion must be at least 2 weeks before the Hgb measurement during screening.)
    b. Transfusion-dependent: Participant has received at least 4 units of RBC transfusions during the 28 days immediately preceding Cycle 1 Day 1 OR has received at least 4 units of RBC transfusions in the 8 weeks immediately preceding Cycle 1 Day 1, for an Hgb level of < 8.5 g/dL, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days before Cycle 1 Day 1.
8. Histologically confirmed diagnosis of PMF (see Appendix B), post–PV, or post–ET MF (see Appendix C) according to the 2016 WHO criteria (Swerdlow et al 2017).
9. Ineligible to receive or have not responded to available therapies for anemia such as ESAs.
10. Participants with BM and peripheral blood myeloblast count < 10%.

For TGA:

11. Participants previously treated with JAK inhibitors for at least 12 weeks and are resistant, refractory, or lost response to a JAK inhibitor, OR are intolerant, OR are not eligible to receive a JAK inhibitor treatment (eg, participants who did not receive any JAK inhibitor treatment due to severe anemia and/or without any symptoms except ones due to anemia and without splenomegaly) are eligible.
12. Participants with intermediate-2 or high DIPSS MF (according to IWG-MRT criteria; Passamonti et al 2010).

For TGB:

13. Participants must have been on a therapeutic and stable regimen of ruxolitinib (ie, the dose and dose regimen of ruxolitinib to treat the MF has not been modified at any time) for at least 12 consecutive weeks immediately preceding the first dose of study treatment (see Section 6.1 for the possible starting doses).
14. Participants with intermediate-1, intermediate-2, or high DIPSS MF (according to IWG-MRT criteria; Passamonti et al 2010).

For TGC:

15. Participants must be JAK inhibitor treatment naive (no prior treatment with any JAK inhibitor) and have an indication for initiation of ruxolitinib treatment.
16. Participants with intermediate-1, intermediate-2, or high DIPSS MF (according to IWG-MRT criteria; Passamonti et al 2010).

5.2. Exclusion Criteria

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

1. Undergone any prior allogenic or autologous stem cell transplantation or a candidate for such transplantation.
2. Any major surgery within 28 days before the first dose of study treatment.
3. Any prior chemotherapy, immunomodulatory drug therapy, immunosuppressive therapy, biological therapy, endocrine therapy, targeted therapy, antibody or hypomethylating agent to treat the participant's disease, with the exception of ruxolitinib for TGB only, within 5 half-lives or 28 days (whichever is shorter) before the first dose of study treatment.
    a. Exceptions include hydroxyurea (may be used if stable dose to treat hyperproliferative disease providing the dose is stable during the 2 weeks prior to Cycle 1 Day 1).
4. Undergoing treatment with another investigational medication or having been treated with an investigational medication within 28 days before the first dose of study treatment.
5. Undergoing treatment with a potent/strong inhibitor or inducer of CYP3A4/5 within 28 days or 5 half-lives (whichever is longer) before the first dose of study treatment, or expected to receive such treatment during the study.
6. Any prior radiation therapy within 28 days before the first dose of study treatment. Palliative radiation therapy to single sites or small fields is allowed with at least a 1-week washout before the first dose of study treatment.
7. Presence of any hematological malignancy other than PMF, post–PV, or post–ET MF, as applicable.
8. Active invasive malignancy over the previous 2 years. Exceptions include participants with early-stage basal cell or squamous cell skin cancer, completely resected intraepithelial carcinoma of the cervix, or completely resected papillary thyroid and follicular thyroid cancers, who may be eligible to participate at the investigator's discretion. Participants with malignancies with indolent behavior such as prostate cancer treated with radiation or surgery may be enrolled as long as they have a reasonable expectation to have been cured with the treatment modality received.
9. Known active disease involving the CNS.
10. History of clinically significant or uncontrolled cardiac disease, including recent (within the last 12 months) unstable angina or acute myocardial infarction, or New York Heart Association Class III or IV congestive heart failure, or clinically significant arrhythmias not controlled by medication. Participants with a pacemaker and well-controlled rhythm for at least 1 month before the first dose of study medication will be allowed.

11. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 450 milliseconds is excluded unless approved by the sponsor's medical monitor (see Section 8.3.5). 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. Participants with left bundle branch block determined to be clinically significant by the investigator will be excluded. Participants with QTc prolongation due to a pacemaker may enroll with prior approval from the sponsor's medical monitor.
12. Presence of chronic or current active infectious disease requiring systemic antibiotic, antifungal, or antiviral treatment. Participants with acute infection requiring antibiotic, antifungal, or antiviral treatment use should delay screening/enrollment until the course of antibiotic antifungal, or antiviral therapy has been completed and the infection is not active anymore.
13. Participants with diagnosis of chronic liver disease (eg, chronic alcoholic liver disease, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, hemochromatosis, nonalcoholic steatohepatitis).
14. Participants with known active hepatitis A, HBV, or HCV infection, or at risk of HBV reactivation or who are HIV-positive.

    Active HBV or at risk of reactivation is defined as follows: positive HBsAg result (laboratory tests required at screening), and/or positive total anti-HBcAb result (laboratory tests required at screening), and/or quantitative HBV-DNA test result greater than the lower limits of detection of the assay (if known, laboratory tests not required for eligibility purpose, but can be done as part of screening if locally available).

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

    Active HCV is defined as follows: positive anti–HCV antibody (laboratory test required at screening) and quantitative HCV-RNA test result greater than the lower limits of detection of the assay (laboratory test required if anti–HCV antibody—positive only; this can be done as part of screening if available locally).

    Note: Anti–HCV 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 at least 12 weeks after last dose of therapy. Anti–HCV antibody—positive participants with no available confirmatory negative HCV-RNA test results will be excluded.
15. Unwillingness to be transfused with blood components including RBC packs and platelet transfusions.
16. Any condition in the investigator's judgment that would interfere with full participation in the study (eg, unable, unlikely, or unwilling to comply with the dose schedule and study evaluations), including administration of study treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.

17. Active alcohol or drug addiction that would interfere with their ability to comply with the study requirements.
18. Gastroesophageal reflux disease not controlled by medication (ie, currently symptomatic or endoscopic evidence of esophagitis) within 28 days before the first dose of study treatment.
19. Has any unresolved toxicity ≥ Grade 2 from previous therapy except for stable chronic toxicities (≤ Grade 2) not expected to resolve, such as stable Grade 2 peripheral neuropathy.
20. Known hypersensitivity, severe reaction, or any known contraindications to the use of any of the active substances or excipients in INCB000928 or ruxolitinib (refer to the country-specific label [for Canada, refer to the Canadian Product Monograph] for any contraindication as applicable) as appropriate to the relevant treatment group.
21. Women who are pregnant or breastfeeding. For Japan, women who are breastfeeding and wish to enroll must discontinue breastfeeding at least 90 days before receiving study drug/treatment. They must also refrain from breastfeeding during the course of study and for 90 days after the last dose of study treatment.
22. Unable to swallow and retain oral medication.
23. Current use of prohibited medication described in Section 6.7.3.
24. Participants with laboratory values at screening as defined in Table 12.

Table 12: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	TGA: < 25 × 10^9/L; participants who are refractory to platelet transfusions per investigator assessment are excluded
		TGB and TGC: < 50 × 10^9/L without the assistance of growth factors, thrombopoietic factors, or platelet transfusions
b	ANC	< 1.0 × 10^9/L
Hepatic		
c	ALT	≥ 2.5 × ULN
d	AST	≥ 2.5 × ULN
e	Bilirubin	≥ 2.0 ULN, unless conjugated (direct) bilirubin is ≤ 1.5 ULN (direct bilirubin only needs to be tested if total bilirubin exceeds the ULN) (except known Gilbert's syndrome, in which case direct bilirubin has to be tested). If there is no institutional ULN, then direct bilirubin must be < 40% of total bilirubin
Renal		
f	Creatinine clearance	< 30 mL/min according to Cockcroft-Gault formula
Others		
g	Iron metabolism	Serum ferritin level of ≥ 1000 ng/mL and documented clinically significant iron overload as per investigator opinion (eg, leading to liver cirrhosis) on liver MRI or biopsy (CT scan may be accepted).

25. Participants undergoing treatment with ESAs, G-CSF, GM-CSF, romiplostim, or eltrombopag at any time within 4 weeks or 5 half-lives, whichever is shorter, before the first dose of study treatment.
26. Treatment with iron chelators is allowed before the first dose of study treatment, provided the dose is stable during the 2 weeks prior to the first dose of INCB000928.
27. Participants with coexistent causes of anemia including but not limited to iron, folate, or vitamin B12 deficiency or bleeding.
28. The following participants are excluded in France: vulnerable populations according to article L.1121-6 of the French Public Health Code and adults under legal protection or who are unable to express their consent per article L.1121-8 of the French Public Health Code.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants should refrain from consumption of Seville oranges, grapefruit or grapefruit juice, pomegranates or pomegranate juice from the time of ICF signature until after the final dose of study treatment.

For TGB and TGC, refer to the ruxolitinib country-specific label (for Canada, refer to the Canadian Product Monograph) for any contraindications as applicable.

5.3.2. Hospitalization (Only Applicable for Participant in Japan)

For Part 1, all participants in Japan have to be hospitalized from the day before Day 1 to Day 8 in Cycle 1 in order to assess their ability to tolerate the study treatment. The investigator will judge whether to discharge the participant based on the outcome of physical examination, vital signs, hematology, and serum chemistries assessments scheduled on Day 8. The investigator may judge the further necessity of the hospitalization depending on the condition of the participant.

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.

Individual tests with results that fail eligibility requirements may be repeated during screening if the investigator believes the result to be in error.

Additionally, a participant who does not meet the criteria for participation in this study (ie, screen failure) and so fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who are rescreened must reconsent and be assigned a new participant number.

5.5. Replacement of Participants

Participants may be replaced for any of the following reasons:

- In the dose-escalation stages
  - For both the monotherapy and the combination portions, each participant will be observed for at least the first treatment cycle (ie, 28 days) to be evaluable to assess safety of the dose/dose regimen for the purposes of DLT assessment. Participants who receive at least 75% of doses of study treatment at the level assigned to that cohort (ie, 21 days of treatment) or have a DLT during the first study treatment cycle will be considered evaluable for determining safety of the dose and for DLT assessment purposes. Participants presenting dose reductions, dose interruptions (but not meeting DLT criteria), or treatment withdrawal because of an event that does not meet the criteria for a DLT, which results in < 75% of the prescribed study treatment dose being administered, will be considered nonevaluable for the purposes of determining the MTD and will be replaced.
  - A participant who had to receive any strong or potent CYP3A4/5 inhibitor or inducer during the first study treatment cycle (DLT assessment period) will be replaced.
  - A participant who had a dose reduction of ruxolitinib during the first study treatment cycle (DLT assessment period) will be replaced.
  - Participants who do not meet all the eligibility requirements of the study will be replaced.
- In the expansion stage, an evaluable participant is defined as a participant who has received at least 1 dose of study treatment and had at least 1 postbaseline on-study assessment.
  - The nonevaluable participants in any of the expansion stages will be replaced.
  - Participants who do not meet all the eligibility requirements of the study will be replaced.

Upon implementation of Amendment 9, expansion cohorts will not be enrolled.

5.6. Data Monitoring Committee

This study will use a DMC to monitor safety and efficacy at the planned analyses.

The DMC will review the study information provided to them before each meeting and make recommendations to the sponsor regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will consider the overall risk and benefit to study participants and provide recommendations such as study continuation in accordance with the Protocol or suggest study protocol amendments, study interruption, or study termination, as applicable.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members, the sponsor, and the protocol team, and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all DMC members.

6. STUDY TREATMENT

6.1. Study Treatment Administered

Table 13 presents the study treatment information.

The treatment period begins on the day the participant receives the first dose of study treatment and ends when the investigator determines the participant will be permanently discontinued from study treatment. The first dose on Cycle 1 Day 1 must be no more than 56 days after the participant has signed the ICF and no more than 7 days after the date of enrollment (ie, enrollment approved by medical monitor).

INCB000928 and ruxolitinib, as applicable, will be administered daily (unless modified as per the dose-escalation results for INCB000928) by oral route in consecutive, continuous, 28-day treatment cycles. Upon implementation of Amendment 9, cycles will be 3 months after Cycle 12. The doses of INCB000928 and ruxolitinib, as applicable, can be administered by hospital personnel in an inpatient setting or self-administered by the participant in an outpatient setting.

Alternative administrations schedules of INCB000928 may be explored as described in Section 4.1.2.

The following will apply for the first study treatment cycle of the dose-escalation stages only:

- Participants in TGA will start receiving INCB000928 on Cycle 1 Day 1.
- Participants in TGB will receive ruxolitinib alone 1 to 3 days before receiving the combination of INCB000928 plus ruxolitinib on Cycle 1 Day 1.

  The remainder of the treatment cycles for TGB participants (ie, from Cycle 2 onward in the dose-escalation stage and for all cycles in the expansion stage) will be performed as described in the paragraph above.
- Participants in TGC will start receiving INCB000928 and ruxolitinib concurrently on Cycle 1 Day 1.

INCB000928 and ruxolitinib, as applicable, will be administered to the study participants as long as they benefit from the study treatment and they do not present any study treatment discontinuation criterion as per investigator's assessment (see Section 7.1) for up to 12 months of treatment. The participants who are still receiving INCB000928 and are deriving clinical benefit at this time may remain on-study treatment if the study is still open with sponsor's approval.

The investigator may decide to start ruxolitinib in TGA participants after completing the 6-month period of monotherapy if it is considered potentially beneficial to the participant. Ruxolitinib will be used as guided by the country-specific label as applicable (for Canada, refer to the Canadian Product Monograph), and after the investigator verifies that the participant has met the anemia response criteria.

Table 13: Study Treatment Information

	INCB000928 (Study Drug)	Ruxolitinib
Mechanism of action:	Inhibition of ALK2, an upstream regulator of hepcidin	Inhibition of JAK1 and JAK2
Dosage formulation:	Tablets	Tablets
Unit dose strength(s)/ dosage level(s):	**Starting doses**	
	Dose escalation for TGA: 50 mg QD	TGA: See Section 6.1.
	Dose escalation for TGB: Based on safety results from Study INCB 00928-102, the dose escalation in TGB will start at 100 mg (50% of the safe and tolerated tested dose in Study INCB 00928-102) and will not exceed the monotherapy MTD if identified in this current study. **Dose escalation for TGC**: Safe and tolerable dose as defined in TGB dose-escalation cohorts (see Section 4.1.1).	Possible doses for the TGB dose-escalation: 10 mg BID, 15 mg BID, 20 mg BID, and 25 mg BID; QD doses are not allowed. **Dose for the TGC dose-escalation:** 10 mg BID or guided by the country-specific label as applicable (for Canada, refer to the Canadian Product Monograph) for all participants with platelet counts between 50 and 75×10^9/L. For TGC, treatment with INCB000928 starts the day the participant takes their first dose of ruxolitinib.
	Dose expansion for TGB: RDE(s) as defined in the dose escalation. **Dose expansion for TGC**: RDE(s) as defined in the dose escalation. Note: Upon implementation of Amendment 9, dose expansion groups will not be enrolled.	**Possible doses for the TGB dose-expansion:** 5 mg BID, 10 mg BID, 15 mg BID, 20 mg BID, and 25 mg BID; QD doses are not allowed. The starting dose of ruxolitinib in TGC will be at least 10 mg BID or guided by the country-specific label as applicable (for Canada, refer to the Canadian Product Monograph) for all participants with platelet counts between 50 and 75×10^9/L. **Possible doses for the TGC dose-expansion:** 5 mg BID, 10 mg BID, 15 mg BID, 20 mg BID, and 25 mg BID; QD doses are not allowed. For TGC, treatment with INCB000928 starts the day the participant takes their first dose of ruxolitinib.
	On-study doses for all treatment groups	
	Refer to Section 4.1, Section 6.5, and Section 6.6.	5 mg BID, 10 mg BID, 15 mg BID, 20 mg BID, or 25 mg BID.
Administration instructions:	• INCB000928 can be taken together with ruxolitinib and without regard to food. Participants will be instructed not to make up for any missed doses. • If vomiting occurs during the course of treatment, participants will be instructed not to take the study treatment again before the next scheduled dose. • On days of predose PK sampling, participants should refrain from taking the study treatment until PK samples are collected.	• Ruxolitinib should be self-administered approximately 12 hours apart at approximately the same hour in the morning and in the evening and without regard to food. • Participants will be instructed not to make up for any missed doses. • If vomiting occurs during the course of treatment, participants will be instructed not to take the study treatment again before the next scheduled dose. • On days of predose PK sampling, participants should refrain from taking the study treatment until PK samples are collected.
Packaging and labeling:	Each bottle will be labeled as required per country requirement.	—
Storage:	Room temperature (between 15°C and 30°C [59°F and 86°F]).	Store in accordance with the Jakafi®/Jakavi® country-specific label
Status of treatment in participating countries:	Investigational drug	Marketed drug

6.2. Preparation, Handling, and Accountability

The investigator or designee, or investigational drug storage manager (for Japan), must confirm appropriate temperature conditions have been maintained during transit for study drug INCB000928 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 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, investigational drug storage manager (for Japan), and authorized staff.

The investigator, investigational drug storage manager (for Japan), 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, investigational drug storage manager (for Japan), or designee must maintain records that document the following:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Participant use of the study drug, including tablet and bottle counts from each supply dispensed.
- Return of study drug to the investigator, investigational drug storage manager (for Japan), or designee by participants.

The investigational product must be used only in accordance with the Protocol. The investigator, investigational drug storage manager (for Japan), or designee will also maintain records adequately documenting that the participants were provided the specified study treatment. 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, investigational drug storage manager (for Japan), 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, investigational drug storage manager (for Japan), or designee will oversee the destruction of any remaining study drug according to institutional SOPs. If, however, local procedures do not allow on-site destruction, shipment of the study drug back to the sponsor is allowed. In this case, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

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

See Appendix E for instructions to participants for the handling of INCB000928.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; no comparisons will be made between participants or against historical controls. Measurements of safety and efficacy are objective measurements, and only comparisons to pretreatment conditions will be made.

Study treatment will be dispensed at the study visits summarized in the SoA (see Table 3 and Table 4) and refer to Section 4.1.3 regarding randomization in Dose expansion stages.

Returned study treatment should not be redispensed to the participants.

6.4. Study Treatment Compliance

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

6.5. Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose and/or Pharmacologically Active Dose

6.5.1. Definition of a Dose-Limiting Toxicity

Dose-limiting toxicity will be defined as the occurrence of any of the toxicities in Table 14 occurring during the first treatment cycle, from Cycle 1 Day 1 up to and including Cycle 1 Day 28 (per regimen cycle schedule), except those with a clear alternative explanation (eg, disease progression) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination.

All DLTs will be assessed for severity by the investigator using the CTCAE v5.0. Participants who receive at least 75% of doses of study treatment at the level assigned or have a DLT will be considered evaluable for determining tolerability of the dose.

Individual participant dose reductions may be made based on events observed at any time during study treatment; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the MTD of INCB000928 administered alone or in combination with ruxolitinib, decisions will be made based on events that are observed from Cycle 1 Day 1 through and including the final day of Cycle 1 (ie, Day 28). A lower MTD may subsequently be determined based on relevant toxicities that become evident after Day 28. All safety data including the data of participants who are not evaluable for determining tolerability of the dose will be considered to determine a lower MTD.

Table 14: Definition of Dose-Limiting Toxicity

Toxicity	Definition
Nonhematologic	• Any ≥ Grade 3 nonhematologic toxicity of any duration EXCEPT: – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. ***NOTE: All Grade 4 electrolyte abnormalities will be considered a DLT regardless of duration***. – Grade 3 nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours. ***NOTE: All Grade 4 vomiting and diarrhea will be considered a DLT regardless of prophylactic treatment, response to management, or duration.*** – Grade 3 rash in the absence of desquamation, with no mucosal involvement, that does not require systemic steroids and that resolves to Grade 1 in ≤ 14 days. – Changes in cholesterol and triglycerides. – An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity. • Singular or nonfasting elevations in blood glucose (ie, blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate occasions).
Chemistry	• AST or ALT elevation – AST and/or ALT elevation is > 5.0 and ≤ 20 × ULN (Grade 3) for > 3 days (72 hours) or recurs on rechallenge. – AST and/or ALT is > 20 × ULN (Grade 4) of any duration**.** • Any abnormalities that meet the definition of Hy's Law, defined as 1) ALT or AST ≥ 3 × ULN concurrent with 2) serum total bilirubin elevation to > 2 × ULN without findings of cholestasis (serum ALP < 2 × ULN) and 3) no other reason or apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including but not limited to viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic can be found to explain the combination of increased ALT and total bilirubin.
Hematologic	• Any Grade 5 toxicity. • Grade 3 and higher thrombocytopenia with bleeding. • Grade 4 thrombocytopenia or requiring transfusion of platelets (only if the participant has a platelet count value > 75 × 10^9/L at baseline without the assistance of thrombopoietic factors, or platelet transfusions, otherwise not applicable). • Febrile neutropenia (ANC < 1.0 × 10^9/L with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour). • Grade 4 neutropenia > 7 days. • Anemia will not be considered in the definition of DLT.
Iron studies	• Iron abnormalities that are symptomatic or affect an organ function will be defined as DLTs.
Other toxicities not meeting DLT criteria	• While the rules for adjudicating DLTs in the context of dose escalation are specified above, an AE not listed above may be defined as a DLT after a consultation with the sponsor and investigators based on the emerging safety profile.

Additional blood samples may be drawn (per investigator discretion) to confirm a potential DLT event or to better define its duration.

6.5.2. Procedures for Cohort Review and Dose Escalation

6.5.2.1. Assessment of Safety and PK Results

Safety telephone conferences will be scheduled by the sponsor with study investigators in order to review cohort-specific data and overall safety and available PK data collected during at least the first treatment cycle of the participants from each cohort in order to agree on dose escalation/dose de-escalation/cohort expansion, adjudicate individual high-grade AEs as potentially dose limiting, and guide other major study decisions.

The decision to proceed to the next dose level of INCB000928 (dose increase or dose decrease) will be made by the study team and the investigators based on safety and available PK data obtained in at least the first cycle for 3 evaluable participants at the prior dose level.

The sponsor, in consultation with participating investigators, may elect to expand dose cohorts deemed tolerable, beyond what is described above, in order to obtain supplemental PK, PD, and safety data.

6.5.2.2. Intercohort Dose Increase Algorithm

The dose level of the next subsequent cohort will be based on the type and severity of the toxicity and on the available PK data observed during at least the first cycle (ie, 28 days, from Cycle 1 Day 1 to Cycle 1 Day 28) in the 3 participants included in the previous cohort; the dose increase will never exceed 100% increase (2-fold increase). Additional participants may be enrolled to ensure the minimum of 3 evaluable participants per cohort is achieved.

The initial dose level in TGA will be 50 mg QD.

Dose increases will be performed up to 2-fold until a Grade 2 or greater toxicity that has a reasonable possibility of being related to the study treatment is observed in that treatment group (not including toxicities with clear alternative explanation or transient abnormal laboratory values without clinically significant signs or symptoms). Once the toxicity is observed, subsequent increases in study drug will be limited to no more than 50% in successive cohorts.

6.5.3. Definition of the Maximum Tolerated Dose

As per the BOIN design, MTD is defined as the dose at which the observed DLT rate is closest to the target DLT rate of 28% using an isotonical method that takes the assumption of a monotonic dose-toxicity relationship into account.

If the first cohort of any of the 2 treatment groups exceeds the MTD for this specific population, a dose de-escalation may be considered.

6.5.4. Definition of the Recommended Dose for Expansion

In TGA, TGB, and TGC, the RDE dose(s), as applicable, will be determined in an independent fashion by evaluation of all available data (ie, safety, PK, and PD data) from the respective dose-escalation stage of the study for further investigation in the expansion cohort, including safety (eg, low-grade but chronic toxicities, dose reduction, dose interruption, or missed doses of INCB000928 and/or ruxolitinib).

The RDE(s) will never exceed the MTD in each treatment group.

Upon implementation of Amendment 9, expansion cohorts will not be enrolled.

6.6. Dose Modifications

Individual participant dose reductions, interruptions, or modifications may be performed based on events observed at any time during study treatment, as applicable.

The occurrence of DLTs (see Section 6.5.1) and other toxicities (related or unrelated to study treatment) will guide decisions for treatment interruptions and discontinuation for individual participants.

Individual decisions regarding dose modifications of INCB000928 should be made using clinical judgment in consultation with the sponsor's medical monitor (whenever possible), taking into account relatedness of the AE to the study treatment and the participant's underlying condition.

If moderate or severe AE are consistently observed across participants in a cohort or if unacceptable pharmacological effects, reasonably attributable to INCB000928 in the opinion of the investigator are observed in more than 33% of the participants in a cohort, then dose escalation will be temporarily halted, and no further participants will be administered study treatment until a full safety review of the study has taken place.

6.6.1. Management of Dose-Limiting Toxicities or Other Urgent Situations

Investigators may employ any measures or concomitant medications necessary to optimally treat the participant after discussion with the sponsor's medical monitor (whenever possible).

6.6.2. Follow-Up of Dose-Limiting Toxicities

Any DLT should be monitored until it resolves to baseline or appears to have stabilized for a minimum of 4 weeks. During follow-up, participants should be seen as often as medically indicated to assure safety.

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

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Because participants may enter the study with extensive pretreatment and/or severe BM infiltration/suppression due to the primary disease, the dose reduction/interruption rules are provided as guidelines (see Table 15). Individual decisions regarding dose reductions/interruptions should be made using clinical judgment and in consultation with the sponsor's medical monitor (whenever possible), taking into account relatedness of the AEs to the study treatment 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-reduction/interruption rules.

Treatment with INCB000928 may be delayed up to 21 days to allow for an adequate recovery from toxicity. Participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further participation in the study. The treating investigator should contact the sponsor's medical monitor

to discuss the case of any participant whose treatment has been delayed for more than 21 days before restarting treatment with INCB000928.

Hematologic and biochemistry events (eg, thrombocytopenia, anemia, neutropenia, LFT abnormalities) occurring and precipitating dose reductions or interruptions during Cycle 1 of treatment will be evaluated as potential DLTs and managed as per the guidelines in Table 15. Hematologic and biochemistry AEs that precipitate dose interruptions should be monitored for recovery at least on a weekly basis, if feasible.

Table 15: Guidelines for Interruption and Restarting of Study Drug

Adverse Event		**Action Taken**
Toxicity	**NCI CTCAE Grade**	
Hematology		
Neutropenia (ANC count)	Grade 3	Continue study drug, and monitor ANC counts as clinically indicated.
	Grade 4 (ANC count < 0.5×10^9/L)	Hold study drug up to 21 days, and monitor ANC counts at least weekly until toxicity resolves to ≤ Grade 1 or baseline level. • If toxicity lasts ≤ 21 days, the participant may resume INCB000928 at the next lower tolerable dose or at least at a 25% reduction, and monitor ANC counts as clinically indicated. • If toxicity lasts > 21 days, permanently discontinue INCB000928.
Febrile neutropenia	ANC count < 1.0×10^9/L + a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for > 1 hour	Hold study drug up to 21 days, and monitor ANC counts at least weekly and temperature at least daily until toxicity resolves (disappearance of febrile neutropenia). • If febrile neutropenia lasts ≤ 21 days, the participant may resume INCB000928 at the next lower tolerable dose or at least at a 25% reduction, and monitor ANC counts as clinically indicated. • If febrile neutropenia lasts > 21 days, permanently discontinue INCB000928.
Thrombocytopenia (platelet count) Applicable if the participant's platelet count value > 75×10^9/L at baseline OR if the participant's platelet count value < 75×10^9/L at baseline, decrease from baseline > 50%.	Grade 3	Continue study drug, and monitor platelet counts as clinically indicated.
	Grade 3 (platelet count ≥ 25×10^9/L and < 50×10^9/L) associated with any bleeding	Hold study drug up to 21 days, and monitor platelet counts at least weekly and bleeding at least daily until toxicity resolves to ≤ Grade 1 or baseline level. • If toxicity lasts ≤ 21 days, the participant may resume INCB000928 at the next lower tolerable dose or at least at a 25% reduction, and monitor platelet counts as clinically indicated. • If toxicity lasts > 21 days, permanently discontinue INCB000928.
	Grade 4 (platelet count < 25×10^9/L)	Hold study drug up to 21 days, and monitor platelet counts at least weekly until the toxicity resolves to ≤ Grade 1 or baseline level. • If toxicity lasts ≤ 21 days, the participant may resume INCB000928 at the next lower tolerable dose or at least at a 25% reduction, and monitor platelet counts as clinically indicated. • If toxicity lasts > 21 days, permanently discontinue INCB000928.

Table 15: Guidelines for Interruption and Restarting of Study Drug (Continued)

Adverse Event		Action Taken
Toxicity	**NCI CTCAE Grade**	
Blood chemistry		
ALT/AST elevation	Grade 2	Continue study drug, and monitor LFTs at least every 2 weeks until toxicity resolves to ≤ Grade 1 or baseline level.
	ALT/AST elevation > 5 and < 10 × ULN	Interrupt study drug up to 21 days, and monitor LFTs at least weekly until the toxicity resolves to ≤ Grade 1 or baseline level. • If LFTs resolve to ≤ Grade 1 or baseline level within 7 days after interruption, the participant may resume INCB000928 at the same dose, and monitor as clinically indicated. • If LFTs do not resolve to ≤ Grade 1 or baseline level within 7 days after study drug interruption, permanently discontinue INCB000928.
	ALT/AST elevation ≥ 10 and ≤ 20 × ULN	Interrupt study drug up to 21 days, and monitor LFTs at least weekly until the toxicity resolves to ≤ Grade 1 or baseline level. • If LFTs resolve to ≤ Grade 1 or baseline level within 21 days after interruption, the participant may resume INCB000928 at the next lower tolerable dose or at least at a 25% reduction, and monitor as clinically indicated. • If LFTs do not resolve to ≤ Grade 1 or baseline level within 21 days after study drug interruption, permanently discontinue INCB000928.
	Recurrence of Grade 3 on rechallenge (ALT/AST elevation > 5.0 and ≤ 20 × ULN)	If AST and/or ALT > 5.0 × ULN recurs upon restart of study drug, interrupt study drug up to 21 days, and monitor LFTs at least weekly until the toxicity resolves to ≤ Grade 1 or baseline level. • If LFTs resolve to ≤ Grade 1 or baseline level within 21 days after interruption, the participant may resume INCB000928 at the next lower tolerable dose or at least at a 25% reduction, and monitor as clinically indicated. • If LFTs do not resolve to ≤ Grade 1 or baseline level within 21 days after study drug interruption, permanently discontinue INCB000928.
	Grade 4 or Hy's Law	Discontinue permanently, recommend liver biopsy, ultrasound or other imaging, as well as hepatitis serology (even if negative at baseline).

Table 15: Guidelines for Interruption and Restarting of Study Drug (Continued)

Adverse Event		Action Taken
Toxicity	**NCI CTCAE Grade**	
Other toxicities		
For participants with a screening ferritin level of < 1000 ng/mL: when the ferritin level during the study becomes > 1.5 × the ferritin screening level AND the ferritin level is ≥ 1000 ng/mL		Interrupt treatment, perform non–contrast-enhanced MRI in conjunction with software used for the estimation of hepatic iron concentration (ie, MRI T2) to noninvasively measure liver iron concentrations. If there is a concomitant need to stage hepatic fibrosis or evaluate for alternate liver diseases, then liver biopsy may be performed. If MRI or liver biopsy documents one of the following: a newly identified, clinically significant iron overload; indication to initiate iron chelation; or if the increased ferritin/iron overload may be due to the study treatment (per investigator opinion, eg, liver cirrhosis), then study treatment will be permanently discontinued. Otherwise, if the ferritin level is back to screening or lower, within 21 days after interruption, the participant may resume INCB000928 at the next lower tolerable dose, or at least at a 25% reduction, and should be monitored as clinically indicated.
For participants with a screening ferritin level of ≥ 1000 ng/mL WITHOUT documented clinically significant iron overload on liver MRI or biopsy: when the ferritin level during the study become > 1.5 × than that at the ferritin screening level		Perform non–contrast-enhanced MRI in conjunction with software used for the estimation of hepatic iron concentration (ie, MRI T2) to noninvasively measure liver iron concentrations. If there is a concomitant need to stage hepatic fibrosis or evaluate for alternate liver diseases, then liver biopsy may be performed. If MRI or liver biopsy documents one of the following: a newly identified, clinically significant iron overload; indication to initiate iron chelation; or if the increased ferritin/iron overload may be due to the study treatment as (per investigator opinion, eg, liver cirrhosis), then study treatment will be permanently discontinue. Otherwise, if elevated ferritin is deemed to be the result of transfusion, and there is no clinically significant change in liver iron content or evidence of clinically significant iron overload, then dose administration can be maintained and MRI monitoring will increase to every 3 months.
Any Grade 1 or Grade 2 toxicity		Continue study drug treatment and treat the toxicity; monitor as clinically indicated.

Table 15: Guidelines for Interruption and Restarting of Study Drug (Continued)

Adverse Event		Action Taken
Toxicity	**NCI CTCAE Grade**	
Any Grade ≥ 3 toxicity, if clinically significant and not manageable by supportive care (including Grade 3 QTc prolongation [QTcF > 500 ms] without life-threatening arrhythmias)		Interrupt study drug up to 21 days until toxicity resolves to ≤ Grade 1 or to baseline. • If toxicity resolves to ≤ Grade 1 or baseline level within 21 days after interruption, the participant may resume INCB000928 at the next lower tolerable dose or at least at a 25% reduction, and monitor as clinically indicated. • If toxicity does not resolve to ≤ Grade 1 or baseline level within 21 days after interruption, permanently discontinue study drug. • If assessed as NOT related to study drug, INCB000928 may be resumed at the same dose.
Any recurrent Grade ≥ 3 toxicity after 2 dose reductions		Permanently discontinue study drug administration, and follow-up per Protocol (exceptions require approval of sponsor's medical monitor).
Any other Grade 4 toxicity except Grade 4 neutropenia and Grade 4 thrombocytopenia		Permanently discontinue study drug administration, and follow-up per Protocol unless considered not related to study treatment.
Other		
In the event that the participant's Hgb level becomes greater than 14 g/dL		Momentarily halt administration of INCB000928 when the participant's Hgb level is > 14 g/dL. Administration of INCB000928 may be resumed when the participant's Hgb level is < 12 g/dL.
The dose reductions for INCB000928 will be of at least 25% and depending upon the study drug strengths available at the site.		

6.6.3.1. Dose Reductions of Study Drug for Concomitant Usage of Inducer/Inhibitor of CYP3A4/5

The preclinical studies have shown the following:

- INCB000928 is primarily metabolized by CYP3A4/5 (77% to 87%) and CYP2D6 (13% to 23%), and therefore PK of INCB000928 may be affected by coadministration of potent inhibitors or inducers of CYP3A4/5.
- INCB000928 is a substrate of the efflux transporter P-gp with minimal involvement of BCRP and MRP2. It is a weak inhibitor of BCRP and a very weak inhibitor of P-gp (MDR1).

6.6.3.1.1. Dose Reductions for Concomitant Usage of Strong/Potent Inducer/Inhibitor of CYP3A4/5

The usage of strong/potent inhibitors or inducers of CYP3A4/5 is restricted in the present study (see Section 6.7.2) and in particular during DLT assessment in the first study treatment cycle, and all efforts should be employed to avoid the utilization of strong/potent inhibitors or inducers of CYP3A4/5. If a participant MUST receive one of these compounds, the INCB000928 dose will have to be decreased by at least 50% as compared to the theoretical dose. The precise dose

will be determined according to the available INCB000928 tablet strength. If feasible, blood samples will be drawn for PK purposes as defined for Cycle 1 Day 1 (ie, predose, and 2 hours, 4 hours, and between 6- and 8-hours postdose) during the first cycle when the participant is administered the strong/potent inhibitor or inducer of CYP3A4/5.

6.6.3.1.2. Dose Reductions for Concomitant Usage of Weak-to-Moderate Inducer/Inhibitor of CYP3A4/5, Inhibitors or Inducers of CYP2D6, and for Compounds Affecting the P-gp or the BCRP

No dose adjustment/restriction are recommended for the use of weak-to-moderate CYP3A4/5 inhibitors or inducers, for CYP2D6 inhibitors or inducers, or for compounds affecting the P-gp or the BCRP.

Note that CYP2D6 inhibitors or inducers and compounds affecting the efflux transporter P-gp or the BCRP are not restricted nor prohibited, but additional care should be taken to instruct the participant not to take them at the same time as the study drug, and additional monitoring should be performed if clinically indicated.

6.6.4. Criteria for Permanent Discontinuation of Study Drug

See Section 7 for details and discontinuation procedures.

6.6.5. Criteria and Procedures for Dose Increases of Study Drug

Intraparticipant dose escalation will be performed at the investigator's discretion with sponsor preapproval for the participants in one of the dose-escalation or -expansion stages of the study in the following circumstances:

- The Protocol eligibility criteria are met at the time of escalation.
- The participant has received ≥ 2 cycles (≥ 6 cycles for participants in the dose expansion stages) of study treatment without drug-related toxicity ≥ Grade 3 and does not present drug-related toxicity ≥ Grade 2 at time of dose escalation.
- The participant is still receiving RBC transfusions or there is an Hgb increase of less than 1.5 g/dL in any of their assessments.
- The next higher dose level has been determined to be safe based on the MTD criteria (ie, does not exceed the MTD level as determined for this treatment group during the dose-escalation stage).
- In the opinion of the investigator, the participant does not have any concurrent condition or circumstance that would complicate the dose escalation or pose increased risk to the participant.

INCB000928 doses will never exceed the MTD as identified in the dose-escalation stages as applicable for the corresponding treatment group.

6.6.6. Criteria and Procedures for Dose Interruptions or Adjustments of Ruxolitinib

A standardized dosing paradigm will be used to determine dose adjustments for safety and efficacy so that each participant is titrated to their most appropriate dose. Ruxolitinib doses will not exceed 25 mg BID and will not be below 5 mg QD at any time during the study.

Acceptable starting doses for TGB and TGC are detailed in Table 13.

Dose interruptions and modifications for ruxolitinib because of hematologic toxicity, nonhematologic toxicity, or concurrent use of a strong/potent inducer or inhibitor of CYP3A4/5 are detailed in Section 6.6.6.1, Section 6.6.6.2, and Section 6.6.6.3, respectively.

6.6.6.1. Dose Modification Guidelines for Ruxolitinib Due to Hematologic Toxicity

Ruxolitinib dosing should be discontinued in participants if their platelet count is less than 50×10^9/L or ANC is less than 0.5×10^9/L while receiving ruxolitinib.

After recovery of platelet and/or ANC counts above this level, as applicable, dosing may be restarted or increased following recovery of platelet and ANC counts to acceptable levels.

The investigator should exercise caution in resuming any dose of ruxolitinib that resulted in a platelet count $< 50 \times 10^9$/L or ANC falling below 0.5×10^9/L. After restarting, using the guidelines in Table 16, if it is found that a participant cannot tolerate the lowest allowed dose (5 mg BID) without platelets falling below 50×10^9/L, neutrophils falling below 0.5×10^9/L, or Hgb falling below 6.5 g/dL despite the use of transfusion therapy, ruxolitinib treatment must be permanently discontinued.

Based on limited clinical data, long-term maintenance at a 5 mg BID dose has not shown responses, and continued use at this dose should be limited to participants for whom the benefits outweigh the potential risks. Dose reductions to daily doses below 5 mg BID are not recommended and will result in the discontinuation of the participant from the treatment.

Table 16 illustrates the maximum allowable dose that may be used in restarting ruxolitinib after a previous interruption due to thrombocytopenia.

Table 16: Maximum Restarting Dose for Ruxolitinib After Interruption Due to Thrombocytopenia

Current Platelet Count Value	Maximum Allowed Dose When Restarting Ruxolitinib Treatment[a]
$\geq 125 \times 10^9$/L	20 mg BID
100×10^9/L to $< 125 \times 10^9$/L	15 mg BID
75×10^9/L to $< 100 \times 10^9$/L	10 mg BID for at least 2 weeks; if stable, may increase to 15 mg BID
50×10^9/L to $< 75 \times 10^9$/L	5 mg BID for at least 2 weeks; if stable, may increase to 10 mg BID
$< 50 \times 10^9$/L	Continue hold

[a] Maximum doses are displayed. When restarting, begin with a dose at least 5 mg BID below the dose at interruption.

In order to provide sufficient data to make the dose adjustment decisions, it is recommended that hematology parameters be obtained at least weekly for platelet count $< 100 \times 10^9$/L or ANC $< 1.0 \times 10^9$/L and at least twice weekly for platelet count $< 50 \times 10^9$/L or ANC $< 0.5 \times 10^9$/L.

The dose reduction strategy in Table 17 covers the possible doses after an increase for inadequate efficacy (20 mg BID and 25 mg BID) and doses that might be present for TGB and TGC participants (down to 5 mg BID).

Dose reduction should be considered if the participant's platelet counts decrease as outlined in Table 17 with the goal of avoiding dose interruptions due to thrombocytopenia.

Table 17: Dose Reduction Recommendations for Ruxolitinib Due to Thrombocytopenia

Participant's Platelet Count Value	▼ Dose at Time of Platelet Decline ▼				
	25 mg BID	**20 mg BID**	**15 mg BID**	**10 mg BID**	**5 mg BID**
	▼ New Dose That MUST be Instituted ▼				
≥ 125 × 10^9/L	No dose reduction required				
100 × 10^9/L to < 125 × 10^9/L	20 mg BID	15 mg BID	No change	No change	No change
75 × 10^9/L to < 100 × 10^9/L	10 mg BID	10 mg BID	10 mg BID	No change	No change
50 × 10^9/L to < 75 × 10^9/L	5 mg BID	5 mg BID	5 mg BID	5 mg BID	No change
< 50 × 10^9/L	Hold dosing				

Similarly, ANC levels that decline to < 0.5 × 10^9/L necessitate immediate dose interruption. Absolute neutrophil count level recovery to > 0.5 × 10^9/L but < 0.75 × 10^9/L will allow dosing to be restarted at 5 mg BID, and ANC levels > 0.75 × 10^9/L and < 1.0 × 10^9/L may restart at 10 mg BID. Absolute neutrophil count level increases to above 1.0 × 10^9/L will allow a further dose increase to a maximum of 20 mg BID.

Table 18 details the recommended ruxolitinib doses after interruption(s) or dose reduction(s) due to safety (hematological) reasons.

Table 18: Restarting or Increasing Ruxolitinib Dose After Safety Interruptions or Dose Reductions Due to Neutropenia

Current ANC Levels	▼ Dose Restart or Dose Increase Guidelines ▼
≥ 1.5 × 10^9/L	20 mg
1.0 to < 1.5 × 10^9/L	15 mg BID for at least 2 weeks; if stable, may increase to 20 mg BID
0.75 to < 1.0 × 10^9/L	10 mg BID for at least 2 weeks; if stable, may increase to 15 mg BID
0.5 to < 0.75 × 10^9/L	5 mg BID for at least 2 weeks; if stable, may increase to 10 mg BID
0.5 × 10^9/L	Continue hold

6.6.6.2. Dose Modification Guidelines for Ruxolitinib Due to Nonhematologic Criteria

Except for the hematologic criteria specified above, interruption of ruxolitinib for safety reasons is at the discretion of the investigator with approval from the sponsor's medical monitor (when possible). In some circumstances, it may be necessary to temporarily interrupt treatment as a result of adverse experiences that may have an unclear relationship to study treatment or thought to be more likely attributable to ruxolitinib. Except for cases specified in Table 16 through Table 18, restart of ruxolitinib administration should occur at the original dose. If the same AE recurs after restart of ruxolitinib, the investigator should consider reducing the ruxolitinib dose for any subsequent restart after recovery.

6.6.6.3. Dose Reductions of Ruxolitinib for Concomitant Usage of Inducer/Inhibitor of CYP3A4/5

Ruxolitinib is metabolized in the liver by the CYPP450 metabolizing enzyme system, predominantly by the 3A4 isozyme. With concomitant dosing of potent CYP inhibitors such as oral ketoconazole, plasma exposure of ruxolitinib increases approximately 2-fold. Thus, a dose reduction of approximately 50% for ruxolitinib is appropriate for participants who take ketoconazole or other potent/strong CYP3A4/5 inhibitors as concomitant medication (University of Washington School of Pharmacy 2020). Twice daily doses will be decreased to the corresponding QD dose as follows:

- If dose is 25 mg BID, change dose to 25 mg QD.
- If dose is 20 mg BID, change dose to 20 mg QD.
- If dose is 15 mg BID, change dose to 15 mg QD.
- If dose is 10 mg BID, change dose to 10 mg QD.
- If dose is 5 mg BID, change dose to 5 mg QD.

Based on the very low overall bioavailability of topical ketoconazole, no dose adjustment of ruxolitinib is needed for use with topical ketoconazole.

6.6.6.4. Dose Increase of Ruxolitinib Based on Insufficient Response

If efficacy is considered insufficient and platelet and neutrophil counts are adequate (as defined below), ruxolitinib doses may be increased in 5-mg increments to a maximum of 25 mg BID. In TGB only, doses should not be increased during the first 6 months of treatment in the framework of this study in order to allow evaluation of anemia response and not more frequently than every 2 weeks.

A dose increase may be considered in participants who meet all of the following conditions:

- Failure to achieve a reduction from pretreatment baseline in either palpable spleen length of 50% as measured by palpation or a 35% reduction in spleen volume as measured by MRI or CT scan.
- Platelet count values are greater than 125×10^9/L during the prior 4 weeks.
- Absolute neutrophil count values are greater than 0.75×10^9/L during the prior 4 weeks.

Following a dose increase, platelet count and ANC levels should be assessed approximately 2 weeks after the dose adjustment. If a regularly scheduled study visit or laboratory-only visit does not coincide with this required blood draw (within the visit window), an unscheduled visit should be held to collect samples for hematology.

Ruxolitinib dose will never be increased during the DLT assessment period (first treatment cycle in the study).

6.6.7. Treatment After Initial Radiologic Evidence of Disease Progression

See Section 7.1 and Section 8.10.

6.7. Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine participant eligibility.

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 from 30 days before Cycle 1 Day 1 and up to 30 days after the last dose of study treatment or until the participant begins a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. All COVID 19 vaccines administered to the study participants prior to and during the study period will be recorded in their CRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered after 30 days after the last dose of study treatment should be recorded for SAEs as defined in Section 9.2. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The sponsor's medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.7.1. Permitted Medications and Procedures

With the exception of those mentioned in Section 6.7.2 and Section 6.7.3, all medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) necessary for the study participants' optimal clinical care and management can be administered to the study participants (refer to the ruxolitinib country-specific label as applicable [for Canada, refer to the Canadian Product Monograph]).

6.7.2. Restricted Medications and Procedures

The following medications have restrictions on use or doses or require changes to the way in which INCB000928 and/or ruxolitinib is administered during the study.

- Low dose aspirin (≤ 150 mg/day) and nonsteroidal anti-inflammatory agents (ibuprofen) may be used; however, caution should be used when administering ibuprofen or other nonsteroidal anti-inflammatory drugs with long elimination half-lives; participants should be monitored closely for toxicity, especially for myelosuppression and renal and GI toxicity.
- Systemic corticosteroid doses ≥ 10 mg/day prednisone or equivalent are prohibited, unless use is part of a ruxolitinib dose tapering strategy (see Section 7.1.1.2). If a participant requires steroids for a comorbid condition during study participation, then continuation in the study will be considered on an individual basis by the sponsor and the investigator.
- G-CSF, or GM-CSF, romiplostin, and eltrombopag. Ruxolitinib may interfere with efficacy, and they may cause an increase in spleen size or leukemia transformation.
- If a participant is to receive a COVID-19 vaccination during the study, the sponsor does not recommend performing this vaccination during the DLT assessment period (ie, during the first study treatment cycle).

- Inducers or inhibitors of the metabolizing enzyme CYP3A4/5:
  - When concomitant administration of a strong/potent inhibitor of CYP3A4/5 is required for participant management, the dose of ruxolitinib must be adjusted as described in Section 6.6.6.3 and the dose of INCB000928 as presented in Section 6.6.3.1.
  - The use of weak-to-moderate inhibitors or inducers of CYP3A4/5 is discouraged; alternative therapies should be considered wherever possible. Should one of these medications be medically necessary, its use should be documented; however, dose adjustment of INCB000928 and/or ruxolitinib is not required. Differences in individual sensitivity and variation in potency of inhibition of various CYP enzymes may result in the need for a reduced dose of INCB000928 and/or ruxolitinib during a period of concomitant medication use. If required for safety, then the ruxolitinib dose may be reduced from BID to QD and the dose of INCB000928 reduced to at least 50% in these circumstances; this should be clearly documented in the participants' medical source. The sponsor's medical monitor may be consulted for advice when using these agents.
- In participants for whom an anticoagulant/antiplatelet medication (eg, warfarin, heparin) use will be initiated, the history and degree of thrombocytopenia should be considered, coagulation parameters monitored, and dose of anticoagulant adjusted accordingly.
- Chronic acetaminophen use is discouraged; however, if it is required and no alternative therapies are available, acetaminophen up to 1000 mg per 24 hours for pain and discomfort is permitted.

6.7.3. Prohibited Medications and Procedures

The following medications are prohibited during the study for all 3 treatment groups:

- Any investigational medication other than INCB000928. Use of such medications within 28 days or 5 half-lives, whichever is longer, before the first dose of study treatment and during the study through the safety follow-up visit is prohibited.
- Use of interferon, thalidomide, busulfan, lenalidomide, or anagrelide is not permitted at any time during participation in the study.
- Aspirin at doses exceeding 150 mg per day is prohibited.
- Potent/strong inducers and inhibitors of CYP3A4/5 are not permitted with the exception of topical ketoconazole, based on its low overall bioavailability.
- ESAs.

6.7.4. Rescue Medicine

Not applicable.

6.8. Study Treatment After the End of the Study

After the end of the study, the participants will receive therapy(ies)/treatment(s) as per the local institution standard of care applicable to their disease (see Section 4.2 for the definition of the study end). Eligible participants who are deriving clinical benefit with INCB000928 may be considered for poststudy drug provisions allowing them to continue receiving INCB000928 until a suitable alternative treatment option is identified.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Study Treatment Discontinuation – All Treatment Groups

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

- Occurrence of unacceptable toxicity, defined as the occurrence of an AE that is related study treatment 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. The occurrence of unacceptable toxicity not caused by the underlying malignancy will be presumed to be related to study treatment and will require that the study treatment be permanently discontinued.
- The participant becomes pregnant.
- The participant requires additional antineoplastic systemic therapy, which will qualify as disease progression.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- The participant withdraws their consent to participate in the study. 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 to be followed for progression and post-treatment assessments (see Table 3).
- The study or individual cohort(s) (see Section 4.3) is/are terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- In Canada only, if, during the course of the study, a participant is found not to have met all eligibility criteria, the participant will be permanently discontinued from study treatment.

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

- If a participant is noncompliant with study procedures or study treatment administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.
- If a Grade 4 clinical event has NOT been confirmed upon rechallenge with the study treatment, at the option of the investigator.

In the event that any participant permanently discontinues the study treatment, regardless of reason(s), reasonable efforts should be made to have the participant return for an early EOT visit as well as the safety follow-up visit and have evaluations completed as described in Table 3 and Table 4.

7.1.1.1. Reasons for Study Drug INCB000928 Discontinuation – All Treatment Groups

In addition to the criteria described above, INCB000928 will be permanently discontinued in the event of the following:

- The participant presents a treatment failure defined as either:
  - Decrease of Hgb during the study treatment period of at least 1.5 g/dL relative to baseline sustained for at least 4 weeks, or
  - Absence of any Hgb increase of at least 1.5 g/dL relative to baseline or persistence of transfusion requirement during at least 6 months (24 weeks) of the study treatment period.
- A persistent AE requiring an interruption of INCB000928 administration for more than 21 days, unless a longer interruption has been approved by the sponsor's medical monitor.
- Treatment-emergent iron overload with symptoms or damage in organ function.
- The participant is unable to tolerate INCB000928 at a reduced dose specified for the cohort due to one of the following reasons:
  - Recurrence of a Grade 3 toxicity after 2 dose reductions (see Table 15).
  - Any Grade 4 toxicity other than Grade 4 neutropenia and Grade 4 thrombocytopenia (see Table 15).

In addition to the criteria above, the investigator is able to discontinue INCB000928 administration if in their opinion, the participant is no longer benefitting from INCB000928 treatment. In such a situation, the investigator will document their assessment and decision in the participant's eCRF and source documents.

At the time of INCB000928 permanent discontinuation, the EOT and safety follow-up visit assessments (see Table 3 and Table 4) should be completed, and the participant will enter the post-treatment follow-up period.

7.1.1.2. Reasons for Study Treatment Discontinuation – Treatment Groups B and C

In addition to the criteria described above, participants from TGB and TGC will permanently discontinue ruxolitinib in the following events:

- If ruxolitinib is interrupted for any reason for more than 8 weeks.
- After 6 months in the absence of spleen size reduction or symptom improvement since initiation of treatment with ruxolitinib.
- The participant is unable to tolerate ruxolitinib at the lowest possible dose of 5 mg BID (or 5 mg QD with concomitant strong/potent CYP3A4/5 inhibitor or inducer) due to one the following conditions:
  - Platelet counts cannot be maintained $\geq 50 \times 10^9$/L.
  - ANC cannot be maintained $\geq 0.5 \times 10^9$/L.
  - Hgb cannot be maintained ≥ 6.5 g/dL (despite the use of transfusion therapy or if the participant will not accept blood transfusions).
  - Occurrence of a Grade 4 laboratory abnormality (nonhematological) considered at least possibly related to the study treatment and clinically significant in the view of the investigator. Exceptions NOT requiring permanent discontinuation of ruxolitinib are serum iron, total bilirubin not accompanied by direct bilirubin of 2 × ULN, triglycerides, total cholesterol, HDL cholesterol, or abnormalities in urinalysis not accompanied by at least a Grade 3 elevation of serum creatinine.
  - Recurrence of a Grade 4 clinical event (nonlaboratory based) after rechallenge with the study treatment. Exceptions NOT requiring permanent discontinuation of ruxolitinib are fatigue, insomnia, obesity, constitutional symptoms (disabling but not life-threatening), salivary gland changes, arthritis, and joint effusion.
- The participant meets one of the following disease progression/leukemia transformation criteria:
  - Disease progression criteria:
    - Increase in spleen volume of ≥ 25% from baseline confirmed by MRI or CT scan, as applicable.
    - Splenic irradiation.
    - Splenectomy.
    - Palpable spleen:
      - Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or
      - A ≥ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm, or
      - A 50% increase in palpable distance, below LCM, for baseline splenomegaly of > 10 cm.

- Leukemic transformation defined by:
  - A BM blast count of ≥ 20% at any time during the study treatment period, or
  - For participants with a peripheral blood blast count of ≥ 20%, the participant should continue treatment with ruxolitinib until the increase has been sustained at all sampling times for a period of 8 weeks or more, indicating leukemic transformation. At the discretion of the investigator, an unscheduled BM biopsy may be conducted to confirm leukemic transformation as an alternative to awaiting confirmation from peripheral blood samples. Once confirmed by either means, the participant is discontinued from ruxolitinib treatment.

The investigator may decide to discontinue INCB000928 at the time of discontinuation of ruxolitinib if they believe the participant is no longer deriving clinical benefit from the study drug. In such a situation, the decision will be documented in the participants' medical source and be recorded in the participants' eCRF.

7.1.1.2.1. Optional Dose Tapering Strategy in the Event of Ruxolitinib Discontinuation

When a decision is made to permanently discontinue ruxolitinib for reasons other than low platelet counts or ANC levels, a dose tapering strategy may be considered based on evaluation of the condition of the participant, current dosing regimen, and the clinical judgment of the investigator. If considered medically necessary, the investigator may use any treatment to manage discontinuation of ruxolitinib, including a gradual tapering of the ruxolitinib dose or use of other medications to manage side effects of discontinuation. Short-term courses of corticosteroids have been used to moderate the withdrawal symptoms of ruxolitinib and may be considered as part of a tapering strategy. Corticosteroids may be started before or concurrent with ruxolitinib tapering in anticipation of the possibility of occurrence of withdrawal symptoms. When a decision has been made to discontinue the participant with utilization of a tapering strategy, regardless of the use of concomitant medications, safety data will continue to be assessed in accordance with the Protocol for a period at least through the continued administration on ruxolitinib.

7.1.2. Discontinuation Procedures

The decision to discontinue study treatment will not constitute study withdrawal or study completion.

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted, the treatment period will be considered complete, and the follow-up period will begin. Reasonable efforts should be made to have the participant return for the safety follow-up visit. These visits are described in Table 3 through Table 6. The last date of the last dose of study treatment and the reason for discontinuation of study treatment 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 withdrawal must be documented in the participant's medical record and the primary reason for withdrawal must be included in the eCRF.
- The EOT visit should be performed and date recorded.
- The status of the participant should be updated to EOT in the IRT.
- Participants must be followed for safety until the time of the safety follow-up visit or until study treatment-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up), 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.

7.2. Participant Withdrawal From the Study

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

If 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, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See Table 3 through Table 6 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are 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, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Upon implementation of Amendment 9, study assessments will be streamlined and data collection reduced to safety assessments only. See Table 3 and Table 5 for Protocol assessments required prior to implementation of Amendment 9. See Table 4 and Table 6 for Protocol-required assessments for subjects consented to Amendment 9.

Further details of study procedures and assessments can be found in the Investigator Site File.

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. The sponsor or its designee will provide a template. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template, and all site-specific changes must be approved by the IRB/IEC and the sponsor or its designee. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements including optional samples/procedures (eg, optional biopsy) and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that their 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 their 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.

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 receives the first dose of study treatment. Screening may not exceed 56 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 informed consent 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 56 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 the administration of study treatment. Individual tests with results that fail eligibility requirements may be repeated during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before receiving the first dose of study treatment will be used to determine eligibility. Treatment should start as soon as possible, but within 2 days after confirmation of participant's eligibility.

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 at screening. Upon determining that the participant is eligible for study entry, the IRT will be contacted to obtain the study treatment. Additionally, the IRT will be contacted as appropriate to update the study treatment supply and the participant's status in the study. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Forms

Symptoms of MF will be assessed using a symptom form (MPN-SAF; see Appendix D).

Detailed directions for the administration of the MPN-SAF will be provided in the Investigator Site File.

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 10 years that are considered to be clinically significant by the investigator.

As race and/or ethnicity data are not to be analyzed from a scientific or medical perspective, but rather are to be reported in a descriptive format only in the CSR, data on race and/or ethnicity from France must not be collected as per GDPR and local data protection law requirements.

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 stage, tumor histology, relevant disease characteristics, and prior treatments, including systemic treatments, radiation, and surgical procedures will be recorded.

8.2. Efficacy Assessments

The following pieces of information will be collected for each transfusion:

- The blood product(s) transfused and quantity (units).
- The date of the transfusion.
- The Hgb/platelet value that triggered the transfusion.

The collection of RBC transfusions and Hgb values will be performed as follows:

- Before study entry
  - RBC transfusions and Hgb values have to be recorded for at least 12 weeks before the first study treatment dose. The collection of Hgb values and RBC transfusions are mandatory only during the 8 weeks immediately preceding the first study treatment dose.
- During study treatment period
  - The RBC transfusions will be collected from the first study treatment dose, throughout the whole study treatment period and until 30 days after the last study treatment.
  - The Hgb values will be collected at least weekly the first cycle, every 2 weeks thereafter (optional after Cycle 6), and at the EOT and safety follow-up visits.

The primary efficacy assessment for participants with MF is the anemia response, modified from Tefferi et al (2013) definitions.

Magnetic resonance imaging is the preferred method for obtaining spleen volume data. However, CT scans may be performed at the visits where MRI would be conducted if the participant is not a candidate for MRI (eg, presence of metal clips in the body, claustrophobia),

or if MRI is unavailable to the study site. The same method (MRI or CT scan) should be used for all visits for a given participant unless a new contraindication to the use of MRI (eg, pacemaker insertion) occurs. The sponsor's medical monitor should be consulted if a modality change is required.

Spleen length will be assessed by manual palpation and will be used to determine if dose increases for lack of efficacy should be considered. Investigators will use a soft centimeter ruler so that palpable spleen length is not measured in fingerbreadths. The edge of the spleen shall be determined by palpation, and measured in centimeters, using a soft ruler, from the costal margin to the point of greatest splenic protrusion. The same person should perform all assessments of a particular participant whenever possible.

Upon implementation of Amendment 9, imaging with CT scans or MRI for the purposes of efficacy will no longer be required (only liver MRI for the evaluation of iron overload is required). In instances where CT scan is logistically more convenient, CT is acceptable.

The BM aspirate and biopsy assessments will be performed locally as per the local standards and will include at least a staining for fibrosis and a cytogenetic assessment. The cytogenetics testing will be repeated after screening only if the participant had cytogenetic abnormalities at screening. Staining will continue at all assessments. The BM aspirates and biopsies will be performed at screening (unless already performed within 3 months prior to screening) and at the end of every 6 cycles (ie, end of Cycles 6 and 12) during the study treatment period. Bone marrow biopsies and aspirates collected at screening should be evaluated locally. Upon implementation of Amendment 9, BM aspirates and biopsy assessments are not required after Cycle 6.

Response in transfusion-dependent participants (see Section 5.1) requires the absence of any RBC transfusions during any consecutive, rolling 12-week interval during the treatment period. However, transfusions should be avoided unless the Hgb value is < 8.5g/dL, anemia is symptomatic, or active bleeding is detected.

The disease response assessment will be performed at the end of every sixth cycle, beginning at Cycle 6 (see Table 3).

8.2.1. Patient-Reported Outcomes

Symptom burden assessment will be performed using the MPN-SAF (Emanuel et al 2012); the baseline assessment will be the one performed before the first dose of study treatment (see also Section 8.1.4 and Appendix D for the items included in the form).

8.2.2. Medical Resource Utilization and Health Economics

Not applicable.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (see Table 3 through Table 6).

See Section 6.6 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

The safety assessments described in the following sections apply to all 3 treatment groups.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last dose of study treatment or until the start of new anticancer therapy Adverse events for participants that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study treatment. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver or surrogate). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following-up on AEs that are serious, that are considered related to the study treatment/procedures, or that caused the participant to discontinue the study treatment or withdraw from study. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?" is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

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

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

All SUSARs will be reported to EudraVigilance in accordance with EU CTR No. 536/2014.

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 ICF signature by the participant and up until 30 days after the last study treatment dose constitute an AE if they worsen from baseline, they are considered clinically meaningful in the medical and scientific judgment of the investigator, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment. They will be graded as per the NCI CTCAE v5.0 where applicable. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.3. Eastern Cooperative Oncology Group Performance Score

The ECOG performance status will be assessed at screening and other study visits per Table 3 and Table 4. Performance status must be assessed by a medically qualified individual, scored as per Table 19, and recorded in the participant's eCRF.

Table 19: Eastern Cooperative Oncology Group Performance Status

Score	ECOG Performance Status
0	Fully active, able to carry on all predisease 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.

8.3.4. Vital Signs

See Table 3 and Table 4 for the timing and frequency of assessments.

Vital sign measurements (to be taken before blood collection for laboratory tests, except during screening) include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after at least 5 minutes of rest. 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.

Weight will also be assessed at screening and at each study visit.

Abnormal vital sign results identified after the ICF signature by the participant and up until 30 days after the last study treatment dose constitute an AE if they worsen from baseline, are considered clinically meaningful in the medical and scientific judgment of the investigator, induce clinical signs or symptoms, require concomitant therapy, or require changes in the study treatment.

8.3.5. Cardiac Function Assessments

8.3.5.1. 12-Lead ECGs and Cardiac Echography or MUGA Scan

Cardiac function will be assessed by the following exams, which will be performed as indicated in Table 20:

- 12-lead ECGs: At minimum, the heart rate and measurement of PR, QRS, QT, and QTc will be collected.
- Cardiac echography or MUGA scan: At minimum, the ejection fraction will be recorded.

The 12-lead ECG will be obtained as outlined in the SoA (see Table 3 and Table 4) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. 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 and cardiac echography or MUGA scan exams will be interpreted by the investigator at the site to be used for immediate participant management. Additional 12-lead ECGs or echocardiography examinations 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.

In the event that a participant's QTc is > 450 milliseconds at screening, the participant may enroll with prior approval from the sponsor's medical monitor. For participants with an intraventricular conduction delay (QRS interval > 120 milliseconds) at screening, the JTc interval may be used in place of the QTc with medical monitor approval. In addition, the JTc interval should be used for all subsequent assessments.

Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator and that occur from the ICF signature up until 30 days after the last study treatment dose as applicable are to be reported as AEs and graded as per the NCI CTCAE v5.0 where applicable.

8.3.5.2. Triplicate 12-Lead ECGs – For Treatment Group A Participants Only

Triplicate 12-lead ECGs will be obtained on the days and times noted in Table 3, Table 4, and Table 20. On Cycle 1 Days 1 and 15, timed 12-lead triplicate ECGs will be conducted predose and then at 2, 4, and between 6-8 hours postdose, approximately within 5 minutes before the PK blood draw at the corresponding timepoints. The specified postdose timepoint(s) may be adjusted based on emerging PK data. Additional ECGs may be performed if clinically indicated. Electrocardiograms from Cycle 2 and beyond only need to be performed in triplicate if there has been either a QT prolongation on-study or the ECG shows a clinically significant abnormality not present at baseline.

All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after approximately 5 to 10 minutes of rest. Baseline ECG intervals will be equal to the average of all ECG intervals obtained before the first study drug dose administration. All 12-lead ECGs obtained at subsequent timepoints during the study will be compared with these baseline 12-lead ECG intervals. For ECG morphology, the ECG performed closest to the time of administration on Day 1 of Cycle 1 will be used as the baseline.

The study manual for procedures that must be followed for the recording and transmission of ECGs to a central vendor and the operator's manual with instructions for operating the digital capture module will be shipped to the site along with the device.

In addition, the 12-lead ECGs will be interpreted by the investigator at the site and will be used for immediate participant management. The decision to include or exclude a participant or discontinue a participant's participation in the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator. Twelve-lead ECGs that are identified by the investigator as "Abnormal, Clinically Significant" may need evaluation by a consultant cardiologist as per the institution standard of care.

Table 20: Schedule of Cardiac Function Assessments

Visit/Examination	Any Time	Predose[a]	Postdose[b]
12-lead ECGs			
Screening	X	—	—
Cycle 1 Day 1	—	X	
Cycle 2 Day 1	—	X	—
Day 1 of every third cycle until Cycle 12 (Cycles 3, 6, 9and 12)	—	X	
EOT	X	—	—
Cardiac echography/MUGA scan			
Screening	X	—	—
Day 1 of every sixth cycle until Cycle 12 (Cycles 6 and 12)	X[c]	—	—
EOT	X	—	—
Triplicate 12-lead ECGs[d]			
Screening	X	—	—
Within 7 days prior to Cycle 1 Day 1	X	—	—
Cycle 1 Day 1 and Cycle 1 Day 15	—	X	2 h, 4 h, and between 6-8 h

[a] Predose is before the morning dose of INCB000928, within 90 minutes before receiving the study treatment.
[b] Postdose is 4 hours (± 5 minutes) after the morning dose of INCB000928.
[c] Within 3 days of the visit.
[d] Three records aligned with the PK/PD blood draw as applicable, within approximately 5 minutes before the respective PK or PD blood draw. (TGA participants only).

8.3.6. Iron Overload Assessment

Iron homeostasis assessment will be performed at screening; on Days 1, 8, 15, and 22 of Cycle 1; on Days 1 and 15 of Cycle 2; on Day 1 of each cycle after Cycle 2; and is optional for participants with elevated ferritin at the safety follow-up visit.

A noncontrast-enhanced MRI will be performed in conjunction with software used for the estimation of hepatic iron concentration (ie, MRI T2) to noninvasively measure liver iron concentrations in the following situations. Note: If there is a concomitant need to stage hepatic fibrosis or evaluate for alternate liver diseases, then a liver biopsy may be performed. Note that the screening MRI may not be repeated if already performed within 3 months prior to screening.

- For participants with a screening ferritin level of < 1000 ng/mL:
  - When the ferritin level during the study becomes > 1.5 × the ferritin screening level AND the ferritin level is ≥ 1000 ng/mL, then every 3 cycles afterwards providing the conditions are maintained
  - EOT

- For participants with a screening ferritin level of ≥ 1000 ng/mL:
  - Every 6 cycles (ie, at cycles 6, 12, 18, 24, 36, 42 as applicable), and
    - When the ferritin level during the study becomes > 1.5 × the ferritin screening level, with increased frequency to every 3 cycles afterwards providing the conditions are maintained (see Table 15)
    - EOT

At sites where MRI is not available or CT is logistically more convenient, a CT scan may be used to identify any liver lesion(s) or disease.

8.4. Laboratory Assessments

See Table 21 for the list of clinical laboratory tests to be performed and Table 5 and Table 6 for the timing and frequency. These analytes will be measured for safety, efficacy, and/or PD purposes (see Section 8.6). All parameters from Table 5 and Table 6 will be measured locally, only hepcidin and sTfR parameters will be measured centrally. A certified laboratory local to the investigative site will perform all clinical laboratory assessments for safety (ie, serum chemistries, hematology assessments, coagulation tests, serology, lipid panel, and urinalysis). Additional tests may also be performed if clinically indicated.

Screening laboratory assessments must be performed within 56 days of Cycle 1 Day 1. If performed more than 56 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study treatment administration on Cycle 1 Day 1. Laboratory samples collected on Cycle 1 Day 1 must be performed before study treatment administration. 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.

Procedures conducted as part of the participant's routine clinical management obtained before signing the ICF may be used for screening or baseline purposes provided that the procedure meets the Protocol-defined criteria and has been performed in the screening interval.

The clinical findings from blood hematology, blood chemistry, lipid panel, coagulation panel, and urinalysis assessments will be recorded as AEs if considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment and will be graded as per the NCI CTCAE v5.0 where applicable.

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 (see also the definition in Section 9.1). All laboratory tests with values considered clinically significantly abnormal during participation in the study (from ICF signature) or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline, stabilized or are no longer considered clinically significant by the investigator or medical monitor.

Urinalysis measurements will be performed using a dipstick and abnormal/doubtful results may be confirmed by a quantitative measurement. Whenever possible, a diagnosis should be recorded in the eCRF rather than the abnormal laboratory result.

Whenever possible, the blood samples for all laboratory tests will be collected at each visit as applicable before dosing, in the morning, before any RBC transfusions. Every effort should be made to minimize the volume of blood drawn for each participant.

See Section 6.6 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

Table 21: Required Laboratory Analytes

Blood Chemistries	Hematology	Urinalysis (Dipstick)	Screening Serology	Coagulation
Ions: Bicarbonate or CO_2, calcium, chloride, magnesium, phosphate, potassium, sodium Iron homeostasis: TSI, ferritin, transferrin, TSAT, TIBC, UIBC Pancreatic markers: Amylase, lipase, glucose Hepatic markers: Albumin, total bilirubin, direct bilirubin, ALP, ALT, AST, total protein Renal markers: Blood urea nitrogen or urea, creatinine, uric acid Others: LDH, vitamin B12, and MMA[a]	CBC, including: • Hgb • Hct • Platelet count • RBC count • WBC count Differential count (absolute values), including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils • Myeloblasts	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein	Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis B core antibody HCV antibody HBV-DNA[b] HCV-RNA[b]	PT PTT or aPTT INR
		Lipid Panel	**Participants With MPNs**	**Pregnancy Testing**
		Total cholesterol Triglycerides LDL HDL	JAK-2 mutation status (part of the PD assessments)	Female participants of childbearing potential only. Serum test at screening, at EOT and safety follow-up visits and urine pregnancy test before the first study treatment dose on each cycle. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data.
[a] Methylmalonic acid is not applicable in Japan.
[b] DNA and RNA only if serology is positive.

8.4.1. Pregnancy Testing

A locally-performed serum pregnancy test will be required for all women of childbearing potential during screening (within 3 days of Cycle 1 Day 1 for TGA participants and TGB/TGC participants in the expansion stages and within 3 days of Cycle 1 Day −1 for TGB and TGC participants in the dose-escalation stages) before the first dose of study treatment (in all cases, the investigator should confirm the test result is negative before starting study treatment administration) and at the EOT and safety follow-up visits.

In addition, a urine pregnancy test will be performed locally before the start of each cycle, and as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement. If a urine pregnancy test is positive or doubtful, 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 treatment and continue participation in the study.

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

8.4.2. Serology

Hepatitis screening assessments will be performed at the screening visit to rule out hepatitis infection; required analytes are shown in Table 21. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

8.5. Pharmacokinetic Assessments

Upon implementation of Amendment 9, PK sampling will no longer be required.

Blood and urine samples will be collected for measurement of concentrations of INCB000928 and/or ruxolitinib and as specified in Table 5. A maximum of 4 samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor. Samples collected for analyses of INCB000928 and/or ruxolitinib concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. The actual date and time (24-hour clock time) of each sample will be recorded.

8.5.1. Blood Sample Collection

Timing of blood PK assessments are outlined in Table 22. Details and methods for obtaining, processing, handling, and shipping samples will be provided in the Laboratory Manual for this study. After the predose PK sample is drawn, participants will begin the study treatment. Predose is defined as within 90 minutes before administration of study treatment. Adjustments to the timing of blood sampling may be made based on emerging PK data.

In the event a BID administration schedule is explored (see Section 4.1.2), the reference for PK blood sampling will be the morning dose.

For TGB participants only (see Section 6.1), the PK samples drawn on Cycle 1 Day −1 (could be drawn within 7 days before Day 1), when only ruxolitinib is administered to the participants, will

allow to determine the PK profile of ruxolitinib. The data will be compared to the results obtained from PK measurements on Cycle 1 Day 1 (first day of combination treatment) and Cycle 1 Day 15 as appropriate, when both INCB000928 and ruxolitinib are administered to the participants, in order to confirm the absence of any potential DDI between INCB000928 and ruxolitinib.

Table 22: Pharmacokinetics Blood Sample Timing

Study Visit	Timing of Samples
TGA: dose-escalation and expansion stages[a]	
Cycle 1 Day 1 Cycle 1 Day 15	• Predose[b] • 2 hours postdose (± 15 minutes) • 4 hours postdose (± 15 minutes) • 1 sample between 6 and 8 hours postdose
Cycle 3 Day 1 Cycle 6 Day 1	• Predose[b] • 2 hours postdose (± 15 minutes) • 1 sample between 4 and 8 hours postdose
TGB and TGC: dose-escalation stage	
Cycle 1 Day −1 (ruxolitinib only; in TGB only) Cycle 1 Day 1 (first day with combination therapy) Cycle 1 Day 15 (combination therapy)	• Predose[b] • 2 hours postdose (± 15 minutes) • 4 hours postdose (± 15 minutes) • 1 sample between 6 and 8 hours postdose
Cycle 3 Day 1[a] Cycle 6 Day 1[a]	• Predose[b] • 2 hours postdose (± 15 minutes) • 1 sample between 4 and 8 hours postdose
TGB and TGC: expansion stage	
Cycle 1 Day 1 (first day with combination therapy) Cycle 1 Day 15 (combination therapy)	• Predose[b] • 2 hours postdose (± 15 minutes) • 4 hours postdose (± 15 minutes) • 1 sample between 6 and 8 hours postdose
Cycle 3 Day 1[a] Cycle 6 Day 1[a]	• Predose[b] • 2 hours postdose (± 15 minutes) • 1 sample between 4 and 8 hours postdose
First cycle of INCB000928 with intraparticipant dose escalation[a]	
On Day 15 of the first cycle with intraparticipant dose escalation	• Predose[b] • 2 hours postdose (± 15 minutes) • 4 hours postdose (± 15 minutes) • 1 sample between 6 and 8 hours postdose

[a] For plasma PK study only, ruxolitinib PK not needed for TGA, at Cycles 3 and 6 for TGB and TGC, and in the event of intraparticipant INCB000928 dose increase.
[b] Within 90 minutes before receiving the first study treatment.

8.5.2. Urine Sample Collection

Urine collection will be performed at Cycle 1 Day 15, and the urine will be collected for all participants during the first 4 hours immediately after study treatment administration (from 0 [dose time] to 4 hours after dose). The details of collection will be provided in the Investigator Site File.

8.6. Pharmacodynamic and Translational Assessments

Upon implementation of Amendment 9, PD/biomarker/translational sampling will no longer be required.

Blood samples will be obtained for PD studies as detailed in Table 5.

8.6.1. Blood Sample Collection

Table 23 presents the timing of the PD/translational research sampling schedule. Details and methods for obtaining, processing, handling, and shipping samples will be provided in the Laboratory Manual.

Table 23: Biomarker/Translational Sample Timing

Biomarker Assessment	Study Visit	Timing of Sample		
		Any Time	Predose[a]	Postdose
For all participants				
Plasma PD[b]	Day −1 of Cycle 1 in TGA, TGB and TGC participants (Draw within 7 days before Day 1)[c]	—	X[d]	2 hours (± 15 min) 4 hours (± 15 min) 1 sample between 6 and 8 hours
	Days 1 and 15 of Cycle 1	—	X[d]	2 hours (± 15 min) 4 hours (± 15 min) 1 sample between 6 and 8 hours
	Day 1 of each cycle after Cycle 1 until Cycle 24 Day 1	—	X[d]	—
	Day 1 of Cycle 3 and Day 1 of Cycle 6	—	—	1 sample between 4 and 8 hours
Iron homeostasis, erythropoiesis parameters, and EPO	Screening	X	—	—
	Days 1, 8, 15, and 22 of Cycle 1 Days 1 and 15 of Cycle 2 Day 1 of each cycle after Cycle 2	—	X	—
	EOT and safety follow-up	X	—	—
Serum biomarker	Day 1 of Cycles 1, 2, 4, and 7	—	X	—
	EOT	X	—	—
Whole blood correlative DNA	Day 1 of Cycle 1	—	X[e]	—
	Day 1 of Cycle 7	—	X[e]	—
Whole blood correlative RNA	Day 1 of Cycle 1	—	X[e]	—

[a] Within 90 minutes before receiving the study treatment.
[b] Plasma PD will be used to measure hepcidin levels in blood.
[c] For TGA, TGB, and TGC, the Cycle 1 Day −1 PD sampling should be obtained between 8-10 AM; this will be considered the "Predose" sample. Additional PD samples will follow at 2, 4, and between 6-8 hours after the "Predose" sample.
[d] The predose blood samples for the measurement of hepcidin will have to be performed between 8 and 10 AM before dose administration.
[e] May not be collected if local restrictions apply.

Additional translational parameters may be evaluated at the discretion of the sponsor using excess PK samples. Analyses will be conducted by Incyte Corporation (Wilmington, DE) or by Incyte's designee.

Biological samples will be stored in safe conditions (ie, locked and only accessible by authorized individuals at a testing institution designated by the sponsor) for a given period of time (noted in the ICF) from the publication of the first clinical study report. After this storage period, the remaining samples will be disposed of in accordance with the most recent biospecimen guidelines for handling biological samples at the designated testing institution.

Only the medical institution that provided the participants' biological samples, and the researchers at the testing institution designated by the sponsor, will be able to access and use the biological samples. During the storage period of the samples (maximum of 10 years from the first CSR), the samples may be used to perform tests and research related to the trial to support the objectives of the study, assess the safety or efficacy of any drug or treatment included in the study, improve the design of future studies, or develop a better scientific understanding of MF. The sponsor and researchers at the testing institution designated by the sponsor are not permitted to conduct additional research using the biological samples for any purpose other than the Protocol. The results of tests and research on the biological samples related to the study drug are exploratory; as a result, their details will not be communicated to the participants.

8.7. Storage and Future Use of Biological Samples

Biological samples (eg, biomarkers, PD, PK) may be stored from the date of the last participant's last visit to perform study-related research. Additional research outside of study-related research will not be performed. Anonymized participant samples will be transported to the sponsor or designated vendor (outside EEA/UK, including US) for analysis as detailed in the laboratory-specific study manual(s). Pharmacokinetic samples will be destroyed after the final bioanalysis report or CSR. Biomarker and PD/translational samples may be stored for up to 10 years from the first CSR for study-related research only, unless otherwise agreed with national regulatory requirements in participating countries and/or local health authorities in separate site and/or participant documents.

8.8. Unscheduled Visits

Clinic visits or diagnostic laboratory visits not prescribed in the Protocol may be performed at any time clinically indicated at the investigator's discretion. Results of assessments performed at these visits should be entered as unscheduled visits in the eCRF. The sponsor may also request additional visits to be performed, if needed, based on emerging safety data.

8.9. End of Treatment and/or Early Termination

When the participant permanently discontinues study treatment, 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 safety follow-up visit.

8.10. Follow-Up

8.10.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled safety follow-up visit, which should occur 30 to 35 days after the last dose of study treatment. Adverse events and SAEs must be reported up until 1) at least 30 days after the last dose of study treatment 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 safety 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, and the investigator or designee should document this contact in the source.

If a participant is scheduled to begin a new anticancer therapy before the end of the 30-day safety follow-up period, the safety follow-up visit should be performed before a new anticancer therapy is started.

8.10.2. Post-Treatment Follow-Up

Upon implementation of Amendment 9, post-treatment follow-up will no longer be required.

Participants who discontinue study treatment will move into the post-treatment follow-up period and should be assessed as per institution's standard of care (ideally every 6 months [180 days ± 14 days] for up to 1 year after study treatment discontinuation) to collect information on disease/life status. Every effort should be made to collect information regarding disease/life status until one of the following conditions occurs:

- Withdrawal of consent
- Death
- End of the study

For participants having entered the post-treatment follow-up period 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), and life status if applicable 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, participant records, and public records/databases at intervals of no longer than 6 months.

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 drug/treatment.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug/treatment. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low Hgb, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after the start of study drug/treatment administration are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from dosing errors of a study drug/treatment (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy," "disease progression," or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. • A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after obtaining informed consent. If the condition is present before entering the study, then it should be captured as medical history. • Pre-existing diseases, pre-existing conditions, or new conditions with expected fluctuations in signs or symptoms 'should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization or death due to 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 (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 or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE. Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) are not considered SAEs.
d. Results in persistent or significant disability/incapacity The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is an important medical event An important medical event is an event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers, intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency or drug abuse, or suspected transmission of an infectious agent via a medicinal product. Secondary malignancies should always be considered SAEs. An event that may lead to disability is also considered an important medical event. It includes a case that is exposed to a risk of dysfunction to an extent that interferes with daily life when the adverse drug reaction occurs. It does not include an adverse drug reaction that, had the reaction been more severe, may have caused disability.

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

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

- The severity grade (CTCAE v5.0 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 drug/treatment: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study drug/treatment as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Nondrug Therapy).

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 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 drug/treatment and each occurrence of each AE/SAE. If reference therapy is used in combination with an Incyte study drug or if multiple Incyte study drugs are used, then the relationship to each study drug/reference therapy must be assessed (ie, for the Incyte product[s] and for the other product[s] that are used in combination with the Incyte product). If appropriate, the relationship to the combination may be assessed as well.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the RSI in the IB or Study Product Information for study drug or marketed products, respectively, in making their assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug/treatment administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and 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 based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change their opinion of causality in light of follow-up information and submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • Once an AE is detected, it should be followed in the Adverse Events Form in the eCRFs 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/treatment, the interventions required to treat the event, and the outcome. • When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology. • Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (in the SAE EDC CRF or via email/fax if paper SAE form is used due to unavailability of eCRF) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. • Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) immediately without undue delay but no later than 24 hours of receipt of the information.

See Appendix F for the management of PHL cases.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study treatment, reference therapies, or study procedure[s]), all SAEs occurring after the participant has signed the ICF through 30 days after the last dose of study drug/treatment ***or*** until the participant starts a new anticancer therapy, must be reported to the sponsor (or designee) immediately, without undue delay but not later than within **24 hours** of obtaining knowledge of its occurrence unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) immediately, without undue delay but not later than within 24 hours of it being available.

For Japan, this information must also be reported immediately to the head of the study site.

Investigators are not obligated to actively seek SAE information after the safety follow-up visit or more than 30 days after the last dose of study drug/treatment. If the investigator learns of any SAE, including death, at any time during this period, and they consider the event to be reasonably related to the study drug/treatment or study participation, then the investigator must notify the sponsor (or designee) immediately but no later than 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 (see Section 7.3).

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

If the SAE is not documented in RSI of the IB for the study drug/treatment (new occurrence) and is thought to be related to the study drug/treatment, the sponsor or its designee may urgently require further information from the investigator for expedited reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to relevant ethics committees and to competent authorities via the EudraVigilance database in accordance with the Clinical Trials Regulation (EU) No. 536/2014, Clinical Trials Information System guidelines, and in accordance with FDA 21 CFR part 312 for the US; or as per national regulatory requirements in participating countries.

For Japan, the sponsor will report suspected expected deaths and life-threatening events to the PMDA as per local regulatory requirements.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug/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 serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the 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 report immediately but at least within 24 hours of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form, in English (only if the EDC system is not available). The contact information for notifying Incyte Pharmacovigilance by email/fax is listed in the Investigator Site File or as per the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor within 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form. Once the EDC system is functional, the SAE report should be retroactively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form for details and for the email address or fax number).

- Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study drug/treatment because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

9.5. 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 treatment 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 treatment, the following procedures should be followed in order to ensure safety:

- The study treatment must be interrupted immediately (female participants only).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee immediately but no later than within **24 hours** of learning of the pregnancy.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluations. 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. This form 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 and reported as described in Section 9.4.

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 treatment, derived from safety information collected by the sponsor or its designee, are presented in Section 6 and 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 their designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be recorded as described in Section 9.3.

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

Complaints associated with unapproved medical devices will be reported to the sponsor with a Medical Device Defect Report Form, and the sponsor will report medical device defects to the PMDA as per local regulatory requirements.

9.9. Treatment of Overdose

Overdose (accidental or intentional) is to be reported as an AE (see Section 9.1). If the overdose meets serious criteria, the overdose term should be reported as an SAE (see Section 9.2). Additionally, signs and/or symptoms resulting from overdose are to be reported as an AE/SAE.

There has been no clinical experience with overdose of INCB000928. Treatment of overdose should consist of general supportive measures.

There is no known antidote for ruxolitinib overdose and what constitutes an overdose has not been defined. Single ruxolitinib doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia, and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of ruxolitinib.

For the purposes of this study, an overdose will be defined as the use of study treatment in doses in excess of those specified in the Protocol. Participants overdosed should be treated with appropriate supportive care until recovery. Use of study treatment in doses in excess of those specified in the Protocol should not be recorded in the eCRFs as an AE of Overdose. An

overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE and SAE forms in the eCRFs. An overdose with associated nonserious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the eCRFs. An overdose without associated symptoms should not be recorded as an AE in the eCRFs.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until appropriate recovery/stabilization (at least 14 days).
- Obtain plasma samples (same schedule as for Cycle 1 Day 1) for PK analysis within 1 day from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

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

10. STATISTICS

10.1. Sample Size Determination

10.1.1. Part 1 – Dose-Escalation Stages of Treatment Groups A, B, and C

The exact number of participants treated in each dose-escalation stage will depend upon the number of participants required per dose level and upon the number of dose levels studied (see Section 4.1 for more details).

10.1.2. Part 2 – Expansion Stages of Treatment Groups A, B, and C

Upon implementation of Amendment 9, expansion cohorts will not be enrolled.

In dose-expansion stages, the RDEs identified in the dose-escalation stages will be evaluated in at least 9 participants at each RDE dose level in TGA, and at least 25 participants at each RDE dose level in the TGB and TGC dose-expansion stages independently.

In the expansion stage for TGA, 9 participants per cohort will provide a 57.2% chance of identifying a toxicity with a true event rate of 9%.

In the expansion stage for TGB and TGC, assuming an unacceptable anemia response rate of 0.07 (H_0: $p \leq 0.07$ vs H_a: $p > 0.07$) and a target response rate of 0.25, twenty-five participants per cohort will provide an actual Type I error of 0.0936 and a power of 0.904 using the exact binomial test (null hypothesis will be rejected if at least 4 out of 25 responses are observed). This cohort will provide a ≥ 90% chance of identifying a toxicity with a true event rate of 9%.

More details for sample size calculation are provided in Table 24.

Table 24: Sample Size and Power Calculation for TGB and TGC

Cohort	Sample Size at Each RDE Dose Level	Unacceptable Anemia Response Rate	Target Anemia Response Rate	Number of Responders Observed to Reject H_0	Type I Error	Power
TGB	25	0.07	0.25	≥4	0.0936	0.904
TGC	25	0.07	0.25	≥4	0.0936	0.904

10.2. Populations for Analyses

The populations for analyses are provided in Table 25.

Table 25: Populations for Analyses

Population	Description
FAS	The FAS includes all participants who received at least 1 dose of INCB000928 or ruxolitinib. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy data.
Safety	The safety population includes all enrolled participants who received at least 1 dose of INCB000928 or ruxolitinib. All safety analyses will be conducted using the safety population.
PK/PD evaluable	The PK evaluable population will include all participants who received at least 1 dose of INCB000928 or ruxolitinib and provided at least 1 postdose plasma sample (1 PK measurement). The PD evaluable population will include all participants who received at least 1 dose of INCB000928 or ruxolitinib and provided at least 1 postdose plasma/serum sample (1 pharmacodynamic measurement).

10.3. Level of Significance

For the secondary efficacy endpoint in TGB and TGC dose-expansion stages, the 1-sided Type 1 error will be controlled at 0.1. For other endpoints, CIs will be reported at a 95% confidence level for each group. Note that this level of significance does not account for the multiple expansion groups.

10.4. Statistical Analyses

10.4.1. Primary Analysis

10.4.1.1. Part 1: Safety Analyses

The safety of INCB000928 administered alone or in combination with ruxolitinib will be analyzed using the following parameters descriptively by part, treatment group, and dose level in the safety population:

- Frequency and severity of AEs, SAEs, and DLTs.
- Changes in vital signs and clinical evaluations including ECGs.
- Changes in clinical blood and urine laboratory parameters.
- The rate of DLTs will be summarized for each cohort of the dose-escalation stages.

10.4.2. Secondary Analyses

10.4.2.1. Part 1 and Part 2: Efficacy Analyses

Upon implementation of Amendment 9, Part 2 cohorts will not be enrolled, and therefore the following analyses will not be performed.

The proportion of participants with an anemia response defined as an Hgb increase ≥ 1.5 g/dL for ≥ 12 weeks during treatment if TI at baseline or achieving TI for ≥ 12 weeks if TD at baseline, if applicable, will be estimated with its 95% CI.

For TGB and TGC, the proportion of participants will be tested under H_0: $p \leq 0.07$ versus H_a: $p > 0.07$ (p is the response rate) using the exact binomial test in the FAS population at a 1-sided alpha of 0.1.

Participants with missing assessments that prevent the evaluation of the secondary efficacy endpoint will be considered as nonresponders on that treatment arm. No data imputation will be applied.

The efficacy of INCB000928 administered alone or in combination with ruxolitinib will also be analyzed using the following parameters:

- Duration of anemia response will be estimated separately for TD (see Section 5.1) and TI participants at baseline using the Kaplan-Meier method with 95% CI, is defined as follows:
  - The interval from the first onset of Hgb increase ≥ 1.5 g/dL for ≥ 12 weeks to the earliest date of loss of anemia response that persists for at least 4 weeks, or death from any cause for the TI participants at baseline,

    OR
  - Duration of RBC-TI, defined as the interval from the first onset date of TI to the earliest onset date of TD or death from any cause for the TD participants at baseline.
- Mean change from baseline in the Hgb value over 12-week treatment periods will summarized descriptively.
- Rate of RBC transfusion through Weeks 24 and 48, defined as the average number of RBC units per participant-month during the treatment period. The proportion of participants receiving RBC transfusions over each month postbaseline period will be estimated, and the total number of RBC units received per participant over each month postbaseline period will be calculated.

10.4.2.2. Part 2 Only: Efficacy Analyses for Treatment Groups B and C – Dose Expansion

Upon implementation of Amendment 9, Part 2 cohorts will not be enrolled, and therefore the following analyses not performed:

- The splenic volume response rate at Week 24, defined as the proportion of participants achieving a ≥ 35% reduction in spleen volume at Week 24 relative to baseline as measured by MRI or CT scan, will be estimated with 95% CI.
- Spleen length response, defined as the proportion of participants achieving a ≥ 50% reduction in spleen length at any visit relative to baseline as measured by palpation, will be estimated.
- Percentage of participants with CR or PR according to the Tefferi et al (2013) definitions will be estimated with 95% CI.
- The morphologic effects of the combination of INCB000928 with ruxolitinib on BM will be summarized descriptively.

- PFS, defined as the interval from the first dose of study treatment until the first documentation of definitive disease progression or death due to any cause as per the Tefferi et al (2013) definitions, will be estimated with the Kaplan-Meier method.
- LFS, defined as the interval from the first dose of INCB000928 until the first documented leukemia transformation or death from any cause, will be estimated with the Kaplan-Meier method.

For PFS, the event time is defined as the earliest time of the scenarios below:

- For spleen volume increase, the progression date will be the date of the first MRI showing a 25% or greater increase in spleen volume as compared to the on-study nadir (the on-study period includes the baseline evaluation).
- For splenic irradiation, splenectomy, or death, the date of progression will be the actual date of the event.
- For leukemic transformation:
  - Determined by BM blast count of 20% or greater, the progression date will be the date of the BM aspirate or biopsy, as applicable.
  - Determined by peripheral blast count, the date of progression will be the date of the first peripheral blast count of 20% or greater that is subsequently confirmed by either 8 weeks of sustained high blast counts (ie, no intervening counts of < 20%) or by BM aspirate/biopsy.

10.4.2.3. Part 1 and Part 2: Pharmacokinetic and Pharmacodynamic Analyses

The following PK parameters will be summarized for INCB000928 alone, for ruxolitinib alone, or for the combination of INCB000928 with ruxolitinib, as applicable, descriptively by part, stage, treatment group, and dose level in the PK evaluable population at each visit. Population PK analysis will be specified in a separate SAP and conducted by the pharmacokineticist, and the details of the analysis methodology and results will appear in a separate report. The PK assessments will include the following:

- C_{max}
- t_{max}
- AUC_{0-t}

The following PD parameters will be summarized descriptively by part, stage, treatment group, and dose level in the PD evaluable population at each visit:

- Plasma hepcidin levels
- PD parameters to assess the iron homeostasis: TSI, ferritin, transferrin, TSAT, TIBC, and UIBC
- PD parameters to assess the erythropoiesis: RC, NRBC, MCV, MCH, Hgb, Hct, RBC count, MCHC, RDW, and the reticulocyte hemoglobin content
- Other PD parameters: EPO

The details of the analysis methodology of biomarkers and PD will be specified in a separate report. Both the specific SAP and analysis will be handled by the translational science group, and the results will be reported in a separate report.

Upon implementation of Amendment 9, Part 2 will not be enrolled and no analyses will be performed.

10.4.3. Safety Analyses

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

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE v5.0 toxicity grades, and tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 27).

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (see Table 26). Participants exhibiting clinically notable ECG abnormalities will be listed.

Table 26: Criteria for Clinically Notable Electrocardiogram Abnormalities

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

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

Table 27: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mm Hg	< 85 mm Hg
Diastolic blood pressure	> 100 mm Hg	< 40 mm Hg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38°C	< 35.5°C
Respiratory rate	> 24 breaths/min	< 8 breaths/min

10.4.4. Exploratory Analyses

10.5. Interim Analysis

No formal interim analysis is planned in this study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

The Protocol, Protocol Amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator. All documents must be reviewed and approved by the IRB/IEC and health authorities before the study is initiated. In accordance with EU CTR No. 536/2014, the sponsor will be responsible for submitting all documents in participating countries.

- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both health authorities and the 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:
  - Recording and documenting AEs or laboratory abnormalities identified in the Protocol as critical to the safety evaluation and reporting them to the sponsor according to the reporting requirements specified in the Protocol.
  - Recording and documenting all AEs, unless the Protocol provides different guidance in Section 9.
  - Reporting to the sponsor all SAEs occurring to participants treated by them in the clinical study unless the Protocol provides different guidance in Section 9.
  - Reporting an SAE to the sponsor per Section 9 procedures and timelines if they become aware of an SAE with a suspected causal relationship to the study treatment that occurs after the end of the study.
  - Providing written summaries of the status of the study to the 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.
  - Ensuring (along with the sponsor) that the clinical study is conducted in accordance with the Protocol and with the principles of GCP.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
  - Ensuring study-site compliance with the requirements of EU CTR No. 536/2014.

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

- The investigator will adhere to the Protocol as described in this document and 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.
  - The investigator will retain the content of the clinical trial master file, essential documents, AE documentation, and medical and other study records in accordance with all local, national, and regulatory laws but for a minimum period of at least 30 years for the US, 25 years for EEA countries, and a flexible approach of up to 30 years for regions outside the US and EEA, unless specific country regulations dictate otherwise, after completion or discontinuation of the study or as described in the final executed copy of the individual site agreement, or 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 formal discontinuation of clinical development of the test article and the regulatory authority is notified, whichever is longer, to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study during the retention period without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

- For Japan, the record retainer (delegated by the head of the study site) will retain the J-GCP–defined essential documentation at this site until the regulatory approval of the study treatment or at least 3 years after the discontinuation or completion of the study conduct, whichever is longer. If the sponsor requires retention of these documents for a longer period of time, the duration and method of retention will be decided upon through discussion between the sponsor and the study site. It is the responsibility of the sponsor to inform the head of the study site as to when the documents no longer need to be retained.

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor 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, study charters, or biomarker plans, as applicable.

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

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

The investigator will be responsible for the following:

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

reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; participants' files; and e-records/records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study).
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.
- Sending participants' data, either as unique samples, copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
  - As required by privacy and data protection regulations and Incyte's privacy policies, if any photographs of participants are to be used in the study, even if occasionally, or are to be taken, the photographs must be limited to the area of the face or the body that is strictly necessary and the photographs should be masked (ie, identifying features such as eyes, mouth, scars, tattoos, or unique markings or features should be either obscured with a black bar or digitally pixelated so as to not permit the reidentification of the participants and preserve their confidentiality) prior to sending the photographs to Incyte or any other third-party vendors for analysis or further processing.
  - In accordance with French regulations, sites in France must perform the masking before the photographs are transferred, including to any specially designated photography vendor, Incyte, or any other third party vendors for analysis or further processing. In addition, the participant's specific consent for photographs shall be collected.

- 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 Quality Assurance

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

11.4. Data Privacy and Confidentiality of Study Records

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

To ensure confidentiality of records and protect personal data, participant names will not be supplied to the sponsor or its designee. There may be certain duly authorized and contracted vendors managing participants' services such as for travel and meal reimbursement, home

delivery services, and/or parking, in which case those vendors will have the participant's directly identifiable personal information but in no circumstances will that directly identifiable information be transferred or sent to the sponsor. Only the participant number will be recorded in the eCRF; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

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

11.5. Financial Disclosure

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

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

11.6. Publication Policy

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

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.

11.7. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study or individual cohort(s) (see Section 4.3) at any time for any reason at the sole discretion of the sponsor or the IRB/IEC. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

For Japan, when the study is completed, the investigator should inform the head of the study site of the completion in writing and submit a written summary of the study's outcome, and then the head of the study site should promptly inform the IRB and sponsor or designee of the completion in writing.

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

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

- Failure of the investigator to comply with the Protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures or site agreement, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.
- Circumstances beyond the control of the sponsor or investigator that make it unreasonable to require the continuation of the study or site.
- Failure to carry out the study in the interest of the health of the participants.
- Failure to demonstrate that the continuation of an IRB-/IEC-approved study (ie, the IRB/IEC had previously issued a positive decision on the study) has scientific merit.
- Financial reasons (eg, the sponsor is declared insolvent or a bankruptcy petition has been filed.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

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

Women in the following categories are not considered WOCBP:

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

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

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

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 less than 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.[d]
  - oral
  - intravaginal (administration route is not approved in Japan).
  - transdermal (administration route is not approved in Japan).
- Progestogen-only hormonal contraception associated with inhibition of ovulation[d] (progesterone-only hormonal contraception is not approved in Japan, so this bullet and its sub-bullets will not apply for Japan)
  - oral
  - injectable
  - implantable[e]
- Intrauterine device[e]
- Intrauterine hormone-releasing system[e]
- Bilateral tubal occlusion[e]
- Vasectomized partner[e,f]
- Sexual abstinence[c] (sexual abstinence is not approved in Japan).

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
[b] If the male participant has a partner with child-bearing potential the partner should also use contraceptives.
[c] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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.
[d] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.
[e] Contraception methods that in the context of this guidance are considered to have low user dependency.
[f] 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 (2020).

APPENDIX B. 2016 WHO DIAGNOSTIC CRITERIA FOR PRIMARY MYELOFIBROSIS

2016 WHO Diagnostic Criteria for PMF

(Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion)	
Major criteria	
Criterion 1 (morphologic)	
BM morphology	Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3
Criterion 2 (morphologic)	
WHO criteria for ET, PV, BCR-ABL1 + CML, MDS, or other myeloid neoplasms	Not meeting
Criterion 3 (genetic)	
JAK2, *CALR*, or *MPL* mutation, or	Presence
Clonal marker,† or	Presence
Reactive BM reticulin fibrosis‡	Absence
Minor criteria	
Anemia not attributed to a comorbid condition	Presence
Leukocyte count	$\geq 11 \times 10^9$/L
Spleen size	Palpable
Serum LDH	Increased to above upper normal limit of institutional reference range
Leukoerythroblastosis	Presence

CML = chronic myelomonocytic leukemia, MK = megakaryocyte.
Note: Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: Hgb levels > 18.5 g/dL in men (Hct 55.5%) or > 16.5 g/dL in women (Hct 49.5%) if major criterion 3 and the minor criterion are present.
† In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) are of help in determining the clonal nature of the disease.
‡ Minor (Grade 1) reticulin fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

Source: Passamonti and Maffioli 2016.

APPENDIX C. IWG-MRT RECOMMENDED CRITERIA FOR POST-POLYCYTHEMIA VERA MYELOFIBROSIS AND POST-ESSENTIAL THROMBOCYTHEMIA MYELOFIBROSIS

Criteria for post-polycythemia vera myelofibrosis

Required criteria:

1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria[1]
2. Bone marrow fibrosis grade 2–3 (on 0–3 scale)[3] or grade 3–4 (on 0–4 scale)[4,a]

Additional criteria (two are required):

1. Anemia[b] or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis
2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of $\geqslant 5$ cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4. Development of $\geqslant 1$ of three constitutional symptoms: $>10\%$ weight loss in 6 months, night sweats, unexplained fever ($>37.5^{\circ}$C)

Criteria for post-essential thrombocythemia myelofibrosis

Required criteria:

1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria[1]
2. Bone marrow fibrosis grade 2–3 (on 0–3 scale)[3] or grade 3–4 (on 0–4 scale)[4,a]

Additional criteria (two are required):

1. Anemia[b] and a $\geqslant 2\,\text{mg}\,\text{ml}^{-1}$ decrease from baseline hemoglobin level
2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of $\geqslant 5$ cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4. Increased LDH (above reference level)
5. Development of $\geqslant 1$ of three constitutional symptoms: $>10\%$ weight loss in 6 months, night sweats, unexplained fever ($>37.5^{\circ}$C)

[a] Grades 2-3 according to the European classification: 3 diffuse, often-coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grades 3-4 according to the standard classification: 4 diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

[b] Below the reference range for appropriate age, sex, gender, and altitude considerations.

Source: Barosi et al 2008.

APPENDIX D. MYELOFIBROSIS NEOPLASMS SYMPTOM ASSESSMENT FORM

Subject Number _____ _____

Symptom	1 to 10 (0 if absent) ranking - 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past 24 hours.	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes, during the past week, how much difficulty you had with each of the following symptoms	
Night sweats	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse, not joint pain or arthritis)	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (> 100°F)	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss in the last 6 months	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Filling up quickly when you eat (early satiety)	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration - compared to prior to my MPD	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
	TSS: _____
MD Signature/Date	Per IWG-MRT 2013 Criteria: TSS to include fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers.
Staff Signature/Date	

Source: Emanuel et al 2012.

APPENDIX E. INSTRUCTION TO PARTICIPANTS FOR HANDLING STUDY DRUG INCB000928

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

- Store the study drug INCB000928 at room temperature, in a safe place, and out of reach of children.
- Only remove the number of tablets needed at the time of administration.
- Do not remove tablets in advance of the next scheduled administration.
- Make every effort to take doses on schedule in the morning around the same time every day.
- INCB000928 can be taken together with ruxolitinib with a full glass of water, as applicable.
- If vomiting occurs after taking study drug, do not take another dose.
- Bring all used and unused study drug bottles to the site at each visit.
- Refrain from taking study drug on the day of the clinic visits until after blood samples are collected.
- If an INCB000928 dose is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be administered at the usual time.

APPENDIX F. 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 PhV 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 treatment.

The investigator fulfills 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 6.6.3.

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/study treatment as applicable.
- 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 eCRF 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 PhV 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/study treatment as applicable. 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 ALP is increased. Malignant interruption of the biliary tract also should be considered.
- Concomitant treatment
- Other causes, such as systemic infections (eg, 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 an SAE.

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate eCRF 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/study treatment as applicable 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/study treatment as applicable 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 G. 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 of time to perform 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.

Participant SARS-CoV-2 Infection and Study Treatment

An event of active SARS-CoV-2 infection in 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 may 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 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 (see Section 6.7.2). 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.

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 local laboratory visit[s], cost of local [proximate] laboratory tests).

APPENDIX H. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	25 MAR 2020
Amendment 2	15 APR 2020
Amendment 3	27 AUG 2020
Amendment 4	10 MAY 2021
Amendment 5	02 SEP 2021
Amendment 6	22 DEC 2021
Amendment 7	21 DEC 2022
Amendment 8	05 DEC 2023
Amendment 9	20 FEB 2025

Amendment 9 (20 FEB 2025)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to reduce study assessments to those related to safety only and to incorporate administrative changes, including those required by EU CTR. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 1: Primary and Key Secondary Objectives and Endpoints; Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 3, Objectives and Endpoints (Table 8: Objectives and Endpoints); Section 4.1, Overall Design; Section 4.1.3, Part 2 – Expansion Stages of Treatment Groups A, B, and C; Section 5.5, Replacement of Participants; Section 6.5.4, Definition of Recommended Dose for Expansion; Section 10.1.2, Part 2 – Expansion Stages of Treatment Groups A, B and C; Section 10.4.2.1, Part 1 and Part 2: Efficacy Analyses; Section 10.4.2.2, Part 2 Only: Efficacy Analyses for Treatment Groups B and C – Dose Expansion**

   Description of change: Updated to indicate that Part 2 of the study will not be enrolled.

   Rationale for change: Sponsor decision to close overall study enrollment and discontinue development of INCB000928 in this indication.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Table 4: Amendment 9: Schedule of Activities; Table 6: Amendment 9: Schedule of Laboratory Activities); Section 4.2, Overall Study Duration; Section 6.1, Study Treatment Administered; Section 6.6.5, Criteria and Procedures for Dose Increases of Study Drug; Section 8, Study Assessments and Procedures; Section 8.2, Efficacy Assessments; Section 8.3.5, Cardiac Function Assessments (Table 18: Schedule of Cardiac Function Assessments); Section 8.3.6, Iron Overload Assessment; Section 8.4, Laboratory Assessments (Table 21: Required Laboratory Analytes); Section 8.5, Pharmacokinetic Assessments; Section 8.6, Pharmacodynamic and Translational Assessments; Section 8.10.2, Post-Treatment Follow-Up**

   Description of change: The frequency of study visits has been extended, and study assessments have been reduced to those required for safety only.

   Rationale for change: To streamline study procedures for participants deriving benefit from study treatment.

3. **Section 2.3.4, Justification for Dose; Section 4.1.1, Part 1-Starting Dose, Dose-Escalation, and De-Escalation**

   Description of change: Updated safety data per Investigator's Brochure Edition 6 (12 DEC 2024).

   Rationale for change: To provide current data from the INCB000928 program.

4. **Section 6.8, Treatment After the End of Study**

   Description of change: Added text confirming continued provision of study drug to those deriving benefit after study closure.

   Rationale for change: Declaration of Helsinki update.

5. **Section 9.4, Reporting of Serious Adverse Events; Section 11.1, Investigator Responsibilities**

   Description of change: Updated SAE reporting and record retention details.

   Rationale for change: EU CTR requirements.

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

Amendment 8 (05 DEC 2023)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to consolidate country-specific amendments (Amendment 7-CA and Amendment 7-FR), to harmonize the Protocol prior to CTR transition, and to address administrative inconsistencies.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Table 3: Schedule of Activities; Table 4: Schedule of Laboratory Assessments); Section 4.2, Overall Study Duration; Section 5.1, Inclusion Criteria; Section 6.1, Study Treatment Administered; Section 8.1.2, Screening Procedures; Section 8.4, Laboratory Assessments**

   Description of change: The screening period has been expanded from 28 to 56 days.

   Rationale for change: To add flexibility to perform all screening assessments.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities; Table 4: Schedule of Laboratory Assessments); Section 8.2, Efficacy Assessments**

   Description of change: Text was added to indicate that the Day 15 Hgb measurements after Cycle 8 are optional.

   Rationale for change: To avoid unnecessary blood samples.

3. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 8.5.1, Blood Sample Collection (Table 20: Pharmacokinetics Blood Sample Timing)**

   Description of change: Additional PK blood samples were added on Cycle 3 Day 1 and Cycle 6 Day 1.

   Rationale for change: To better characterize the absorption phase of the study drug and the trough concentrations at later cycles.

4. **Section 3, Objectives and Endpoints (Table 8: Objectives and Endpoints); Section 8.4, Laboratory Assessments; [redacted]; Section 10.4.4, Exploratory Analyses**

   Description of change: [redacted]

   Rationale for change: [redacted]

5. **Section 4.1.1, Part 1 – Starting Dose, Dose-Escalation, and De-Escalation Schema; Section 4.1.3, Part 2 – Expansion Stages of Treatment Groups A, B, and C; Section 6.1, Study Treatment Administrated (Table 11: Study Treatment Information)**

   Description of change: Text was added to indicate the starting dose of ruxolitinib for participants with platelet counts between 50 and 75 × 10^9/L in both the dose escalation and dose expansion parts must be guided by the country-specific label as applicable (for Canada, refer to the Canadian Product Monograph).

   Rationale for change: Clarification.

6. **Section 4.1.1, Part 1 – Starting Dose, Dose-Escalation, and De-Escalation Schema; Section 4.1.3, Part 2 – Expansion Stages of Treatment Groups A, B, and C; Section 6.6.6.4, Dose Increase of Ruxolitinib Based on Insufficient Response**

   Description of change: Clarified the duration of treatment with the starting dose of 10 mg BID in TGC.

   Rationale for change: Clarification.

7. **Section 4.2, Overall Study Duration**

   Description of change: Clarified the study duration for the participants.

   Rationale for change: Clarification.

8. **Section 4.2, Overall Study Duration; Section 4.3, Study Termination; Section 7.1.1. Reasons for Study Treatment Discontinuation – All Treatment Groups; Section 11.7, Study and Site Closure**

   Description of change: Added text to indicate that that the sponsor can close individual cohorts(s) based on emerging data.

   Rationale for change: Clarification.

9. **Section 5.2, Exclusion Criteria (Criterion 20); Section 5.3.1, Meals and Dietary Restrictions**

   Description of change: Text was added to indicate that the ruxolitinib country-specific label as applicable and for Canada, the Canadian Product Monograph, must be considered by the investigators with respect to any contraindication related to ruxolitinib.

   Rationale for change: Clarification.

10. **Section 5.2, Exclusion Criteria (Criterion 27)**

    Description of change: Added Exclusion Criterion 27 for participants with coexistent causes of anemia.

    Rationale for change: To exclude participants with coexisting causes of anemia.

11. **Section 5.2, Exclusion Criteria (Criterion 28)**

    Description of Change: Added Exclusion Criterion 28 to exclude vulnerable populations and adults under legal protection.

    Rationale for Change: French regulations.

12. **Section 5.5, Replacement of Participants**

    Description of change: Updated text to specify that participants who do not meet all the eligibility requirements of the study will be replaced.

    Rationale for change: Health Canada requirement.

13. **Section 6.1, Study Treatment Administered**

    Description of change: Added the possibility for the investigators to start ruxolitinib in TGA participants.

    Rationale for change: Requested by the investigators.

14. **Section 6.6.3, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 13: Guidelines for Interruption and Restarting of Study Drug)**

    Description of change: Removed requirement for medical monitor discussion and provided guidance for management of Grade 3 or higher AST/ALT elevation.

    Rationale for change: Clarification.

15. **Section 6.6.6.4, Dose Increase of Ruxolitinib Based on Insufficient Response**

    Description of change: Added flexibility to criteria for ruxolitinib intraparticipant dose increase.

    Rationale for change: To allow for better management of the participant's ruxolitinib dose.

16. **Section 6.7.1 Permitted Medications and Procedures**

    Description of change: Text added to refer to the ruxolitinib country-specific label as applicable and for Canada, to the Canadian Product Monograph for any concomitant treatment to be administered to the study participants.

    Rationale for change: Clarification.

17. **Section 7.1.1. Reasons for Study Treatment Discontinuation – All Treatment Groups**

    Description of change: Updated text to specify that any Canadian participant found not to have met all eligibility criteria must be permanently discontinued from study treatment.

    Rationale for change: Health authority request.

18. **Section 10.1.2, Part 2 – Expansion Stages of Treatment Groups A, B, and C**

    Description of change: Added statistical clarification for the expansion stage in TGA.

    Rationale for change: Clarification.

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

Amendment 7 (21 DEC 2022)

Overall Rationale for the Amendment:

The primary purpose of the amendment is 2-fold: to add a new treatment group (ie, TGC) composed of MF participants naive to JAK inhibitor treatment, and to explore more extensively the safety and efficacy of INCB000928 in the TGA, TGB, and TGC treatment groups.

1. **Section 1, Protocol Summary (Table 1: Primary and Key Secondary Objectives and Endpoints; Table 2: Key Study Design Elements; Figure 1: Study Design Schema; Table 3: Schedule of Activities; Table 4: Schedule of Laboratory Assessments); Section 2.1.2, Anemia in Patients With Myelofibrosis; Section 2.3.3, Scientific Rationale for Study Design; Section 2.3.4: Justification for Dose; Section 3, Objectives and Endpoints; Section 4.1.1, Part 1 – Starting Dose, Dose-Escalation, and De-Escalation Schema; Section 4.1.3, Part 2 – Expansion Stages of Treatment Groups A, B, and C; Section 5.1, Inclusion Criteria; Section 5.2, Exclusion Criteria (Table 10: Exclusionary Laboratory Values); Section 5.3.1, Meals and Dietary Restrictions; Section 6.1, Study Treatment Administered (Table 11: Study Treatment Information); Section 6.5.4, Definition of the Recommended Dose for Expansion; Section 6.6.6, Criteria and Procedures for Dose Interruptions or Adjustments of Ruxolitinib; Section 7.1.1.2, Reasons for Study Treatment Discontinuation – Treatment Groups B and C; Section 8.4.1, Pregnancy Testing; Section 8.5.1, Blood Sample Collection (Table 20: Pharmacokinetics Blood Sample Timing); Section 8.6.1, Blood Sample Collection (Table 21: Biomarker/Translational Sample Timing); Section 10.1.2, Part 2 – Expansion Stages of Treatment Groups A, B, and C (Table 22: Sample Size and Power Calculation for TGB and TGC); Section 10.3, Level of Significance; Section 10.4.2.1, Part 1 and Part 2: Efficacy Analyses; Section 10.4.2.2, Part 2 Only – Efficacy Analyses for Treatment Groups B and C – Dose Expansion**

   Description of change: Added TGC and clarified as to when dose expansion will be performed in 1 or more RDE(s) for each treatment group. Updated the sample size from 100 to ~206 participants and added the Phase 2 REALISE study.

   Rationale for change: To determine the safety and efficacy of INCB000928 with ruxolitinib in MF participants naive to treatment with any JAK inhibitor, and to further explore the safety and efficacy in the TGA and TGB treatment groups by expanding 1 or more RDE dose(s).

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities; Table 4: Schedule of Laboratory Assessments); Section 8.5.1, Blood Sample Collection; Section 8.6.1, Blood Sample Collection (Table 21: Biomarker/Translational Sample Timing)**

   Description of change: The Day −1 assessments may be performed within 7 days prior to Cycle 1 Day 1.

   Rationale for change: Flexibility, as requested by key investigators.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.2, Efficacy Assessments**

   Description of change: Added that the record of all Hgb values and transfusions are mandatory within 8 weeks prior to Cycle 1 Day 1 as well as the schedule for disease response assessment.

   Rationale for change: Clarification to insist upon recording all Hgb and transfusions within 8 weeks prior to Cycle 1 Day 1.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.3.5, Cardiac Function Assessments (Table 18: Schedule of Cardiac Function Assessments)**

   Description of change: Added triplicate ECGs on Screening and on Cycle 1 Days 1 and 15 in TGA participants, as well as 12-lead ECGs on Cycle 2, predose, and on Cycles 3 and 6 postdose in all participants.

   Rationale for change: To evaluate more completely the effects of the study drug on the cardiac parameters using triplicate ECG recordings in TGA participants and additional 12-lead ECGs in all participants.

5. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 8.5.1, Blood Sample Collection (Table 20: Pharmacokinetics Blood Sample Timing); Section 8.6.1, Blood Sample Collection (Table 21: Biomarker/Translational Sample Timing)**

   Description of change: Additional blood sample collection for PK and PD purposes were added on Cycle 3 Day 1 and Cycle 6 Day 1 between 4 and 8 hours postdose. Updated text to state that plasma PD samples were to be collected until Cycle 24 Day 1.

   Rationale for change: Better assess the PK and PD profile of the study drug and the length of time plasma PD samples are to be collected during the study is clarified.

6. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 8.6.1 (Table 21: Biomarker/Translational Sample Timing); Section 8.6.2.1, Pharmacodynamic and Translational Research Parameters**

   Description of change: Added information on genomic testing and specified the blood volume for whole blood correlative DNA/RNA samples.

   Rationale for change: Clarification.

7. **Section 4.1.1, Starting Dose, Dose-Escalation, and De-Escalation Schema; Section 4.1.3, Part 2 – Expansion Stages of Treatment Groups A, B, and C**

   Description of change: Added a statement to clarify that at least 1 Japanese participant will be enrolled at the RDE in both TGA and TGB.

   Rationale for change: Clarifications as requested by PMDA.

8. **Section 4.1.3, Part 2 – Expansion Stages of Treatment Groups A, B, and C**

   Description of change: Added the percentage of transfusion-dependent participants to be enrolled in TGB and TGC.

   Rationale for change: Clarifications of the percentage of transfusion-dependent participants to be enrolled in TGB and TGC to obtain relevant results.

9. **Section 5.1, Inclusion Criteria; Section 5.2, Exclusion Criteria**

   Description of change: The eligibility criteria regarding definition of anemia (Inclusion Criterion 7) and definition of hepatitis A, B, or C (Exclusion Criterion 14) have been clarified and flexibility has been added to allow hydroxyurea and iron chelators in the study (Exclusion Criteria 3a and 26). Exclusion Criterion 8 was also updated with regard to active invasive malignancy from 5 years to 2 years. The statement in Inclusion Criterion 1 stating that Japanese participants have to be 20 years or older to be enrolled in the study has been removed. The Inclusion Criterion 1 has been update to align with the Japanese new law regarding adulthood age. The definition of TGC participants has been added (Inclusion Criteria 15 and 16).

   Rationale for change: Inclusion of TGC. Clarification of several eligibility criteria and flexibility for the investigators for enrolment of participants in the study have been added. The Inclusion criterion 1 has been updated to align with the Japanese new law regarding adulthood definition.

10. **Section 5.2, Exclusion Criteria (Table 10: Exclusion Laboratory Values); Section 8.3.6, Iron Overload Assessment**

    Description of change: Added clarification that the use of CT scan instead of MRIs to measure a potential iron overload in the liver is allowed at sites where MRI is unavailable.

    Rationale for change: Request from some investigators.

11. **Section 6.5.1, Definition of a Dose-Limiting Toxicity**

    Description of change: Added the possibility to draw supplemental blood samples.

    Rationale for change: Clarification that additional blood samples may be drawn to better define a DLT or a potential DLT event.

12. **Section 6.6.3, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 13: Guidelines for Interruption and Restarting of Study Drug)**

    Description of change: The guidelines for interruption and restarting of the study drug in the event of increased ferritin during the study have been clarified.

    Rationale for change: Clarification.

13. **Section 6.6.5, Criteria and Procedures for Dose Increases of Study Drug**

    Description of change: Clarification of the conditions for intraparticipant dose escalation has been added.

    Rationale for change: Clarification.

14. **Section 6.7, Concomitant Medications and Procedures**

    Description of change: The record of anti-COVID 19 vaccine administration, as related to participants prior to and during the study period is added.

    Rationale for change: Clarification.

15. **Section 6.7.3, Prohibited Medications and Procedures**

    Description of change: Removed hydroxyurea as a prohibited medication.

    Rationale for change: Hydroxyurea as a prohibited medication is removed as requested by key investigators.

16. **Section 8.6.1, Blood Sample Collection**

    Description of change: Added information on the management of biological samples.

    Rationale for change: Clarification.

17. **Section 10.4.2.3, Part 1 and Part 2: Pharmacokinetic and Pharmacodynamic Analyses**

    Description of change: Added information regarding the PK and PD results and how they will be reported.

    Rationale for change: Clarification.

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

Amendment 6 (22 DEC 2021)

Overall Rationale for the Amendment:

The rationale for this amendment is to implement changes to clarify the dose escalation scheme. Additional changes are summarized below.

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

   Description of change: Clarified the definition of the TGA population.

   Rationale for change: To clarify TGA definition to align with Section 5.1; Inclusion Criteria.

2. **Section 2.3.4, Justification for Dose; Section 4.1.1.1, Starting Dose, Dose-Escalation and De-Escalation Schema**

   Description of change: Updated results for the Phase 1 Study INCB 00928-102.

   Rationale for change: To align with latest clinical data.

3. **Section 4.1.2, Exploration of Alternative Administration Schedules; Section 6.1, Study Treatment Administered; Section 8.5.1, Blood Sample Collection**

   Description of change: Added to explore the possibility of alternative administration schedules and/or to expand cohorts.

   Rationale for change: Alternative administration schedules may be explored in order to obtain supplemental PK, pharmacodynamic, and safety data, and cohorts can be expanded as necessary.

4. **Section 8.4, Laboratory Assessments (Table 20: Required Laboratory Analytes)**

   Description of change: Footnote added to state that MMA is not applicable in Japan.

   Rationale for change: Clarification.

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

Amendment 5 (02 SEP 2021)

Overall Rationale for the Amendment:

The rationale for this amendment is to implement changes to clarify the dose escalation scheme and measurement of the potential iron overload.

1. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.2, Efficacy Assessments; Section 8.3.6, Iron Overload Assessment**

   Description of change: Added flexibility to perform the bone marrow sample and MRI assessment within 3 months prior to screening.

   Rationale for change: To add flexibility for the sites to draw some screening samples.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 5.2, Exclusion Criteria (Table 12: Exclusionary Laboratory Values); Section 6.6.3, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 15: Guidelines for Interruption and Restarting of Study Drug); Section 8.3.6, Iron Overload Assessment**

   Description of change: Added liver MRI assessments for participants with a screening ferritin value of < 1000 ng/mL or ≥ 1000 ng/mL to identify a potential iron overload. Table 12 and Table 15 were updated to specify the rules for participant eligibility, and the rules for study drug interruption/restarting based on participant's serum ferritin levels.

   Rationale for change: To assess a potential iron overload and to clarify the rules for study drug interruption/restarting and for participant eligibility.

3. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 4.1.1.1, Starting Dose, Dose-Escalation and De-Escalation Schema**

   Description of change: Updated to specify that TGB can start after a monotherapy dose has been evaluated in at least 3 participants (instead of 6).

   Rationale for change: To update of the conditions to be able to start TGB.

4. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 2.3.3, Scientific Rationale for Study Design; Section 2.3.4, Justification for Dose; Section 4.1.1.1, Starting Dose, Dose-Escalation and De-Escalation Schema; Section 6.1, Study Treatment Administered (Table 13: Study Treatment Information)**

   Description of change: Updated the dose escalation in TGB to start at 100 mg QD (50% of the safe and tolerated tested dose in Study INCB 00928-102) and will not exceed the monotherapy MTD if identified in this current study. Added safety results from Study INCB 00928-102 to Section 4.1.1.1.

   Rationale for change: To update of the starting dose for TGB based on safety data collected in the INCB 00928-102 healthy volunteer study.

5. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 8.6.1, Blood Sample Collection (Table 23: Biomarker/Translational Sample Timing)**

   Description of change: Added a footnote to Table 4 and Table 23 that whole blood correlative DNA and RNA may not be collected in geographic regions with certain restrictions.

   Rationale for change: To comply with local specific restrictions.

6. **Section 2.3.4, Justification for Dose (Table 6: Summary of INCB00928 Pharmacokinetic Parameters for First Dose of 50 mg and 100 mg QC in Study INCB 00928-102; Table 7: Summary of INCB00928 Steady-State Pharmacokinetic Parameters on Day 10 in Study INCB 00928-102)**

   Description of change: Updated the preliminary safety and PK results from the INCB 00928-102 study.

   Rationale for change: Clarification.

7. **Section 2.3.4, Justification for Dose; Section 2.4.1, Potential Risks of INCB000928 Based on Preclinical Toxicology; Section 2.5, Exposure Margins (Table 8: C_{max} and AUC_{0-t} Values [for Total] INCB000928 Associated With Doses That Do Not Cause Adverse Effects in 3-Month Studies in Rats and Dogs; Table 9: Exposure Margins for 50 and 100 mg QC Relative to Doses That Do Not Cause Adverse Effects in 3-Month Studies in Rats and Dogs); Section 4.1.1.1, Starting Dose, Dose-Escalation and De-Escalation Schema**

   Description of change: Updated with results from the 3-month toxicology study and Study INCB 00928-102.

   Rationale for change: Clarification.

8. **Section 6.5.1, Definition of a Dose-Limiting Toxicity (Table 14: Definition of a Dose-Limiting Toxicity)**

   Description of change: Updated to specify that a thrombocytopenia requiring a platelet transfusion will be considered a DLT.

   Rationale for change: To update the definition of DLT in the event of thrombocytopenia requiring a platelet transfusion, and to address a request from the PMDA (Japan).

9. **Section 6.6.5, Criteria and Procedures for Dose Increases of Study Drug**

   Description of change: Change made that the participant has received only 2 cycles of study drug treatment, instead of 6 cycles, to allow a study drug increase. Added that a study drug increase can occur if the participant is still receiving RBC transfusions or there is an Hgb increase of less than 1.5 g/dL in any of their assessments.

   Rationale for change: To clarify the rules allowing an intraparticipant dose escalation.

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

Amendment 4 (10 MAY 2021)

Overall Rationale for the Amendment:

The overall rationale for this amendment is to implement changes and clarifications to the Protocol.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 4.1.1.1, Starting Dose, Dose-Escalation and De-Escalation Schema**

   Description of change: Change made to clarify that at least 6 participants included in the different TGA dose levels need to be evaluated before starting TGB.

   Rationale for change: Clarification.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 4.2, Overall Study Duration; Section 8.9.2, Post-Treatment Follow-Up**

   Description of change: Text added to indicate that for each participant, study data will be collected for up to 1 year after study treatment discontinuation.

   Rationale for change: Clarification.

3. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 3, Objectives and Endpoints (Table 10: Objectives and Endpoints); Section 8.6.1, Blood Sample Collection (Table 23: Biomarker/Translational Sample Timing); Section 8.6.2, Pharmacodynamic and Translational Research Parameters; Section 8.6.2.1, Pharmacodynamic and Translational Research Parameters; Section 10.2, Populations for Analyses (Table 24: Populations for Analyses); Section 10.4.4, Exploratory Analyses**

   Description of change: [redacted].

   Rationale for change: [redacted].

4. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 6.6.3, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 15: Guidelines for Interruption and Restarting of Study Drug); Section 8.4, Laboratory Assessments (Table 21: Required Laboratory Analytes)**

   Description of change: Serum chemistry changed to blood chemistry.

   Rationale for change: Clarification.

5. **Section 1, Protocol Summary; Section 8, Study Assessments and Procedures; Section 8.1.4, Distribution of Forms; Section 8.5.2, Urine Sample Collection; Section 9.3, Recording and Follow-Up of Adverse Events and/or Serious Adverse Events; Section 9.4, Reporting of Serious Adverse Events**

   Description of change: References to the Study Reference Manual and Study Procedures Manual have been replaced by the Investigator Site File.

   Rationale for change: Clarification.

6. **Section 2.3.4, Justification for Dose**

   Description of change: Section updated with preliminary results from INCB 00928-101 and INCB 00928-102 studies.

   Rationale for change: To align with latest data.

7. **Section 2.4.2, Potential Risks of Ruxolitinib Based on Clinical Safety Results; Section 4.1.3, Integration of Japan and Japanese Safety Run-In Cohort; Section 4.3, Study Termination; Section 5.1, Inclusion Criteria (Criterion 2); Section 5.2, Exclusion Criteria (Criterion 21); Section 5.3.2, Hospitalization (Only Applicable for Participants in Japan); Section 6.1, Study Treatment Administered (Table 13: Study Treatment Information); Section 6.2, Preparation, Handling, and Accountability; Section 9.2, Definition of Serious Adverse Event; Section 9.4, Reporting of Serious Adverse Events; Section 9.8, Product Complaints; Section 11.1, Investigator Responsibilities; Section 11.6, Study and Site Closure; Appendix A, Information Regarding Effectiveness of Contraceptive Methods and Definitions**

   Description of change: Sections added/updated to include Japanese sites.

   Rationale for change: Study will include sites in Japan.

8. **Section 5.1, Inclusion Criteria (Criterion 11)**

   Description of change: Revised to indicate that participants who are resistant, refractory, or lost response to a JAK inhibitor (after at least 12 weeks of JAK inhibitor treatment), or intolerant or not eligible to receive a JAK inhibitor treatment are eligible to enter the study.

   Rationale for change: Per investigator feedback.

9. **Section 5.1, Inclusion Criteria (Criterion 6); Section 5.2, Exclusion Criteria (Criterion 14); Section 9.1, Definition of Adverse Event; Section 9.2, Definition of Serious Adverse Event; Section 9.3, Recording and Follow-Up of Adverse Events and/or Serious Adverse Events; Section 9.4, Reporting of Serious Adverse Events; Appendix A, Information Regarding Effectiveness of Contraceptive Methods and Definitions; Section 11.2, Data Management**

   Description of change: Sections have been updated to reflect the current template.

   Rationale for change: Template updated.

10. **Section 5.2, Exclusion Criteria (Table 12: Exclusionary Laboratory Values)**

    Description of change: Details added regarding the eligibility thresholds for bilirubin and direct bilirubin values.

    Rationale for change: Clarification.

11. **Section 5.2, Exclusion Criteria (Table 12: Exclusionary Laboratory Values); Section 6.5.1, Definition of a Dose-Limiting Toxicity (Table 14: Definition of Dose-Limiting Toxicity); Section 6.6.3, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 15: Guidelines for Interruption and Restarting of Study Drug)**

    Description of change: The exclusionary laboratory values for platelet count at baseline for TGA and TGB, the definition of DLT, and the guidelines for study treatment interruption have been updated.

    Rationale for change: Per investigator feedback.

12. **Section 6.1, Study Treatment Administered (Table 13: Study Treatment Information)**

    Description of change: A starting dose of 10 mg BID and 5 mg BID was added as a possible starting dose for ruxolitinib for TGB in the dose-escalation and expansion stages, respectively.

    Rationale for change: Per investigator feedback.

13. **Section 6.6.3, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 15: Guidelines for Interruption and Restarting of Study Drug)**

    Description of change: Incorporation of guidance for study treatment interruption if a participant enters the study with a high serum ferritin level.

    Rationale for change: Clarification.

14. **Section 6.7.2, Restricted Medications and Procedures**

    Description of change: Restrictions regarding COVID-19 vaccination during the first study treatment cycle have been added.

    Rationale for change: Clarification.

15. **Section 8.1.1, Informed Consent Process**

    Description of change: The sentence regarding the optional exploratory research has been removed.

    Rationale for change: No longer applicable.

16. **Section 8.4, Laboratory Assessments (Table 21: Required Laboratory Analytes)**

    Description of change: Revised to indicate both bilirubin and direct bilirubin are part of the blood chemistries panel.

    Rationale for change: Clarification of laboratory assessments.

17. **Section 8.4, Laboratory Assessments (Table 21: Required Laboratory Analytes);** [redacted]

    Section 10.4.2.3, Part 1 and Part 2: Pharmacokinetic and Pharmacodynamic Analyses

    Description of change: Added reticulocyte hemoglobin content (as part of the hematological panel) and clarified that this analyte assessment is not required at sites where this parameter cannot be measured by the local laboratory. [redacted]

    Rationale for change: Clarification of laboratory assessments.

18. **Appendix D, Myelofibrosis Neoplasms Symptom Assessment Form**

    Description of change: Changed the worst possible option for fever from "worst imaginable" to "daily."

    Rationale for change: To align with NCCN guidelines.

19. **Appendix G, COVID-19 Pandemic Mitigation Strategies and Instructions**

    Description of change: Guidance to manage study participants during the COVID-19 pandemic has been added.

    Rationale for change: To align with regulatory guidance regarding clinical trial execution during the pandemic.

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

Amendment 3 (27 AUG 2020)

Overall Rationale for the Amendment:

The overall rationale for this amendment is to implement changes for the submission of the Protocol in Europe and to provide updates for clarification.

1. **Cover Page and List of Abbreviations; Section 2.4.2, Potential Risks of Ruxolitinib Based on Clinical Safety Results; Section 4.3, Study Termination; Section 6.1, Study Treatment Administrated (Table 11, Study Treatment Information); Section 7.1.1, Reasons for Study Treatment Discontinuation – All Treatment Groups; Section 8.1.1, Informed Consent Process; Section 9.4, Reporting of Serious Adverse Events; Section 11.1, Investigator Responsibilities; Section 11.2, Data Management; Section 11.6, Study and Site Closure; Section 12, References**

   Description of change: Incorporation of the EudraCT Number on the cover page, mention/incorporation of the IEC together with the IRB in the other relevant sections, and mention/incorporation of Jakavi for Europe in addition to Jakafi for the US.

   Rationale for change: The EudraCT Number and associated relevant pieces of information are added for the protocol submission in Europe.

2. **Section 1, Protocol Summary (Table 1, Primary and Key Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints (Table 8, Objectives and Endpoints); Section 10.4.2.3, Part 1 and Part 2: Pharmacokinetic and Pharmacodynamic Analyses**

   Description of change: Replaced AUC with C_{max} for clarification that the PK parameters analyzed will be C_{max}, t_{max}, and AUC_{0-t} instead of AUC, t_{max}, and AUC_{0-t}.

   Rationale for change: Correction of a typo.

3. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 3, Objectives and Endpoints (Table 8: Objectives and Endpoints); Section 8.6.1, Blood Sample Collection (Table 21: Biomarker/Translational Sample Timing); [redacted] Section 10.4.5, Exploratory Analyses**

   Description of change: [redacted]

   Rationale for change: [redacted].

4. **Section 5.1, Inclusion Criteria**

   Description of change: Included that women of childbearing potential must not donate oocytes during the period from screening through the safety follow-up visit, clarification of the definition of transfusion-dependency, addition of inclusion of participants with BM and peripheral blood myeloblast count < 10%.

   Rationale for change: Clarifications.

5. **Section 5.2, Exclusion Criteria (Table 10: Exclusionary Laboratory Values)**

   Description of change: Updated the threshold value for platelets to be defined as at least 75×10^9/L.

   Rationale for change: Given characteristics of underlying disease and the absence of expected myelo-suppressive effect of the drug.

6. **Section 6.6.3, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 13: Guidelines for Interruption and Restarting of Study Drug)**

   Description of change: Clarification to include ≥ for any Grade ≥ 3 toxicity, if clinically significant and not manageable by supportive care (including Grade 3 QTc prolongation [QTcF > 500 ms] without life-threatening arrhythmias) lead to treatment interruption.

   Rationale for change: To align with the definition of dose-limiting toxicity (Section 6.5.1, Table 12).

7. **Section 8.2, Efficacy Assessments**

   Description of change: Removal of the condition "while maintaining an Hgb level of ≥ 8.5 g/dL" in the definition of response in transfusion-dependent participants at baseline.

   Rationale for change: Clarification of the endpoint/harmonization to align with other sections.

8. **Section 8.4, Laboratory Assessments (Table 19: Required Laboratory Analytes)**

   Description of change: Clarification that "Hepatitis B surface antibody" is measured and not of "Hepatitis B surface ~~antigen~~ antibody."

   Rationale for change: Correction of a typo (laboratory assessments).

9. **Section 8.4, Laboratory Assessments (Table 19: Required Laboratory Analytes); Section 8.6.2.1, Pharmacodynamic and Translational Research Parameters; Section 10.4.2.3, Part 1 and Part 2: Pharmacokinetic and Pharmacodynamic Analyses**

   Description of change: Clarified that NTBI assessment is not required at sites where this parameter cannot be measured by the local laboratory.

   Rationale for change: Clarification of local laboratory assessments.

10. **Section 8.6.2.1, Pharmacodynamic and Translational Research Parameters**

    Description of change: Clarification that the measurements performed are to evaluate any correlation between mutational landscape, gene expression profiling and anemia response to INCB000928 as a single agent or when combined with ruxolitinib.

    Rationale for change: Clarification of response to INCB000928 as a single agent.

11. **Section 9.1, Definition of Adverse Event**

    Description of change: Update AE definitions for clarity and alignment with current template.

    Rationale for change: Incorporation of the new AE definition wording.

12. **Section 9.3, Recording and Follow-Up of Adverse Events and/or Serious Adverse Events; Section 9.4, Reporting of Serious Adverse Events; Section 9.6, Pregnancy**

    Description of change: Reporting of SAEs instructions were updated to specify procedures for reporting via the EDC system.

    Rationale for change: Section clarified to specify that SAEs will be recorded and reported by the sites/investigators through the EDC system.

13. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

    Description of change: Removal of the section defining acceptable birth control methods that result in a failure rate of more than 1%.

    Rationale for change: To remove an inconsistency regarding birth control methods in Appendix A.

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

Amendment 2 (15 APR 2020)

Overall Rationale for the Amendment:

The overall rationale for this amendment is to correct inconsistencies, to clarify sections related to pregnancy prevention and tests and to the participant's symptom burden assessment, and to remove the statements related to meals.

1. **Section 1, Protocol Summary (Table 3: Schedule of Activities; Table 4: Schedule of Laboratory Assessments)**

   Description of change: Reformatted tables to clearly indicate the blood sampling on Day 15 of each cycle from Cycle 3 onward and to indicate that the post-treatment follow-up visits occur every 6 months.

   Rationale for change: Clarification.

2. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 8.6.1, Blood Sample Collection (Table 21: Biomarker/Translational Sample Timing)**

   Description of change: The Day −1 blood sample for plasma PD assessment was removed.

   Rationale for change: This blood sample is no longer required.

3. **Section 3, Objectives and Endpoints (Table 8: Objectives and Endpoints); Section 8.1.4, Distribution of Forms; Section 8.2.1, Patient-Reported Outcomes; Section 10.4.2.2, Part 2 Only: Efficacy Analyses for Treatment Group B – Dose Expansion; Section 10.4.3, Exploratory Analyses; Appendix D: Myelofibrosis Neoplasms Symptom Assessment Form**

   Description of change: The Myeloproliferative Symptom Assessment Form v4.0 was replaced by the MPN-SAF, and the PRO endpoint was clarified and changed to exploratory.

   Rationale for change: The MPN-SAF allows a more relevant data collection.

4. **Section 5.1, Inclusion Criteria; Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: Inclusion criterion 6a was changed to indicate men must agree to take appropriate precautions to avoid fathering children from screening through 90 days after the last study treatment dose (and not through the safety follow-up visit). Inclusion criterion 6b and Appendix A were clarified for female participants regarding the safety follow-up visit.

   Rationale for change: Clarification and harmonization with Appendix A.

5. **Section 8.4, Laboratory Assessments (Table 19: Required Laboratory Analytes)**

   Description of change: Clarification that a serum pregnancy test should also be performed at the safety follow-up visit.

   Rationale for change: Clarification and harmonization with Table 3 and Section 8.4.1.

6. **Section 8.5.1, Blood Sample Collection; Appendix E: Instruction to Participants for Handling Study Drug INCB000928**

   Description of change: Wording regarding meals was removed.

   Rationale for change: Clarification and harmonization with Section 2.3.4 and Section 6.1; coadministration of INCB000928 with a high-fat meal does not significantly impact its PK, so INCB000928 can be administrated without regard to food.

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

Amendment 1 (25 MAR 2020)

Overall Rationale for the Amendment:

The overall rationale for this amendment is to implement changes based on FDA comments and requests.

1. **Study Title; Section 1, Protocol Summary; Section 2, Introduction; Section 3, Objectives and Endpoints; Section 4.1, Overall Design; Section 4.1.1.2, Expansion Stage for Treatment Group A; Section 5.1, Inclusion Criteria; Section 5.2, Exclusion Criteria; Section 6, Study Treatment; Section 7.1.1.1., Reasons for Study Drug INCB000928 Discontinuation – All Treatment Groups; Section 8, Study Assessments and Procedures; Section 10, Statistics; Appendix B, WHO 2016 Classification of Myelodysplastic Syndromes; Appendix C, Revised International Prognostic Scoring System for Myelodysplastic Syndromes; Appendix D, MAYO Prognostic Model for WHO-Defined Chronic Myelomonocytic Leukemia; Appendix E, Prognostic Scoring System for Unclassifiable Myelodysplastic Syndrome and Myelodysplastic Syndrome/Myeloproliferative Neoplasm Syndrome**

   Description of change: Removal of all text related to myelodysplastic syndrome.

   Rationale for change: The patient population to be enrolled in the study was limited to participants with myeloproliferative disorders.

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

   Description of change: Physical examination and assessment of ECOG performance status were changed to a weekly basis during Cycle 1.

   Rationale for change: The frequency was increased to weekly for Cycle 1 to enhance safety.

3. **Section 1, Protocol Summary; Section 3, Objectives and Endpoints; Section 4, Study Design; Section 5, Study Population; Section 6, Study Treatment; Section 7.1.1.1, Reasons for Study Drug INCB000928 Discontinuation – All Treatment Groups; Section 8, Study Assessments and Procedures; Section 10, Statistics**

   Description of change: Update of participant population definitions:

   TGA becomes: participants with transfusion-dependent or symptomatic anemia due to PMF, post-PV, or post-ET MF who were previously treated with JAK inhibitors (intolerant, resistant, refractory, or lost response to a JAK inhibitor) for at least 12 weeks.

   TGB becomes: participants with transfusion-dependent or symptomatic anemia due to PMF, post-PV, or post-ET MF who have been on a stable dose of ruxolitinib for at least 12 weeks.

   Removal of TGC participant population.

   In addition, the exclusion criteria have been updated to exclude participants who are candidates for stem cell transplantation.

   Rationale for change: The patient population to be enrolled in the study was limited to participants with myeloproliferative disorders, and the TGC cohort was removed from the study.

4. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 3, Objectives and Endpoints (Table 8: Objectives and Endpoints);** [redacted]

   Description of change: [redacted]

   Rationale for change: Clarification.

5. **Section 1, Protocol Summary (Table 1: Primary and Key Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints; Section 4, Study Design; Section 10, Statistics**

   Description of change: Redefinition of endpoints and objectives for both treatment groups:

   Primary objective: Safety and tolerability.

   Secondary objectives: Efficacy (only anemia-related endpoints for TGA), pharmacokinetics, and pharmacodynamics.

   [redacted]

   Rationale for change: Clarification of the study objectives and endpoints and adaptation to the new defined participant populations.

6. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 4, Study Design; Section 6.1, Study Treatment Administered (Table 11: Study Treatment Information); Section 10, Statistics**

   Description of change: Clarification of the study design and dose-escalation algorithm.

   No dose expansion for TGA: removal of all sections related to the expansion stage for TGA.

   Once an appropriate monotherapy dose has been identified and evaluated in at least 6 participants, combination therapy with ruxolitinib will start. The TGB dose escalation will start 2 dose levels below the maximum evaluated dose determined to be safe and tolerable in TGA.

   Rationale for change: This change allows for a safer starting dose for TGB.

7. **Section 1, Protocol Summary (Figure 1: Study Design Schema); Section 4.1.1.1, Starting Dose, Dose-Escalation, and De-Escalation Schema; Section 6.1, Study Treatment Administered (Table 11: Study Treatment Information)**

   Description of change: The starting dose for the dose-escalation stage of TGB was changed to 2 dose levels below the safe and tolerable dose from TGA.

   Rationale for change: This change allows for a safer starting dose for TGB.

8. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 4.1.2, Part 2 – Expansion Stage of Treatment Group; Section 10.1.2, Part 2 – Expansion Stages of Treatment Group B Only**

   Description of change: Addition of the rationale for safety being the primary endpoint, as TGB in Part 2 will provide a ≥ 90% chance of identifying a toxicity with a true event rate of 9%.

   Rationale for change: Clarification.

9. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 8.3.6, Iron Overload Assessment**

   Description of change: Iron homeostasis assessments and actions were added.

   Rationale for change: Additional assessments were added to monitor for potential iron overload to enhance safety.

10. **Section 2.3.4, Justification for Dose; Section 6.1, Study Treatment Administered (Table 11: Study Treatment Information)**

    Description of change: Update of the results from the healthy volunteer study (INCB 00928-101 study) with INCB000928 and addition of statement that, providing that an absence of food-effect has been demonstrated in the INCB 00928-101 study, INCB000928 can be administered without regard to food.

    Rationale for change: Incorporation of the recent results from the healthy volunteer study (INCB 00928-101 study) with INCB000928.

11. **Section 4.1, Overall Design; Section 10, Statistics**

    Description of change: Redefinition of Part 1 and Part 2:

    Part 1: Dose-escalation stages for TGA and TGB.

    Part 2: Expansion stage for TGB only.

    Rationale for change: Simplification of the study design and adaptation to the new defined participant populations.

12. **Section 4.1.1.1, Starting Dose, Dose-Escalation and De-Escalation Schema (Table 9: Decision Boundaries); Section 6.5.3, Definition of the Maximum Tolerated Dose**

    Description of change: Updated the criteria for escalation or de-escalation based on the number of participants with DLTs and specified that if the unacceptable toxicity criteria is met, the dose level and higher dose levels will be eliminated. The target DLT rate was reduced from 33% to 28%.

    Rationale for change: Incorporates FDA comments and provides a more conservative dose-escalation strategy.

13. **Section 5.1, Inclusion Criteria**

    Description of change: Removal of inclusion criteria related to the BM myeloblast count before study and not requiring cytoreductive therapy or a therapeutic intervention.

    Addition of eligibility criteria to define the new participant populations: Inclusion criteria were modified to specify that eligible participants have to present with symptomatic anemia or be transfusion-dependent, and the definition of transfusion dependency was clarified by removing the note at the end of the criterion. An inclusion criterion was added to clarify that participants must be ineligible to receive or not have responded to available therapies for anemia such as ESAs.

    Addition of eligibility criterion to define TGA.

    Rationale for change: Definition of the new participant populations and the inclusion criteria were modified to only include a patient population in need of treatment.

14. **Section 5.2, Exclusion Criteria**

    Description of change: An exclusion criterion has been clarified to indicate that any participants undergoing treatment with ESAs, G-CSF or GM-CSF, romiplostin, or eltrombopag at any time within 4 weeks before the first dose of study treatment are excluded from the study.

    Rationale for change: This exclusion criterion was clarified for consistency across the patient populations to be enrolled in TGA and TGB.

15. **Section 5.2, Exclusion Criteria (Table 10: Exclusionary Laboratory Values)**

    Description of change: Addition of the iron metabolism criterion of a serum ferritin level > 1000 ng/mL and documented clinically significant iron overload on liver MRI or biopsy.

    Rationale for change: The criteria were modified to exclude participants with a potential higher risk for iron overload.

16. **Section 6.5.1, Definition of a Dose-Limiting Toxicity (Table 12: Definition of Dose-Limiting Toxicity)**

    Description of change: For the definition of chemistry DLTs, the number of days for AST and/or ALT elevation was reduced from > 7 to > 3 days. For hematologic toxicity, the initial 2 DLT criteria for Grade 4 neutropenia were replaced with Grade 4 neutropenia for > 7 days. For iron studies, the definition that no laboratory finding related to iron will be a DLT unless accompanied with clinical symptoms or impacting an organ function was replaced with iron abnormalities that are symptomatic or affect an organ function will be defined as DLTs.

    Rationale for change: To clarify the DLT criteria and enhance safety.

17. **Section 6.5.2.1, Assessment of Safety and PK Results; Section 6.5.2.2, Intercohort Dose Increase Algorithm; Section 6.5.3, Definition of the Maximum Tolerated Dose**

    Description of change: Wording indicating that the sponsor can explore alternative dosing schedules was removed.

    Rationale for change: Changes to the dosing schedules will require a protocol amendment.

18. **Section 6.6.3, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 13: Guidelines for Interruption and Restarting of Study Drug)**

    Description of change: Guidelines were added for ferritin > 1000 ng/mL.

    Rationale for change: Additional guidelines were added to monitor for potential iron overload to enhance safety.

19. **Section 6.7.2, Restricted Medications and Procedures; Section 6.7.3, Prohibited Medications and Procedures**

    Description of change: Clarification was added to indicate that G-CSF or GM-CSF, romiplostin, and eltrombopag are restricted medications for all participants and that ESAs are prohibited medications for all participants. The statement indicating that hematopoietic growth factor receptor agonists are prohibited was removed.

    Rationale for change: The restricted medications were clarified for consistency across the patient populations to be enrolled in TGA and TGB.

20. **Section 7.1.1.1, Reasons for Study Drug INCB000928 Discontinuation – All Treatment Groups**

    Description of change: The persistence of a transfusion requirement was added to the definition of treatment failure, and treatment-emergent iron overload with symptoms or damage in an organ function was added as a criterion for discontinuation of INCB000928.

    Rationale for change: Additional guidelines were added to monitor for potential iron overload to enhance safety.

21. **Section 8.4, Laboratory Assessments (Table 19: Required Laboratory Analytes)**

    Description of change: Clarification that HCV antibody assessment must be performed for all participants.

    Rationale for change: Clarification.

22. **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 Task	[redacted] Approver [redacted] Biostatistics 20-Feb-2025 16:51:01 GMT+0000
Approval Task	[redacted] r [redacted] Senior Clinical Trial Head 20-Feb-2025 16:55:08 GMT+0000
Approval Task	[redacted] [redacted]of Early Development 21-Feb-2025 07:43:14 GMT+0000

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