Official Title: A Phase 1/2, Open-Label, Multicenter Study of INCB000928 Administered as a Monotherapy in Participants With Anemia Due to Myelodysplastic Syndromes or Multiple Myeloma

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Clinical Study Protocol

INCB 00928-105

A Phase 1/2, Open-Label, Multicenter Study of INCB000928 Administered as a Monotherapy in Participants With Anemia Due to Myelodysplastic Syndromes or Multiple Myeloma

Product:	**INCB000928**
IND Number:	**147,495**
EudraCT Number:	**2020-002771-35**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol:	**10 JUN 2020**
Protocol Amendment 1:	**17 NOV 2020**
Protocol Amendment 2:	**08 APR 2021**
Protocol Amendment 3:	**22 DEC 2021**
Protocol Amendment 4:	**20 DEC 2022**
Protocol Amendment 5:	**06 DEC 2023**

INVESTIGATOR'S AGREEMENT

I have read the INCB 00928-105 Protocol (Amendment 5 dated 06 DEC 2023) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

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(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
ALK	activin receptor-like kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANSM	National Security Agency of Medicines and Health Products
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
AUC	area under the plasma/urine concentration curve
$AUC_{0\text{-}24h}$	area under the plasma concentration-time curve from time 0 to time 24 hours
$AUC_{0\text{-}t}$	area under the plasma concentration-time curve from time 0 to the last quantifiable measurable plasma concentration
AUC_{∞}	area under the concentration-time curve extrapolated to time of infinity
BAP	bone alkaline phosphatase
BCRP	breast cancer resistance protein
BID	twice daily
BM	bone marrow
BMP	bone morphogenetic protein
BOIN	Bayesian optimal interval
C1D1	Cycle 1 Day 1
CFR	Code of Federal Regulations
CI	confidence interval
CL/F_{obs}	observed oral dose clearance
C_{max}	maximum concentration
C_{min}	minimum concentration
CMML	chronic myelomonocytic leukemia
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRP	C-reactive protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome

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
ERFE	erythroferrone
ESA	erythropoietin-stimulating agent
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practices
GDPR	General Data Protection Regulation
GI	gastrointestinal
HAMP	hepcidin antimicrobial peptide
HbA_{1c}	glycated hemoglobin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
Hct	hematocrit
HCV	hepatitis C virus
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
IEC	independent ethics committee
IL-6	interleukin-6
IRB	institutional review board
IRT	interactive response technology

Abbreviations and Special Terms	Definition
JTc	corrected JT interval
LFS	leukemia-free survival
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR1	multidrug resistant gene 1
MDS	myelodysplastic syndromes
MDS-RS	myelodysplastic syndrome with ring sideroblasts
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MMA	methylmalonic acid
MPN	myeloproliferative neoplasm
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRP2	multidrug resistance-associated protein 2
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
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PFS	progression-free survival
P-gp	P-glycoprotein
PHL	potential Hy's law
PhV	pharmacovigilance
PK	pharmacokinetic
PR	partial response
QD	once daily
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RARS	refractory anemia with ringed sideroblasts
RBC	red blood cell
RBC-TI	red blood cell transfusion independence

Abbreviations and Special Terms	Definition
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
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOP	standard operating procedure
STfR	soluble transferrin receptor
Study drug	this term refers to Incyte medicinal investigational product INCB000928
$t_{½}$	half-life
TEAE	treatment-emergent adverse event
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
UIBC	unsaturated iron-binding capacity
ULN	upper limit of normal
V_z/F_{obs}	observed oral dose volume of distribution
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 in Participants With Anemia Due to Myelodysplastic Syndromes or Multiple Myeloma

Protocol Number: INCB 00928-105

Objectives and Endpoints:

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

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the safety and tolerability of INCB000928 monotherapy in participants with MDS or MM.	• 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(s).
Secondary	
To determine the efficacy of INCB000928 in participants with MDS or MM.	**For both MDS and MM disease groups:** • For transfusion-independent participants at baseline: – The proportion of participants with anemia response, defined as an Hgb increase of at least 1.5 g/dL relative to baseline for any 8-week period (with each assessment meeting this requirement) during the first 24 weeks of treatment. – Duration of anemia response, defined as 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 transfusion-dependent participants at baseline: – The proportion of participants with RBC-TI, defined as the absence of any RBC transfusion for at least 8 consecutive weeks during the first 24 weeks of treatment. – Duration of RBC-TI period for participants achieving RBC-TI for at least 8 consecutive weeks during the first 24 weeks of treatment. • Rate of RBC transfusion through Weeks 12 and 24, defined as the average number of RBC units per participant-month during the treatment period. • The largest increase from baseline in the mean Hgb values over any rolling 8-week treatment period during the first 24 weeks of treatment.

Table 1: Primary and Secondary Objectives and Endpoints (Continued)

Objectives	Endpoints
To determine the efficacy of INCB000928 in participants with MDS or MM (continued).	**For MDS participants only:** • Overall response rate, defined as the proportion of participants with CR or PR as per Cheson et al (2006) definitions for MDS and as per Savona et al (2015) definitions for MDS/MPN overlap syndromes, as applicable. • PFS, defined as the interval from the first dose of study drug until the first documented progression or death as per Cheson et al (2006) definitions for MDS and as per Savona et al (2015) definitions for MDS/MPN overlap syndromes. • LFS, defined as the interval from the first dose of study drug until the first documented leukemia transformation or death from any cause. **For MM participants only:** • Overall response rate, defined as the proportion of participants with stringent CR, CR, very good PR, and PR as per Kumar et al (2016). • PFS, defined as the interval from the first dose of study drug until the first documented progression or death as per Kumar et al (2016).
To evaluate the PK of INCB000928 in participants with MDS or MM.	PK parameters: C_{max}, t_{max}, and AUC_{0-t}.
To evaluate the effect of INCB000928 on the iron homeostasis and the erythropoiesis parameters in participants with MDS or MM.	• Blood levels of hepcidin. • Iron homeostasis parameters. • Erythropoiesis parameters.

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	1/2
Clinical Indication	Participants who are transfusion-dependent or present with symptomatic anemia due to: • MDS or MDS/MPN overlap syndromes OR • MM
Population	Male and female participants at least 18 years of age who have not undergone any stem cell transplantation, who are not candidates for such a transplantation, and who are transfusion-dependent or present with symptomatic anemia due to MDS or MM.
Number of Participants	Depending on the number of participants included in the dose-escalation stage, approximately 120 participants will be included.

Table 2: Key Study Design Elements (Continued)

Study Design	Dose escalation Dose escalation utilizing BOIN design (Liu and Yuan 2015) will proceed by including participants from both disease groups until the MTD is reached and/or the RDE(s) are determined. Expansion An additional 15 evaluable participants in each of the disease groups will be included in the expansion stages at each RDE as applicable.
Estimated Duration of Study Participation	Up to 28 days for screening, continuous study drug treatment in consecutive 28-day treatment cycles up to 6 months, as long as participants are receiving benefit from study drug and have not met any criteria for study drug discontinuation, and 30 days for safety follow-up. Treatment duration will vary between participants but is expected to average approximately 6 months.
DMC	Yes (internal)
Coordinating Principal Investigator	To be determined

Treatment Groups and Duration:

One treatment modality:

- INCB000928 administered as a monotherapy in participants who are transfusion-dependent or present with symptomatic anemia due to MDS or MM.

The study has 2 disease groups:

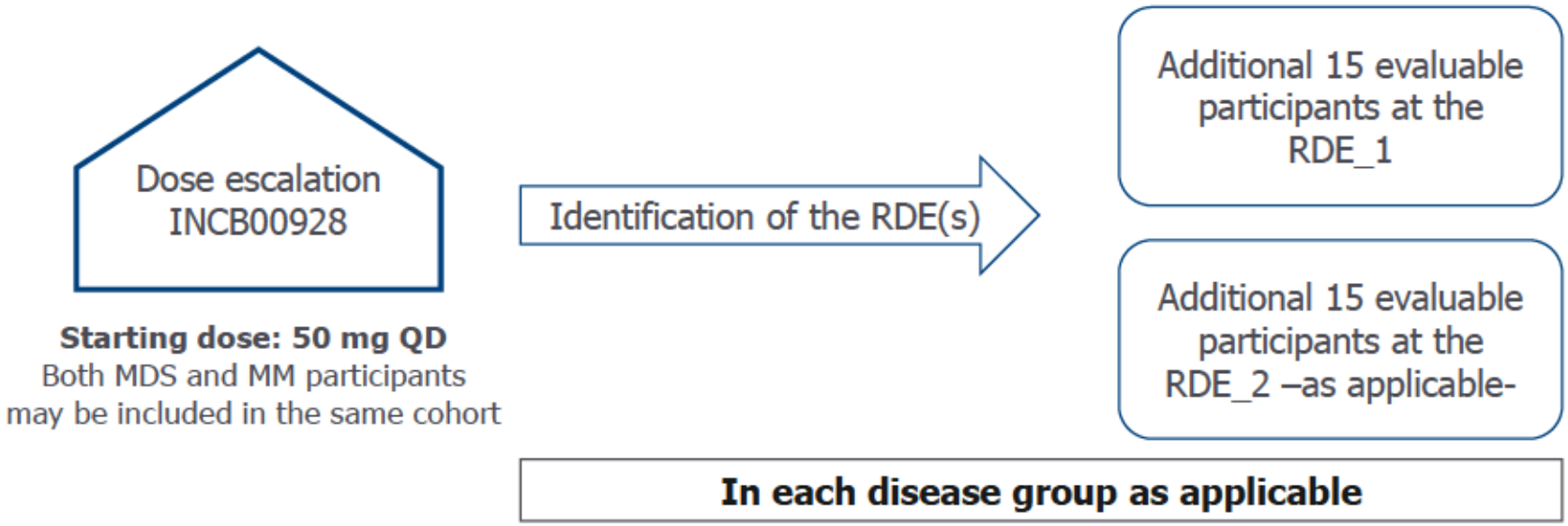
- Participants with MDS or MDS/MPN overlap syndromes, collectively referred to as MDS participants.
- Participants with relapsed/refractory MM.

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 all laboratory assessments will be performed as indicated in Table 4.

Further details of study procedures and assessments can be found in the investigator site file.

Figure 1: Study Design Schema



MDS disease group: MDS participants who are transfusion-dependent or present with symptomatic anemia
MM disease group: Relapsed/refractory MM participants who are transfusion-dependent or present with symptomatic anemia

Table 3: Schedule of Activities

Visit Day (Range)	Screening	Treatment Period								Follow-Up			Notes/Protocol Section
		Cycle 1 (± 1 day for the visits from C1D1 as reference)				Cycle 2 (± 1 day)		≥ Cycle 3 (± 3 days)		EOT (± 7 days)	Safety (30 + 5 days)	Survival (every 180 ± 14 days)	
	Day −28 to Day 0	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15				
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 drug		X				X		X					Section 6.1
Prior/concomitant medications	← From 30 days before C1D1 until 30 days after the last dose of study drug or start of a new anticancer therapy, whichever occurs first →												Section 6.7
Safety Assessments													
AE assessment	← From signature of the ICF until at least 30 days after the last dose of study drug or start of a new anticancer therapy, whichever occurs first →												Section 8.3.1 and Section 9
Physical examination/ECOG performance status	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		Section 8.3.4
12-lead ECG	X	X				X		X*		X	X		*Will be performed predose on Day 1 of every third cycle (Cycles 3, 6, 9, etc). Section 8.3.5.1
Echocardiography or MUGA scan	X							X*		X			*Every sixth cycle. Section 8.3.5.1

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening	Treatment Period								Follow-Up			Notes/Protocol Section
		Cycle 1 (± 1 day for the visits from C1D1 as reference)				Cycle 2 (± 1 day)		≥ Cycle 3 (± 3 days)					
	Day −28 to Day 0	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15	EOT (± 7 days)	Safety (30 + 5 days)	Survival (every 180 ± 14 days)	
Safety Assessments (continued)													
Timed triplicate 12-lead ECGs aligned with PK/PD sampling as applicable	X*	X		X									*At screening and within 7 days prior to C1D1. 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. Section 8.3.5.2
Liver MRI													Section 8.3.6
Participants with screening ferritin level of < 1000 ng/mL*													*When on-treatment ferritin level is > 1.5 × screening ferritin level AND ≥ 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 thereafter and EOT. †May be performed within 3 months prior to screening.

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening	Treatment Period								Follow-Up			Notes/Protocol Section
		Cycle 1 (± 1 day for the visits from C1D1 as reference)				Cycle 2 (± 1 day)		≥ Cycle 3 (± 3 days)					
	Day −28 to Day 0	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15	EOT (± 7 days)	Safety (30 + 5 days)	Survival (every 180 ± 14 days)	
Efficacy Assessments													
For All Participants													
RBC transfusion record	← During a minimum of 8 weeks before C1D1, throughout study drug treatment, and until 30 days after the last dose of study drug →												Section 8.2.1
Hgb	← During a minimum of 8 weeks before C1D1, weekly for Cycle 1, every 2 weeks for Cycles 2 – 6, on Day 1 of each cycle thereafter, at EOT, and at safety follow-up →												
BM aspirate/biopsy	X*	← To confirm a response (CR or PR for MDS and CR for MM) in case of suspected disease progression and as clinically indicated as per institutional standards →											*Archival tissue allowed for MM participants. May be performed within 3 months prior to screening. Section 8.2.1
Disease response assessment								X*					*Every sixth cycle.
For MM Participants Only													
Skeletal survey: x-ray of the skull, long bones, spine, pelvis, and ribs	X*	← As clinically indicated at the discretion of the investigator →											*Unless performed within 8 weeks prior to C1D1.
Serum free light chain, serum and urine (spot) protein electrophoresis, quantitative immunoglobulins, $beta_2$-macroglobulin	X							X*		X			*Every sixth cycle. Section 8.2.1
Post-Treatment Assessments													
Leukemia progression/disease progression/new anticancer therapy												X	Section 8.9.2

Table 4: Schedule of Laboratory Assessments

Procedure	Screening	Treatment Period								Follow-Up			Notes/Protocol Section
	Day −28 to Day 0	Cycle 1 (± 1 day for the visits from C1D1 as reference)				Cycle 2 (± 1 day)		≥ Cycle 3 (± 3 days)		EOT (± 7 days)	Safety (30 + 5 days)	Survival (every 180 ± 14 days)	
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15				
Laboratory Assessments													
Pregnancy testing	X*					X		X		X	X		*Within 3 days of C1D1. Section 8.4.1
Hematology	X	X	X	X	X	X		X		X	X		Section 8.4 and Table 16
Hgb only							X		X*				*From Cycles 3 to 6 only. Section 8.2 and Section 8.4
Blood chemistry	X	X	X	X		X		X		X	X		Section 8.4 and Table 16
HbA_{1c}, vitamin B_{12}, and MMA	X							X*		X			*Every third cycle. Section 8.4
Serology screening	X												Section 8.4.2 and Table 16
Lipid panel	X	X				X		X		X	X		*C3D1 only. Section 8.4 and Table 16
Coagulation panel	X	X				X		X*		X	X		
Urinalysis	X									X			
PK Sampling Schedule													
Blood PK sample		X		X									Section 8.5
PD Sampling Schedule													
As of Protocol Amendment 5, no further PD/translational assessment samples will be collected.													

2. INTRODUCTION

2.1. Background

2.1.1. Overview of Myelodysplastic Syndromes

Myelodysplastic syndromes are clonal stem disorders characterized by ineffective hematopoiesis, morphological dysplasia, peripheral blood cytopenias, and a high risk of progression to acute myelogenous leukemia.

Recent epidemiological studies of MDS in Asia, Europe, and the United States have reported divergent incidence rates of MDS ranging from < 2 to more than 68 per 100,000 people (Chihara et al 2014, Cogle 2015, Dinmohamed et al 2014, McQuilten et al 2013), with a higher incidence among men and a median survival of < 3 years or 3-year survival of < 60% (Gangat et al 2016, Goldberg et al 2010, Ma et al 2007, Rollison et al 2008). In Western countries, among individuals older than 70 years, the incidence is reported to be between 22 and 45 per 100,000 people, and this incidence further increases with age (Dinmohamed et al 2014, Ma 2012).

The majority of patients with MDS present with low or intermediate risk, as defined by the International Prognostic Scoring System criteria. Peripheral blood cytopenias experienced by these patients include anemia, neutropenia, and thrombocytopenia (Fenaux and Adès 2013). Anemia is the most common cytopenia and a major therapeutic challenge in patients with MDS because it affects > 50% of patients at presentation (Bowen and Hellstrom-Lindberg 2001) and up to 90% of patients at some point during the course of the disease, and it eventually requires RBC transfusions in > 80% of patients (Casadevall 1998, Kelaidi et al 2010). Anemia is the main cause of symptoms of MDS, including fatigue and dyspnea, which result in a degradation of quality of life and increased morbidity such as cardiac complications (Santini 2011a).

The pathophysiology of anemia in MDS may overlap with the pathophysiology of anemia of inflammation, particularly in early-stage (ie, lower-risk) MDS. In many patients with MDS, levels of proinflammatory cytokines (eg, in IL-6) have been shown to be associated with high levels of hepcidin. For those patients, the standard of care primarily comprises supportive care for their symptoms: RBC transfusions and ESAs for anemia as well as management of risk of bleeding and infections. Chronic anemia and RBC transfusions are independent risk factors affecting survival and are associated with iron overload, fatigue, impaired quality of life, and increased cardiovascular risks. Erythropoietin-stimulating agents can provide clinical benefit to some patients with MDS. However, only approximately 30% of patients treated with ESAs achieve improvement. The benefit is usually limited to those patients who have a low EPO level at baseline. The majority of patients with MDS have elevated serum EPO concentrations, which indicates that anemia in MDS is due to ineffective erythropoiesis that often cannot be corrected by exogenous ESA administration. Treatment of anemia and reduction of transfusion burden are the major therapeutic goals in patients with low- or intermediate-risk MDS. There are few treatment options for these patients, particularly after failure of ESAs.

2.1.2. Overview of Multiple Myeloma

Multiple myeloma is a malignant plasma cell dyscrasia characterized by monoclonal proliferation of plasma cells together with overproduction of a monoclonal antibody (Vanderkerken et al 2003) that is often accompanied by anemia, hypercalcemia, renal insufficiency, or bone lesions (Kyle and Rajkumar 2004). Fatigue is reported by many patients and may be caused by both physical and psychological factors related to the disease and its treatment, but anemia has been shown to be an important contributory factor (Cella et al 2004).

Multiple myeloma accounts for approximately 1.8% of all cancers and slightly more than 17% of hematologic malignancies in the United States (Siegel et al 2017). It is most frequently diagnosed in people aged 65 to 74 years, with a median age of 69 years (Siegel et al 2017). The American Cancer Society estimated that 32,110 new cases of MM would be diagnosed in the United States in 2019, with an estimated 12,960 deaths (Siegel et al 2017).

In Europe, MM affects approximately 4 of every 100,000 people (Ferlay et al 2013, Palumbo and Anderson 2011). A European population-based study reported an increase in 5-year survival in patients with MM/plasmacytoma from 29.8% in 1997-1999 to 39.6% in 2006-2008 (Sant et al 2014).

Nearly all patients with MM will be affected by anemia during the course of their disease. A retrospective study of 1027 patients with MM from the United States demonstrated that anemia (Hgb concentration < 12 g/dL) was present at diagnosis in 73% of patients (Kyle et al 2003). A European-wide survey of 720 patients with MM showed that 29.7% of patients presented with Hgb levels of ≤ 9.9 g/dL at the time of diagnosis, and 85.3% of these patients were anemic at any time during the survey (Birgegård et al 2006). Approximately 10% of patients with MM have an Hgb level < 8 g/dL (VanderWall et al 2013). Nonresponders and relapsing MM patients often continue to have anemia.

Furthermore, cytoreductive treatments against MM contribute to the development of anemia, and overall 45% to 90% of patients with MM receiving chemotherapy will require RBC transfusions during the course of their treatment (Dammacco et al 1998, Osterborg et al 1996).

Anemia is a common complication of MM that can negatively affect the progression of and survival from the disease (Kyle and Rajkumar 2008). The mechanism of anemia of chronic disease in which iron homeostasis is impaired underlies that of MM-related anemia. The most common form of anemia in MM is anemia of chronic disease (also referred as anemia of inflammation), characterized by inadequate production and blunted response to EPO, inhibition of red cell progenitors, reduced red cell survival and impairment of iron metabolism, and, consequently, iron-restricted erythropoiesis, which is induced by the key iron regulator hepcidin (Goodnough 2007, Weiss and Goodnough 2005).

2.1.3. Anemia in Patients With Myelodysplastic Syndromes and Multiple Myeloma

2.1.3.1. Patients With Myelodysplastic Syndromes

The most frequent clinical problem observed in patients with MDS is anemia (Malcovati et al 2008). Anemia can usually be improved by ESAs and/or RBC transfusions (Park et al 2008). The objectives of transfusion therapy are to maintain quality of life and prevent anemia-related morbidity and mortality. However, regular transfusions can lead to iron

overload, which is frequently encountered in MDS and affects both the overall survival and LFS (Malcovati et al 2005) and can have potentially serious clinical consequences.

Prolonged RBC transfusion therapy appears to be the main contributor of iron overload, but many patients appear to develop it at an early stage of the disease, before the onset of transfusions (Cortelezzi et al 2000). Pullarkat (2009) hypothesized that an altered production of hepcidin, the key hormone regulating iron homeostasis (Ganz and Nemeth 2011), may play a role in this regard.

2.1.3.2. Patients With Multiple Myeloma

The anemia in patients with MM is usually normocytic/normochromic (Kyle et al 2003), with normal to low serum iron levels, elevated serum ferritin levels, and prominent hemosiderin in BM macrophages (Ozkurt et al 2010). This suggests than iron release from reticuloendothelial macrophages is impaired, consistent with anemia of inflammation (Armand et al 2007). The main mediator of anemia of inflammation is the iron-regulatory hormone hepcidin. Recent studies have indicated that the proximal cause of dysregulated iron metabolism and anemia in these patients is cytokine-induced upregulation of hepcidin expression. Pathologic induction of hepcidin by inflammation causes hypoferritinemia, restricts the iron supply for erythropoiesis, and eventually causes anemia (Ganz 2019).

The management of anemia in MM includes the control of the primary disease and the utilization of ESA alone or in combination with intravenous iron or RBC transfusions.

- RBC transfusions produce rapid improvement of the patient's anemic condition. Unfortunately, the effects of RBC transfusions are only transient and can be associated with several risks, including infections and mild to even life-threatening immunologic reactions.
- Although ESAs such as darbepoetin alfa and epoetin alfa were once recommended for the management of anemia in patients with cancer, studies have demonstrated an increased risk of thromboembolic events (Tonia et al 2012). In addition, approximately one-third of patients do not respond to ESAs, mainly due to the impaired iron utility and the development of iron-restricted erythropoiesis occurring either at diagnosis or during treatment with ESAs (Goodnough 2007). Furthermore, reports have also suggested decreased survival and increased risk of cancer progression or recurrence with the use of ESAs in patients with cancer (Leyland-Jones et al 2005, Leyland-Jones et al 2016, Thomas et al 2008, Untch et al 2011).

Although anemia is common in patients with MM, no clear consensus exists as to the use and impact of ESAs on outcome in MM, and randomized studies in patients with MM are still limited (Terpos et al 2015).

2.2. Overview of INCB000928

2.2.1. INCB000928 Mechanism of Action

INCB000928 represents a 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 the 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 beats/min, respectively, over time-matched controls), with concomitant decreases in PR interval, RR interval, and QTc (Van de Water) 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 naïve 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 counts, Hgb levels, and Hct levels similar to those of nonanemic mice.

The results from the in vitro and in vivo pharmacology studies (refer to the INCB000928 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 with 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.

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 transforming growth factor 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 ossificans progressiva, 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 hematologic malignancies in which elevation of hepcidin levels 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 Myelodysplastic Syndrome– and Multiple Myeloma–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 after a single oral dose).

Homeostatic control of hepcidin by iron was observed to be disrupted in most MDS subtypes and almost completely lost in conditions with prominent dysmyelopoiesis such as refractory anemia with excess blasts and in CMML (Santini et al 2011b). In contrast, patients with RARS were found to have lower hepcidin levels. This finding was corroborated by the observation that hepcidin expression is suppressed by a variant of ERFE, which is restricted to SF3B1 splicing factor gene mutated RARS (Bondu et al 2019).

The cause of anemia in patients with MM is multifactorial: BM infiltration by the myeloma itself leads to reduced numbers of erythroid precursors, EPO deficiency (in patients with renal impairment), decreased responsiveness of the pro-erythroblasts and colony-forming unit–erythroid cells to EPO, impaired iron utilization due to increased production of hepcidin because of chronic inflammation, and paraprotein-induced increase of the plasma volume (König et al 2013).

Serum hepcidin levels have been shown to be significantly higher in patients with MM compared with healthy individuals and age-matched controls (Ibricevic-Balic et al 2016, Maes et al 2010, Victor et al 2017). Patients with stage III MM at diagnosis had higher urinary hepcidin levels than normal controls. Hepcidin serum levels are inversely correlated with Hgb concentrations in patients with MM (Katodritou et al 2008) and in patients with MM who have normal renal function, indicating a possible contribution of increased hepcidin levels to the pathogenesis of anemia in MM (Maes et al 2010). Furthermore, in patients with MM who have normal renal function, urinary hepcidin level was inversely correlated with Hgb level at diagnosis, and a strong association between upregulated hepcidin expression and anemia has been demonstrated in patients with advanced-stage MM, suggesting a causal relationship between upregulated hepcidin expression and anemia. Urinary hepcidin levels also significantly correlated with serum ferritin and CRP levels (Sharma et al 2008).

HAMP (the gene coding for hepcidin) mRNA expression in PBMCs and plasma hepcidin levels in patients with MM are all significantly increased when compared with those in control subjects. In patients with MM, the expression of HAMP mRNA showed a positive correlation with serum ferritin level and a negative correlation with Hgb level. Overexpression of HAMP mRNA in PBMCs significantly correlated with increased plasma hepcidin level and may be involved in the pathogenesis of MM-related anemia (Mei et al 2014).

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 participants with MDS and MM.

2.3.3. Scientific Rationale for Study Design

This is a Phase 1/2, open-label study to evaluate the safety, PK, PD, and efficacy (antianemic activity) of INCB000928 administered as a monotherapy in participants with MDS or MM who are transfusion-dependent or present with symptomatic anemia.

INCB000928 tablets will be administered orally at a starting dose of 50 mg QD. One cycle will be defined as 28 consecutive days; treatment will consist of repeating 28-day cycles.

The present study will evaluate increasing doses of INCB000928 administered as a single agent in the dose-escalation stage. The dose-escalation/de-escalation stages will use an open-label BOIN algorithm.

Once an appropriate dose has been determined to be safe and tolerable in the dose-escalation stage (RDE[s]), the dose expansion will start and participants with MDS and MM who are transfusion-dependent or present with symptomatic anemia will receive INCB000928 at each RDE. The expansion stages will aim to further assess the safety and tolerability of INCB000928, assess its PK and PD, and determine its antianemic activity in participants who are transfusion-dependent or present with symptomatic anemia due to MDS or MM in a parallel and independent fashion in each disease group (see Section 4.1).

2.3.4. Justification for Starting Dose

A Phase 1, double-blind, randomized, placebo-controlled, single-dose, dose-escalation and food-effect study is being conducted with INCB000928 to assess the safety, tolerability, and PK

of INCB000928 when administered orally as a single dose to healthy adult participants (Study INCB 00928-101).

Refer to the INCB000928 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.

The proposed starting dose for Study INCB 00928-105 is 50 mg QD as a monotherapy. In agreement with the principles outlined in ICH S9 (2010) for selecting the starting dose for clinical trials in patients with cancer and FDA Guidance for Industry: Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals (2019), the proposed starting dose for INCB 00928-105 is 50 mg QD, which was selected based on available clinical exposure data from INCB 00928-101 to provide a dose that is anticipated to be both pharmacologically active and reasonably safe for use. Based on the PK data from the healthy participants in Study INCB 00928-101, the AUC_t (total) at 50 mg QD is 3.77 µM·h (the AUC_{inf} is 3.86 µM·h) and the C_{max} (total) is 0.184 µM. This C_{max} value approximates 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 $\geq$ 3.2-fold and $\geq$ 11.3-fold lower, respectively, than exposures associated with the NOAELs in 28-day pivotal toxicology studies in rats and dogs; thus, this dose is anticipated to be reasonably safe for use.

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(s) and future development will incorporate safety, PK, and PD data, as available, obtained during this study.

2.3.5. Updated Data From Ongoing Clinical Trials

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 INCB000928 IB.

At the time of data cutoff (29 OCT 2021), 60 participants have received at least 1 dose of blinded study drug (up to 400 mg INCB000928 or placebo).

There have been no deaths, other serious TEAEs, or TEAEs leading to discontinuation from study drug. Twenty-two participants (36.7%) reported at least 1 TEAE. The most frequently reported TEAEs were medical device site reaction (reported term: "contact dermatitis at electrode site(s)" from the leads of the ECG monitor) in 9 participants (15.0%), constipation in 3 participants (5.0%), and headache in 2 participants (3.3%). All other TEAEs occurred in 1 participant each.

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 5). 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 5: Summary of Preliminary Steady-State Pharmacokinetic Parameters for INCB000928 on Day 10 (Study INCB 00928-102)

	Dose (mg)				
Parameter	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 (68100, 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.

2.4. Benefit/Risk Assessment

2.4.1. Potential Risks of INCB000928 Based on Preclinical Toxicology

The toxicologic and toxicokinetic profile of INCB000928 was characterized in a single-dose dog study and in repeat oral dose studies of up to 28 days 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 Good Laboratory Practices rat study. Phototoxicity was evaluated in vitro and in vivo.

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 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), among 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 the 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 gallbladder, 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.

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 rats, 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 dogs, 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.

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 that INCB000928 is not clastogenic or aneugenic. Additionally, no induction of micronuclei was 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 expected benefits and risks of INCB000928 may be found in the IB.

The study design will maximize participant safety while important PK, PD, safety, and efficacy information is collected. All AEs, including hematology, blood chemistry, and LFT abnormalities, and GI-associated AEs will be monitored in all participants to identify occurrences of any safety concerns.

2.4.2. Potential Benefit

Serum hepcidin levels are significantly increased in patients with MDS and MM. 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.

Study INCB 00928-105 will include only participants with MDS or MM who are transfusion-dependent or present with symptomatic anemia.

Participants with MDS must be ineligible to receive or have not responded to available therapies for anemia, and participants with MM must have failed to respond to standard treatments.

In summary, INCB000928 monotherapy should reduce hepcidin levels, increase iron availability, and improve anemia in participants with MDS and MM.

2.5. Exposure Margins

The $AUC_{0\text{-}t}$ and C_{max} values obtained at the NOAEL in the pivotal 28-day rat and dog studies are presented in Table 6, and exposure margins for a 50 mg and 100 mg QD dose relative to the NOAELs in the 28-day studies are summarized in Table 7.

Table 6: $AUC_{0\text{-}t}$ and C_{max} Values (Total) for INCB000928 Associated With Doses That Do Not Cause Adverse Effects in 28-Day Studies in Rats and Dogs

	Rat		Dogs
	10 mg/kg/day (male) and 30 mg/kg/day (female)		5 mg/kg/day
NOAEL	Male	Female	Male and Female (Average)
$AUC_{0\text{-}t}$ (μM·h)	18.8	21.5	11.9
C_{max} (μM)	2.1	3.8	2.1

Table 7: Exposure Margins for 50 mg and 100 mg QD Dose Relative to Doses That Do Not Cause Adverse Effects in 28-Day Studies in Rats and Dogs

	Rat		Dogs
	10 mg/kg/day (male) and 30 mg/kg/day (female)		5 mg/kg/day
NOAEL	Male	Female	Male and Female (Average)
50 mg QD[a]			
AUC_{0-t}	5.0	5.7	3.2
C_{max}	11.3	20.7	11.4
100 mg QD[b]			
AUC_{0-t}	2.2	2.5	1.4
C_{max}	4.8	8.9	4.9

Note: AUC_{0-t} and C_{max} from PK data obtained from healthy participants (INCB 00928-101).
[a] AUC (total) = 3.77 µM·h, AUC (unbound) = 0.56 µM·h, C_{max} (total) = 0.184 µM, C_{max} (unbound) = 0.03 µM.
[b] AUC (total) = 8.67 µM·h, AUC (unbound) = 1.28 µM·h, C_{max} (total) = 0.429 µM, C_{max} (unbound) = 0.06 µM.

3. OBJECTIVES AND ENDPOINTS

Table 8 presents the detailed objectives and endpoints.

Table 8: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the safety and tolerability of INCB000928 monotherapy in participants with MDS or MM.	• 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(s).
Secondary	
To determine the efficacy of INCB000928 in participants with MDS or MM.	**For both MDS and MM disease groups:** • For transfusion-independent participants at baseline: – The proportion of participants with anemia response, defined as an Hgb increase of at least 1.5 g/dL relative to baseline for any 8-week period (with each assessment meeting this requirement) during the first 24 weeks of treatment. – Duration of anemia response, defined as 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 transfusion-dependent participants at baseline: – The proportion of participants with RBC-TI, defined as the absence of any RBC transfusion for at least 8 consecutive weeks during the first 24 weeks of treatment. – Duration of RBC-TI period for participants achieving RBC-TI for at least 8 consecutive weeks during the first 24 weeks of treatment. • Rate of RBC transfusion through Weeks 12 and 24, defined as the average number of RBC units per participant-month during the treatment period. • The largest increase from baseline in the mean Hgb values over any rolling 8-week treatment period during the first 24 weeks of treatment.

Table 8: Objectives and Endpoints (Continued)

Objectives	Endpoints
To determine the efficacy of INCB000928 in participants with MDS or MM (continued).	**For MDS participants only:** • Overall response rate, defined as the proportion of participants with CR or PR as per Cheson et al (2006) definitions for MDS and as per Savona et al (2015) definitions for MDS/MPN overlap syndromes, as applicable. • PFS, defined as the interval from the first dose of study drug until the first documented progression or death as per Cheson et al (2006) definitions for MDS and as per Savona et al (2015) definitions for MDS/MPN overlap syndromes. • LFS, defined as the interval from the first dose of study drug until the first documented leukemia transformation or death from any cause. **For MM participants only:** • Overall response rate, defined as the proportion of participants with stringent CR, CR, very good PR, and PR as per Kumar et al (2016). • PFS, defined as the interval from the first dose of study drug until the first documented progression or death as per Kumar et al (2016).
To evaluate the PK of INCB000928 in participants with MDS or MM.	PK parameters: C_{max}, t_{max}, and AUC_{0-t}.
To evaluate the effect of INCB000928 on the iron homeostasis and the erythropoiesis parameters in participants with MDS or MM.	• Blood levels of hepcidin. • Iron homeostasis parameters. • Erythropoiesis parameters.
Exploratory	
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This Phase 1/2, open-label, multicenter, dose-finding study is intended to evaluate the safety and tolerability, PK, PD, and preliminary efficacy of INCB000928 administered as a monotherapy in participants with MDS or MM who are transfusion-dependent or present with symptomatic anemia.

4.1.1. Dose Escalation and De-Escalation Algorithm

In the dose-escalation stage, a BOIN design (Liu and Yuan 2015) will be used to determine the MTD. In each dose-escalation cohort, data from both participants with MDS and participants with MM will be evaluated together.

The cohort size will be 3. Approximately 24 evaluable participants may be treated in the dose-escalation stages, and the dose-escalation procedure may be stopped if the number of evaluable participants treated at any dose level is > 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 $\leq 0.6 \times 0.28$, dose escalation is required; if the participants have a DLT(s) rate of $\geq 1.4 \times 0.28$, 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 9 will be used to guide dose escalation/de-escalation decisions.

Table 9: Decision Boundaries

Number of participants treated at current dose	1	2	3	4	5	6	7	8	9
Escalate if number of participants with DLT(s) is ≤	0	0	0	0	1	1	1	1	1
De-escalate if number of participants with DLT(s) is ≥	1	1	2	2	2	3	3	3	4
Unacceptable toxicity if number of participants with DLT(s) is ≥	NA	NA	3	3	4	4	4	5	5

NA = not applicable.

If the number of participants with DLT(s) specified in the last row is reached, that dose level and above dose levels will be eliminated. If the number of participants with DLT(s) is between the escalation and de-escalation boundaries specified in the second and third rows in Table 9, another 3 evaluable participants will be enrolled in the current dose level cohort.

The exact number of participants treated in the 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(s) may be defined in each treatment group –as applicable-. The definition of the RDE(s) are as follows:

- Defined 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. Expansion Stages

The RDE(s) identified in the dose-escalation stages will be taken forward and administered to an additional 15 evaluable participants in each of the disease groups and at each of the identified RDE(s), and further evaluation of the safety, efficacy, PK, and PD of the RDE(s) will be performed in a parallel and independent fashion in each disease group. In the event that more than one RDE is explored in a disease group, the participants in this disease group will be randomly allocated to one of the RDEs.

Additional participants may be included at the sponsor's discretion in each disease group to ensure that at least 30% or 10 transfusion-dependent participants are included in each expansion cohort.

Fifteen participants per RDE cohort will provide a > 75% chance of identifying a toxicity with a true event rate of 9%.

Definitions:

- MTD: 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 the isotonical method, which takes the assumption of a monotonic dose-toxicity relationship into account.
- RDE: the RDE(s) will be determined by evaluation of all available data (ie, safety, PD, and PK data) from the dose-escalation stage of the study, which includes data from participants from both disease groups, for further investigation in the expansion cohorts, including low-grade but chronic toxicities, dose reductions, dose interruptions, or missed doses of INCB000928. The RDE(s) will never exceed the MTD.

4.2. Overall Study Duration

The study begins when the first participant signs the ICF. The end of the study will occur when all participants have completed up to 6 months of treatment or have discontinued treatment earlier and completed applicable safety follow-up assessments or when the sponsor terminates the study. The participants who are still receiving INCB000928, who are deriving clinical benefit, and who do not have any evidence of progressive disease at the time of study closure may have the option to continue receiving treatment with INCB000928 under this trial or a rollover protocol.

A participant is considered to have completed the study if he/she has completed all stages of the study, including the safety follow-up visit.

For each participant, the study will comprise the following:

- Up to 28 days for screening.
- Continuous study drug treatment in consecutive 28-day treatment cycles up to 6 months as long as participants are deriving benefit from study drug and have not met any criteria for study drug discontinuation (see Section 7.1).
- An additional 30 days for the safety follow-up period.
- Post-treatment follow-up every 6 months.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB/IEC 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 expansion at the RDE(s) in disease groups MDS and MM, further enrollment of participants will be suspended if 1) more than 1 participant in the first 5 participants enrolled in a specific disease 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 disease group have an AE ≥ Grade 3 that is attributable to the investigational agent. Enrollment of participants will be suspended in the disease group until the sponsor, investigators, and DMC have determined the appropriate course of action and only after regulatory authority approval of the restart.

The sponsor may terminate the study electively, if required by regulatory decision, or upon advice of the DMC. If the study is terminated prematurely, the sponsor will notify the investigators, 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.

The study will be considered closed for data collection for primary analysis when all participants have completed 6 months of study drug treatment or discontinued prematurely.

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. Age 18 years or older at the time of signing the ICF.
3. ECOG performance status 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 > 6 months.
5. 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 after the last dose of study drug and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   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 dose of study drug), 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 Table 3 and Section 8.9.1). 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:

6. Participants who are transfusion-dependent or present with symptomatic anemia, defined 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 C1D1. The most recent measurement must have occurred during the 28 day screening period immediately prior to C1D1 (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 C1D1 OR has received at least 4 units of RBC transfusions in the 8 weeks immediately preceding C1D1, 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 C1D1.

For MDS participants:

7. Ineligible to receive or have not responded to available therapies for anemia such as ESAs or lenalidomide.
8. Not requiring cytoreductive therapy other than hydroxyurea.
9. BM and peripheral blood myeloblast count < 10%.
10. Histologically confirmed diagnosis of the following (according to the 2016 WHO criteria [Swerdlow et al 2017]):
    a. MDS.
    b. CMML.
    c. MDS/MPN overlap syndromes.

Note: Participants presenting with atypical chronic myeloid leukemia, or juvenile myelomonocytic leukemia will not be included.

For MM participants:

11. Histologically confirmed diagnosis of MM (according to the 2016 WHO criteria [Swerdlow et al 2017]).
12. After failure of available standard treatments; standard treatment options include the following: alkylating agents, glucocorticoids, immunomodulatory drugs (lenalidomide, pomalidomide, or thalidomide), proteasome inhibitors (bortezomib or carfilzomib), and daratumumab.

5.2. Exclusion Criteria

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

1. Any prior allogeneic stem cell transplantation or a candidate for such transplantation.
2. Any major surgery within 28 days before the first dose of study drug.
3. Any prior chemotherapy, immunomodulatory drug therapy, immunosuppressive therapy, biological therapy, endocrine therapy, targeted therapy, or antibody or hypomethylating agent to treat the participant's disease within 5 half-lives or 28 days (whichever is shorter) before the first dose of study drug.
    a. Exceptions include glucocorticoids (corticosteroids may be continued during the study if the participant had a stable dose for the 4 weeks immediately before C1D1 and does not present any Grade 2 or higher toxicity due to the treatment) and hydroxyurea (may be used to treat hyperproliferative disease from Cycle 2 in dose-escalation cohorts and from Cycle 1 in dose expansion).

4. Undergoing treatment with another investigational medication or having been treated with an investigational medication within 28 days before the first dose of study drug.

   Note: The sponsor's medical monitor should be contacted in the event a participant received any treatment for signs or symptoms of COVID-19.

5. Undergoing treatment with ESAs, granulocyte colony-stimulating factor or granulocyte/macrophage colony-stimulating factor, romiplostin, or eltrombopag at any time within 28 days or 5 half-lives (whichever is shorter) before the first dose of study drug.

6. Undergoing treatment with a strong or potent inhibitor or inducer of CYP3A4/5 within 28 days or 5 half-lives (whichever is longer) before the first dose of study drug or expected to receive such treatment during the study (see the University of Washington School of Pharmacy Drug Interaction Database Program [2002] for prohibited medications).

7. Any prior radiation therapy within 28 days before the first dose of study drug. Palliative radiation therapy to single sites or small fields is allowed with at least a 1-week washout before the first dose of study drug.

8. Presence of any hematologic malignancy other than MDS or MM, as applicable.

9. 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.

10. Known active disease involving the CNS.

11. History of clinically significant or uncontrolled cardiac disease, including recent (within the past 12 months) unstable angina or acute myocardial infarction, 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.

12. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc > 450 milliseconds is excluded unless approved by the sponsor's medical monitor. For participants with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc 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.

13. 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 treatment has been completed and the infection is no longer active.

14. Diagnosis of chronic liver disease (eg, chronic alcoholic liver disease, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, hereditary hemochromatosis, nonalcoholic steatohepatitis).
15. Known active hepatitis A, HBV, or HCV infection, or at risk of HBV reactivation, or known HIV infection.

    Active HBV or at risk of reactivation are defined as follows: positive HBsAg result (laboratory tests required at screening), and/or positive total anti-HBc antibody 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 who 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.
16. Unwillingness to be undergo transfusion with blood components, including RBC packs and platelet transfusions.
17. 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 drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
18. Active alcohol or drug addiction that would interfere with the participant's ability to comply with the study requirements.
19. Gastroesophageal reflux disease not controlled by medication (ie, currently symptomatic or endoscopic evidence of esophagitis) within 28 days before the first dose of study drug.
20. Presence of any unresolved toxicity $\geq$ Grade 2 from previous therapy except for stable chronic toxicities ($\leq$ Grade 2) not expected to resolve, such as stable Grade 2 peripheral neuropathy.
21. Known hypersensitivity, severe reaction, or any known contraindications to the use of any of the active substances or excipients in INCB000928.
22. Women who are pregnant or breastfeeding.
23. Unable to swallow and retain oral medication.
24. Current use of prohibited medication (see Section 6.7.3).

25. Participants with laboratory values at screening as defined in Table 10.

Table 10: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	$< 25 \times 10^9$/L without the assistance of growth factors, thrombopoietic factors, or platelet transfusions
b	ANC	$< 0.50 \times 10^9$/L
Hepatic		
c	ALT	$\geq 2.5 \times$ ULN
d	AST	$\geq 2.5 \times$ ULN
e	Total 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
Other		
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).

26. Iron chelation treatment is allowed before the first dose of study drug provided the dose is stable during the 2 weeks prior to the first dose of INCB000928.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

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

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 thus 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:
  - Each participant will be observed for at least the first study drug treatment cycle (ie, 28 days) to be evaluable to assess safety of the dose for the purposes of DLT assessment. Participants who receive at least 75% of doses of study drug at the level assigned to that cohort (ie, 21 days of treatment) or have a DLT during the first study drug 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 drug discontinuation because of an event that does not meet the criteria for a DLT, which results in < 75% of the prescribed dose of study drug being administered during the first study drug treatment cycle, 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 drug treatment cycle (DLT assessment period) will be replaced.
  - Participants who do not meet all of the eligibility requirements of the study may be replaced.
- In the expansion stages, an evaluable participant is defined as a participant who has received at least 1 dose of study drug 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 may be replaced.

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 before each meeting and make recommendations 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 study 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 11 presents the study treatment information.

The treatment period begins on the day the participant receives the first dose of study drug (C1D1) and ends when the investigator determines the participant will be permanently discontinued from study drug. The first dose on C1D1 must be no more than 28 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 will be administered daily by oral route in consecutive, continuous, 28-day treatment cycles. The doses of INCB000928 can be administered by hospital personnel in an inpatient setting or self-administered by the participant in an outpatient setting.

INCB000928 will be administered to the study participants as long as they benefit from the study drug and they do not present any study drug discontinuation criterion as per investigator's assessment (see Section 7.1) for up to 6 months of treatment. The participants who are still receiving INCB000928 and are deriving clinical benefit at this time may remain on study drug treatment if the study is still open with the sponsor's approval (see Section 4.2 for options at time of study closure).

Table 11: Study Treatment Information

	INCB000928 (Study Drug)
Mechanism of action:	Inhibition of ALK2, an upstream regulator of hepcidin
Dosage formulation:	Tablets
Unit dose strength(s)/ dosage level(s):	**Starting doses**
	Dose escalation: 50 mg QD Alternative administration schedules may be explored as described in Section 4.1.2. **Expansion:** The RDE(s) as defined in the dose-escalation stage.
	On-study doses
	See Section 4.1, Section 6.5, and Section 6.6.
Administration instructions:	• INCB000928 can be taken 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 drug again before the next scheduled dose. • On days of predose PK sampling, participants should refrain from taking the study drug until PK samples are collected.
Packaging and labeling:	INCB000928 will be provided in bottles. Each bottle will be labeled as required per country requirement.
Storage:	Between 15°C and 30°C (59°F and 86°F)
Status of treatment in participating countries:	Investigational

6.2. Preparation, Handling, and Accountability

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

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

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

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

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

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional SOPs. If local procedures mandate on-site destruction of the investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

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

See Appendix B 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 drug will be dispensed at the study visits summarized in the SoA (see Table 3) and refer to Section 4.1.3 regarding randomization in dose expansion.

Returned study drug should not be redispensed to the participants.

6.4. Study Treatment Compliance

Compliance with study drug 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 study drug accountability (eg, tablet counts), documented by the site staff, and monitored by the sponsor/designee. Participants will be instructed to bring all study drug with them to the study visits in order for site personnel to conduct tablet counts to assess study drug 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 12 occurring during the first study drug treatment cycle, from C1D1 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 CTCAE v5.0. Participants who receive at least 75% of doses of study drug at the level assigned or have a DLT will be considered evaluable for determining tolerability of the dose (see Section 5.5).

Individual participant dose reductions may be made based on events observed at any time during study drug treatment; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the MTD of INCB000928, decisions will be made based on events that are observed from C1D1 through and including the final day of Cycle 1 (ie, Day 28).

Table 12: 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 corticosteroids 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 thrombocytopenia with bleeding. • Grade 4 thrombocytopenia. • Febrile neutropenia (ANC < 1.0×10^9/L with a single temperature > 38.3°C [101°F] or a sustained temperature ≥ 38°C [100.4°F] for more than 1 hour). • Grade 4 neutropenia > 7 days. • Anemia will not be considered in the definition of a DLT.
Iron studies	• Iron abnormalities that are symptomatic or affect an organ function will be considered a DLT.
Other toxicities not meeting DLT criteria	• Although the rules for adjudicating DLTs in the context of dose escalation are specified in this table, an AE not listed in this table may be considered 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 Pharmacokinetic Results

Safety telephone conferences with study investigators will be scheduled by the sponsor to review cohort-specific data and overall safety and available PK data collected during at least the first treatment cycle for 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 sponsor, in consultation with participating investigators, may elect to expand dose cohorts deemed tolerable, beyond what is described in the preceding text, 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 obtained during at least the first study drug treatment cycle (ie, 28 days, from C1D1 to Cycle 1 Day 28) in each cohort as per Section 4.1.1. 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 starting dose level in the dose-escalation stages 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 study drug is observed (not including toxicities with a 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. Dose escalation will continue until the MTD is reached and/or the RDE(s) are determined.

If the first dose level is not tolerable, the reduced dose level will be tested (25 mg). Further dose de-escalations may be performed as needed with at least 25% reductions of the dose and based on available tablet strengths.

If moderate or severe AEs 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 one-third (33%) of the participants in a cohort, then dose escalation will be temporarily halted and no further participants will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the medical monitor, relevant personnel including investigators, and the IRB/IEC as necessary/applicable will take place before resumption of administration.

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.

For the purposes of dose cohort escalation/de-escalation/dose finding and determining the MTD of INCB000928, decisions will be made based on information observed from the first day of

study drug administration through and including the final day of Cycle 1 (Day 28). A lower MTD may subsequently be determined based on relevant toxicities that become evident after Day 28.

6.5.4. Definition of the Recommended Dose for Expansion

The RDE dose(s) as applicable will be determined by evaluation of all available data (ie, safety, PK, and PD data) from the dose-escalation stage of the study for further investigation in the expansion cohorts, including safety (low-grade but chronic toxicities, dose reduction, dose interruption, or missed doses of INCB000928).

The RDE(s) will never exceed the MTD.

6.6. Dose Modifications

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

The occurrence of DLTs (see Section 6.5.1) and other toxicities (related or unrelated to study drug) 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 drug and the participant's underlying condition.

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 13). 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 AE to the study drug and the participant's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-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.

Clinical, hematologic, and biochemistry events (eg, thrombocytopenia, anemia, neutropenia, LFT abnormalities) occurring and precipitating dose reductions or interruptions during Cycle 1 of study drug treatment will be evaluated as potential DLTs and managed as per the guidelines in Table 13. Clinical, hematologic, and biochemistry AEs that precipitate dose interruptions should be monitored for recovery at least on a weekly basis, if feasible.

Table 13: Guidelines for Interruption and Restarting of Study Drug

Adverse Event		Action Taken
Toxicity	**NCI CTCAE Grade**	
Hematology		
Neutropenia (ANC)	Grade 3	Continue study drug, and monitor ANC as clinically indicated.
	Grade 4 (ANC < 0.5×10^9/L)	Hold study drug up to 21 days, and monitor ANC 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 ANC should be monitored as clinically indicated. • If toxicity lasts > 21 days, permanently discontinue INCB000928.
Febrile neutropenia	ANC < 1.0×10^9/L + a single temperature > 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 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 ANC should be monitored as clinically indicated. • If febrile neutropenia lasts > 21 days, permanently discontinue INCB000928.
Thrombocytopenia (platelet count)	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 platelet counts should be monitored as clinically indicated. • If toxicity lasts > 21 days, permanently discontinue INCB000928.

Table 13: Guidelines for Interruption and Restarting of Study Drug (Continued)

Adverse Event		Action Taken
Toxicity	**NCI CTCAE Grade**	
Hematology (continued)		
Thrombocytopenia (platelet count) (continued)	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 platelet counts should be monitored as clinically indicated. • If toxicity lasts > 21 days, permanently discontinue INCB000928.
Serum 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 LFTs should be monitored as clinically indicated. • If LFTs do not resolve to ≤ Grade 1 or baseline level within 7 days after interruption, discuss with the sponsor's medical monitor.
	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 LFTs should be monitored as clinically indicated. • If LFTs do not resolve to ≤ Grade 1 or baseline level within 21 days after interruption, discuss with the sponsor's medical monitor.
	Recurrence of Grade 3 on rechallenge (ALT/AST elevation > 5 and ≤ 20 × ULN)	If AST and/or ALT > 5 × 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 LFTs should be monitored as clinically indicated. • If LFTs do not resolve to ≤ Grade 1 or baseline level within 21 days after interruption, permanently discontinue INCB000928.

Table 13: Guidelines for Interruption and Restarting of Study Drug (Continued)

Adverse Event		Action Taken
Toxicity	**NCI CTCAE Grade**	
Serum chemistry (continued)		
ALT/AST elevation (continued)	Grade 4 or Hy's law	Permanently discontinue INCB000928 and recommend liver biopsy, ultrasound, or other imaging as well as hepatitis serology (even if negative at baseline).
Other toxicities		
For participants with a screening ferritin level of < 1000 ng/mL: when the ferritin level during the study becomes > 1.5 × the screening ferritin level AND the ferritin level is ≥ 1000 ng/mL		Interrupt study drug and perform non–contrast-enhanced MRI in conjunction with software used for the estimation of hepatic iron concentration (ie, T2-weighted MRI) 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 a newly identified clinically significant iron overload, or 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), permanently discontinue INCB000928. Otherwise, if the ferritin level returns to screening level 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 ferritin 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 becomes > 1.5 × the screening ferritin 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 a newly identified clinically significant iron overload or 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), discontinue permanently. Otherwise, if elevated ferritin is deemed to be result of transfusion and no clinically significant change in liver iron content or evidence of clinically significant iron overload, then dose can be maintained and MRI monitoring will be increased to every 3 months.
Any Grade 1 or Grade 2 toxicity		Continue study drug treatment and treat the toxicity; monitor as clinically indicated.

Table 13: Guidelines for Interruption and Restarting of Study Drug (Continued)

Adverse Event		Action Taken
Toxicity	**NCI CTCAE Grade**	
Other toxicities (continued)		
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 toxicity should be monitored as clinically indicated. • If toxicity does not resolve to ≤ Grade 1 or baseline level within 21 days after interruption, permanently discontinue INCB000928. • 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 INCB000928, 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 INCB000928, and follow-up per Protocol unless considered not related to study drug.
Other		
In the event that a participant's Hgb level becomes > 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 at least 25% and depend on the study drug strengths available at the site.		

6.6.3.1. Dose Reductions of Study Drug for Concomitant Use of Inducers or Inhibitors of CYP3A4/5

The preclinical studies have shown the following:

- INCB000928 is primarily metabolized by CYP3A4/5 (77%-87%) and CYP2D6 (13%-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 Use of Strong to Potent Inducers or Inhibitors of CYP3A4/5

The use of strong or potent inhibitors or inducers of CYP3A4/5 is prohibited in the present study (see Section 6.7.2 and refer to the University of Washington School of Pharmacy Drug Interaction Database Program [2002]) and in particular during DLT assessment in the first study drug treatment cycle, and all efforts should be used to avoid the utilization of strong or potent

inhibitors or inducers of CYP3A4/5. If a participant **must** receive one of these compounds, the dose of INCB000928 has to be decreased by at least 50% compared to the theoretical dose. The precise dose will be determined according to the strength of INCB000928 tablets available. If feasible, blood samples will be drawn for PK purposes as defined for C1D1 (predose and 2 hours, 4 hours, and between 6 and 8 hours postdose) during the first cycle when the participant is administered the strong or potent inhibitor or inducer of CYP3A4/5.

If a participant **must** receive one of these compounds during the first study drug treatment cycle, this participant will be declared nonevaluable for DLT assessment and will have to be replaced.

6.6.3.1.2. Dose Reductions for Concomitant Use of Weak to Moderate Inducers or Inhibitors of CYP3A4/5, Inhibitors or Inducers of CYP2D6, and Compounds Affecting P-Glycoprotein or BCRP

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

Please note that weak to moderate inducers or inhibitors of CYP3A4/5, inhibitors or inducers of CYP2D6, and compounds affecting the efflux transporter P-gp and BCRP are restricted or 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 discontinuation procedures.

6.6.5. Criteria and Procedures for Dose Increases of Study Drug

Participants will have the option of escalating INCB000928 to a dose found to be tolerated, as defined in the following text.

Intraparticipant study drug increase will be performed at the investigator's discretion *with sponsor preapproval* 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 drug 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 < 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 during the dose-escalation stages).
- During the first cycle with increased dose, participants must be willing to submit to PK sampling on Day 15 (as in C1D1) and ECG schedule as in Cycle 1 (see Table 3, Table 4, Section 8.3.5, and Section 8.5.1). In addition, the Cycle 1 safety procedures will be repeated for the timepoints of the first cycle with increased dose.

- In the opinion of the investigator, the participant does not have any concurrent condition or circumstance that would complicate the dose escalation or PK sampling or pose increased risk to the participant.

Doses of INCB000928 will never exceed the MTD as identified in the dose-escalation stages as applicable.

6.6.6. Treatment After Initial Radiologic Evidence of Disease Progression

See Section 7.1 and Section 8.9.

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 C1D1 and up to 30 days after the last dose of study drug or until the participant begins a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered after 30 days after the last dose of study drug 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 study participants.

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 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
- If a participant is to receive a COVID-19 vaccination during the present 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 (refer to the University of Washington School of Pharmacy Drug Interaction Database Program [2002]):
  - When concomitant administration of a strong or potent inhibitor of CYP3A4/5 is required for participant management, the dose of INCB000928 must be adjusted 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 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 during a period of concomitant medication use. If required for safety, then the dose of INCB000928 may be reduced to at least 50% compared to the theoretical dose. 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.

6.7.3. Prohibited Medications and Procedures

The following medications are prohibited during the study:

- Any investigational medication other than INCB000928. Use of such medications within 28 days before the first dose of study drug 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/day is prohibited.
- Strong or potent inducers and inhibitors of CYP3A4/5 are not permitted with the exception of topical ketoconazole, based on its low overall bioavailability.
- ESAs.

The sponsor's medical monitor should be contacted in the event a participant received any treatment for signs or symptoms of COVID-19.

6.8. Treatment After the End of the Study

After the end of the study, the participants will receive therapy/treatment as per the local institution's standard of care applicable to their disease (see Section 4.2 for the definition of the end of the study).

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- Occurrence of unacceptable toxicity, defined as the occurrence of an AE that is related to study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest. The occurrence of unacceptable toxicity not caused by the underlying malignancy will be presumed to be related to study drug and will require that the study drug 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 the public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study drug treatment and remain in the study to be followed for progression and post-treatment assessments (see Table 3).
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- The participant presents a study drug treatment failure, defined as either of the following:
  - Decrease of Hgb during the study drug 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 drug 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 Section 6.6.3).
  - Any Grade 4 toxicity other than Grade 4 neutropenia and Grade 4 thrombocytopenia (see Section 6.6.3).

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

- If, during the course of the study, a participant is found not to have met all eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be permanently discontinued from study drug treatment.
- If a participant is noncompliant with study procedures or study drug 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 drug, at the option of the investigator.

In addition to the criteria described in the preceding text, participants with MDS will only permanently discontinue study drug in the event of a blast percentage of ≥ 20% in the BM or the peripheral blood at any time during the study.

Furthermore, the investigator is allowed to discontinue INCB000928 administration if in his/her opinion, the participant is no longer benefitting from treatment with INCB000928. In such a situation, the investigator will document his/her assessment and decision in the participant's eCRF and source documents.

In the event that a participant permanently discontinues study drug, 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.

7.1.2. Discontinuation Procedures

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

In the event that the decision is made to permanently discontinue study drug, the EOT visit should be conducted, the study drug 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 and Table 4. The date of the last dose of study drug and the reason for discontinuation of study drug will be recorded in the eCRF.

If a participant is discontinued from study drug 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 drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the participant discontinues study drug and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, participants will have the option of withdrawing consent for study drug 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 his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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

See Table 3 and Table 4 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 he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

All study assessments will be performed as indicated in the SoA (see Table 3), and all laboratory assessments will be performed as indicated in Table 4. 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 his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

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

8.1.2. Screening Procedures

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

Procedures conducted as part of the participant's routine clinical management (eg, blood count, imaging study) and obtained before signing of 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 28 days of C1D1). 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 first administration of study drug. 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 drug will be used to determine eligibility. Treatment with study drug should start as soon as possible but within 2 days after confirmation of the 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 drug. Additionally, the IRT will be contacted as appropriate to update the study drug supply and the participant's status in the study. Additional details are provided in the IRT Manual.

8.1.4. Demography and Medical History

8.1.4.1. 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.

8.1.4.2. 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

8.2.1. Efficacy Assessments for All Disease Groups

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

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

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 up to 12 weeks before the first study drug dose, if available. The collection of Hgb values and RBC transfusions are mandatory only during the 8 weeks immediately preceding the first dose of study drug, respectively.
- During the study drug treatment period:
  - The RBC transfusions will be collected from the first dose of study drug, throughout the whole study drug treatment period, and until 30 days after the last dose of study drug.
  - The Hgb values will be collected at least weekly for the first cycle, every 2 weeks for each cycle thereafter, and at the EOT and safety follow-up visits.

The BM aspirate/biopsy assessments will be performed and analyzed locally by the investigator as per the local standards during screening. For participants with MM, BM aspirate/biopsy performed within 3 months prior to screening is allowed as long as archival tissue is available. For participants with MDS, a BM aspirate/biopsy should be obtained within 3 months prior to screening. The BM aspirate/biopsy assessments (blood smears allowed for dry taps) will be repeated to confirm a response (CR or PR for MDS and CR for MM) in case of suspected disease progression and as clinically indicated per institutional standards. The disease response assessment will be performed on-site by the investigator as per Table 3.

In addition, for MM participants only, serum and urine protein electrophoresis, serum free light chains, quantitative immunoglobulins, and beta$_2$-macroglobulin assessments will be conducted during screening, every 6 cycles, at the EOT visit, and in case of suspected progression. Skeletal survey should be conducted at screening (unless performed within 8 weeks prior to C1D1) and subsequently as clinically indicated at the discretion of the investigator. These assessments will be performed and analyzed locally by the investigator.

Pretreatment baseline measures of cytopenias are averages of at least 2 measurements (not influenced by transfusions [ie, no RBC transfusions for at least 2 weeks and no platelet transfusions for at least 1 week]) over at least 1 week prior to therapy. During the study drug treatment period, all RBC transfusions received by the participants will account for the definition of transfusion independence, regardless of the reason for the transfusion and irrespective of the Hgb value that triggered the transfusion. However, transfusions should be avoided unless the Hgb value is < 8.5 g/dL, anemia is symptomatic, or active bleeding is detected.

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) and Table 4.

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 both disease 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 drug or until the start of new anticancer therapy, whichever occurs first. The SAEs suspected to be related to study drug as per the investigator's assessment will be recorded anytime. Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study drug. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

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

All SAEs will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

8.3.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual as per Table 3, such as a licensed physician, a physician assistant, or an advanced registered nurse practitioner, as local law permits. Abnormalities identified after signature of the ICF by the participant and up until 30 days after the last dose of study drug constitute an AE if they worsen from baseline,

are considered clinically meaningful in the medical and scientific judgement of the investigator, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. 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 Status

The ECOG performance status will be assessed at screening and other study visits per Table 3. Performance status must be assessed by a medically qualified individual, scored as per Table 14, and recorded in the participant's eCRF.

Table 14: 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 housework, 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 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.

Abnormal vital sign results identified after signature of the ICF by the participant and up until 30 days after the last dose of study drug 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 study drug.

8.3.5. Cardiac Function Assessments

8.3.5.1. 12-Lead Electrocardiograms and Cardiac Echography or Multigated Acquisition

Cardiac function will be assessed by the following examinations, which will be performed as indicated in Table 15:

- 12-lead ECGs: at minimum, the heart rate and measurement of PR, QRS, and QT intervals and QTc will be collected.
- Echocardiography 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) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals and QTc. 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 echocardiography or MUGA scans 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 drug 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 may be used in place of the QTc with medical monitor approval. In addition, the JTc 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 signature of the ICF up until 30 days after the last dose of study drug as applicable are to be reported as AEs and graded as per the NCI CTCAE v5.0 (2017) where applicable.

8.3.5.2. Triplicate 12-lead ECGs

Triplicate 12-lead ECGs will be obtained on the days and times noted in the schedule of assessments (see Table 3) and Table 15 below. On Cycle 1 on Days 1 and 15, the timed 12-lead triplicate ECGs will be conducted predose and 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 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 Cycle 1 Day 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 from 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 15: Schedule of Cardiac Function Assessments

Visit/Examination	Anytime	Predose[a]	Postdose[b]
12-lead ECGs			
Screening	X		
C1D1		X	X
C2D1		X	
Day 1 of every third cycle (Cycles 3, 6, 9, and 12)		X	
EOT	X		
Safety follow-up	X		
Echocardiography/MUGA scan			
Screening	X		
Day 1 of every sixth cycle (Cycles 6 and 12)	X[c]		
EOT	X		
Triplicate 12-lead ECGs[d]			
Screening	X		
Within 7 days prior to C1D1	X		
C1D1 and C1D15		X	X (2, 4, and between 6-8 hours)

[a] Predose is before the morning dose of INCB000928, within 90 minutes before receiving the study drug.
[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 or PD blood draw as applicable: within approximately 5 minutes before the respective PK or PD blood draw.

8.3.6. Iron Overload Assessment

Iron homeostasis assessment will be performed at screening; on Days 1, 8, and 15 of Cycle 1; on Day 1 of Cycle 2; on Day 1 of each cycle after Cycle 2; at the EOT; and at the safety follow-up visits.

A non–contrast-enhanced MRI will be performed in conjunction with software used for the estimation of hepatic iron concentration (ie, T2-weighted MRI) 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 screening ferritin level AND the ferritin level is ≥ 1000 ng/mL, MRI should be performed every 3 cycles thereafter, 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, and 42 as applicable) and
    - When the ferritin level during the study becomes > 1.5 × the screening ferritin level, MRI should be performed every 3 cycles thereafter, providing the conditions are maintained.
    - EOT.

At sites where a MRI is not available, a CT scan may be used to identify any liver lesion(s) or disease, with prior sponsor's medical monitor approval.

8.4. Laboratory Assessments

See Table 16 for the list of clinical laboratory tests to be performed and Table 4 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 4 will be measured locally; only hepcidin and ERFE parameters will be measured centrally. A certified laboratory local to the investigative site will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, serology, lipid panel, and urinalysis). Additional tests may also be performed if clinically indicated.

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

Screening laboratory assessments must be performed within 28 days of C1D1. If performed more than 28 days before C1D1, then the tests must be repeated and eligibility confirmed before study drug administration on C1D1. Laboratory samples collected on C1D1 must be performed before study drug administration. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study drug 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 study drug is initiated.

Procedures conducted as part of the participant's routine clinical management 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 chemistry, hematology assessments, lipid panel, coagulation tests, and urinalysis will be recorded as AEs if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug treatment and will be graded as per the NCI CTCAE v5.0 where applicable.

Clinically significant abnormal laboratory findings are those which 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 signature of the ICF and up to 30 days after the last dose of study drug) should be repeated until the values return to normal or baseline, stabilize, 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 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.

Table 16: Required Laboratory Analytes

Blood Chemistries	Hematology	Urinalysis (Dipstick)	Screening Serology	Coagulation
Ions: Bicarbonate or CO_2, calcium, chloride, magnesium, phosphate, potassium, sodium Iron homeostasis and erythropoiesis: 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: Lactate dehydrogenase, fibrinogen, CRP, HbA_{1c}, vitamin B_{12}, MMA	Complete blood cell count, including: • Hgb • Hct • Platelet count • RBC count • White blood cell count Differential count (absolute values), including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils Additional parameters for erythropoiesis: • RC • NRBC • MCV • MCH • MCHC • RDW • Reticulocyte hemoglobin content[a] • Myeloblasts in peripheral blood • EPO	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]	Prothrombin time Partial thromboplastin time or activated partial thromboplastin time International normalized ratio
		Lipid Panel	**Pregnancy Testing**	
		Total cholesterol Triglycerides Low-density lipoprotein High-density lipoprotein	Female participants of childbearing potential only. Serum tests at screening and EOT and safety follow-up visits; urine pregnancy test before the first study drug dose at each cycle after Cycle 1. 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] Reticulocyte hemoglobin content measurement is not required at investigational sites where this parameter cannot be measured by the local laboratory.
[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 C1D1) before the first dose of study drug (in all cases, the investigator should confirm the test result is negative before starting study drug 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 after Cycle 1 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 drug 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 16. 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

Blood samples will be collected for measurement of concentrations of INCB000928 as specified in Table 4. 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 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 in the eCRF.

8.5.1. Blood Sample Collection

Timing of blood PK assessments is outlined in Table 17. 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 receive the study drug. Predose is defined as within 90 minutes before administration of study drug. Adjustments to the timing of blood sampling may be made based on emerging PK data.

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

Table 17: Pharmacokinetic Blood Sample Timing

Study Visit	Timing of Samples
Cycle 1[a] Day 1 Cycle 1 Day 15	• Predose (within 90 minutes prior to receiving the study drug) • 2 hours postdose (± 15 minutes) • 4 hours postdose (± 15 minutes) • 1 sample between 6 and 8 hours postdose
First cycle of INCB000928 with intraparticipant dose escalation	**Timing of Samples**
On Day 15 of the first cycle with intraparticipant dose escalation	• Predose (within 90 minutes prior to receiving the study drug) • 2 hours postdose (± 15 minutes) • 4 hours postdose (± 15 minutes) • 1 sample between 6 and 8 hours postdose

[a] Cycle 1 of both the dose-escalation and dose-expansion phases.

8.6. Pharmacodynamic and Translational Assessments

8.6.1. Blood and Bone Marrow Sample Collection

As of Protocol Amendment 5, no further PD/translational assessment samples will be collected.

8.6.2. Pharmacodynamic and Translational Research Parameters

- Assessment of iron homeostasis and erythropoiesis comprises the following (part of the hematology and blood chemistry sampling):
  - Iron homeostasis: TSI, ferritin, transferrin, TSAT, TIBC, and UIBC.
  - Erythropoiesis: RC, NRBC, MCV, MCH, Hgb, Hct, RBC count, MCHC, RDW, and reticulocyte hemoglobin content.
  - EPO.
- The plasma PD sample will aim at evaluating, but not restricted to, the level of plasma hepcidin using a validated immunoassay. Hepcidin measurement will be performed centrally.
- The BM aspirate or BM aspirate smears to determine [redacted]. If a fresh BM aspirate is contraindicated or cannot be collected during screening, archival BM smears (collected after the completion of the most recent anticancer treatment and within 3 months before C1D1 of the study) may be submitted. The purposes of the measurements performed on these samples are to evaluate any correlation between [redacted] and anemia response to INCB000928 in MDS and MM participants.
- [redacted]

The results of the analyses of these parameters will be correlated with the safety and efficacy data obtained from the study participants.

8.7. 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.

8.8. End of Treatment and/or Early Termination

When the participant permanently discontinues study drug 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.

8.9. Follow-Up

8.9.1. 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 drug. Adverse events and SAEs must be reported up until 1) at least 30 days after the last dose of study drug or the start of a new anticancer therapy or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the 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. Once a new anticancer therapy has been initiated, the participant will move into the post-treatment follow-up period.

8.9.2. Post-Treatment Follow-Up

Participants who discontinue study drug 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 ± 14 days]) 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.
- Lost to follow-up.
- Death.
- The 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.
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. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in 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 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 or 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 definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurred. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment 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, or 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.

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. 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 diagnostics reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the 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 (INCB000928): suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at final safety follow-up visit.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 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 one 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 and each occurrence of each AE/SAE. If reference therapy is used in combination with an Incyte study drug or multiple Incyte study drugs are used, then the relationship to the study drug/reference therapy must be assessed (ie, for the Incyte product(s) and for the other product(s) that is 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 Product Information for study drug or marketed products, respectively, for making his/her 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 administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change his/her opinion of causality in light of follow-up information and 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 AE 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, 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) within 24 hours of receipt of the information.

See Appendix C for the management of PHL cases.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug, reference therapy or study procedure[s]), all SAEs occurring after the participant has signed the ICF through 30 days after the last dose of study drug ***or*** until the participant starts a new anticancer therapy, whichever occurs earlier, must be reported to the sponsor (or designee) immediately, without undue delay but not later than within **24 hour**s 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.

Investigators are not obligated to actively seek AE or SAE information after conclusion of study participation. If the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, then the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

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

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

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug 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 within 24 hours of learning of its occurrence any SAEs 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 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 retrospectively 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 (eg, resolved or ongoing), treatment provided, action taken with the study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

9.5. Emergency Unblinding of Treatment Assignment

Not applicable.

9.6. Pregnancy

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

- The study drug must be discontinued immediately (female participants only).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

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

Any SAE occurring during pregnancy of a study participant must be recorded on the Serious Adverse Event Form in the eCRF and submitted to the sponsor or designee (see 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 drug, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

9.8. Product Complaints

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

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

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

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

9.9. Treatment of Overdose

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

For the purposes of this study, an overdose will be defined as the use of study drug in doses in excess of those specified in the Protocol. Participants overdosed should be treated with appropriate supportive care until recovery. Use of study drug 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 C1D1) for PK analysis within 1 day from the date of the last dose of study drug 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. Dose Escalation

In the dose-escalation stage, a BOIN design (Liu and Yuan 2015) will be used to determine the MTD. The cohort size will be 3. Approximately 24 evaluable participants may be treated in the dose-escalation stage, and the dose-escalation procedure may be stopped if > 9 evaluable participants are treated at any dose level. The exact number of participants treated will depend on the number of participants required per dose level and the number of dose levels studied.

10.1.2. Dose Expansion

An additional 15 evaluable participants at each identified RDE in each disease group will be enrolled in the expansion stage.

Fifteen participants per cohort will provide a > 75% chance of identifying a toxicity with a true event rate of 9%.

In total, approximately 120 participants will be included in the study.

10.2. Populations for Analyses

The populations for analyses are provided in Table 18.

Table 18: Populations for Analyses

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

10.3. Level of Significance

All statistical analyses are exploratory in nature. All CIs provided will be at the 95% confidence level.

10.4. Statistical Analyses

10.4.1. Primary Analysis: Safety

The safety of INCB000928 administered alone in MDS and MM participants will be analyzed using the following parameters descriptively by disease type, overall, and by dose level in the FAS 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.
- Participants with DLTs will be tabulated for each cohort of the dose-escalation stages.

10.4.2. Secondary Analyses

10.4.2.1. Efficacy

The efficacy of INCB000928 administered alone in MDS and MM participants will be analyzed using the following parameters by disease type and dose level in the FAS population.

The proportion of participants achieving an anemia response, defined as an Hgb increase $\geq$ 1.5 g/dL relative to baseline for any $\geq$ 8-week period during the first 24 weeks of treatment if transfusion-independent at baseline, will be estimated with its 95% CI.

The proportion of participants achieving RBC transfusion independence for $\geq$ 8 consecutive weeks if transfusion-dependent at baseline during the first 24 weeks of treatment will be estimated with its 95% CI.

For transfusion-independent participants at baseline, duration of anemia response, defined as 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, will be estimated using the Kaplan-Meier method. The Kaplan-Meier estimate of median duration of anemia response will be presented with 95% CI.

For transfusion-dependent participants at baseline achieving RBC-TI, defined as the absence of any RBC transfusion for at least 8 consecutive weeks during the first 24 weeks of treatment, duration of RBC-TI period will be estimated using the Kaplan-Meier method. The Kaplan-Meier estimate of median duration of RBC-TI period will be presented with 95% CI.

The rate of RBC transfusion through Weeks 12 and 24, defined as the average number of RBC units per participant-month during the treatment period, will be estimated.

The largest increase from baseline in the mean Hgb values over any rolling 8-week treatment period during the first 24 weeks of treatment will be summarized descriptively.

For MDS participants:

- Overall response rate, defined as the proportion of participants with CR or PR as per Cheson et al (2006) definitions for MDS and as per Savona et al (2015) definitions for MDS/MPN overlap syndromes, as applicable, will be estimated with its 95% CI.
- PFS and LFS will be estimated using the Kaplan-Meier method.

For participants with MM:

- Overall response rate, defined as the proportion of participants with stringent CR, CR, very good PR, and PR as per Kumar et al (2016), will be estimated with its 95% CI.
- PFS will be estimated using the Kaplan-Meier method.

10.4.2.2. Pharmacokinetics

[redacted]

10.4.2.3. Pharmacodynamics

[redacted]

10.4.3. Safety Analyses

Safety analyses will be conducted for the FAS population. Adverse events will be coded by the MedDRA dictionary, and treatment-emergent adverse events (ie, AEs reported for the first time

or worsening of a pre-existing event after first dose of study drug) 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 parameters, 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 disease 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 19).

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 20). Participants exhibiting clinically notable ECG abnormalities will be listed.

Table 19: 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

Table 20: 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 drug will be summarized by means of summary statistics.

10.4.4. Exploratory Analyses

[redacted]

[redacted]

10.5. Interim Analysis

Safety data will be monitored continuously in order to determine dosing in subsequent cohorts, per the algorithm in this Protocol.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol Amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC and health authorities before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both health authorities and IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study during the retention period without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.

- All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor's medical monitor before the end of the study. As part of his or her responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

11.2. Data Management

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

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the Protocol, such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and as designated by the sponsor, will have their own data flow management plans, 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 trial records that include all pertinent observations on each of the site's trial 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 trial necessary for the reconstruction and evaluation of the trial. 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 trial).
  - 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 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) by a specially designated photography vendor prior to sending the photographs to Incyte or any other third-party vendors for analysis or further processing.

- 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. 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 his/her 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 at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

12. REFERENCES

Andl T, Ahn K, Kairo A, et al. Epithelial Bmpr1a regulates differentiation and proliferation in postnatal hair follicles and is essential for tooth development. Development 2004;131:2257-2268.

Andriopoulos B Jr, Corradini E, Xia Y, et al. BMP6 is a key endogenous regulator of hepcidin expression and iron metabolism. Nat Genet 2009;41:482-487.

Armand P, Kim HT, Cutler CS, et al. Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation. Blood 2007;109:4586-4588.

Birgegård G, Gascón P, Ludwig H. Evaluation of anaemia in patients with multiple myeloma and lymphoma: findings of the European CANCER ANAEMIA SURVEY. Eur J Haematol 2006;77:378-386.

Blobe GC, Schiemann WP, Lodish HF. Role of transforming growth factor beta in human disease. N Engl J Med 2000;342:1350-1358.

Bondu S, Alary AS, Lefèvre C, et al. A variant erythroferrone disrupts iron homeostasis in SF3B1-mutated myelodysplastic syndrome. Sci Transl Med 2019;11:eaav5467.

Bowen DT, Hellstrom-Lindberg E. Best supportive care for the anaemia of myelodysplasia: inclusion of recombinant erythropoietin therapy?. Leuk Res 2001;25:19-21.

Casadevall N. Update on the role of epoetin alfa in hematologic malignancies and myelodysplastic syndromes. Semin Oncol 1998;25(suppl 7):12-18.

Cella D, Kallich J, McDermott A, Xu X. The longitudinal relationship of hemoglobin, fatigue and quality of life in anemic cancer patients: results from five randomized clinical trials. Ann Oncol 2004;15:979-986.

Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419-425.

Chihara D, Ito H, Katanoda K, et al. Incidence of myelodysplastic syndrome in Japan. J Epidemiol 2014;24:469-473.

Clinical Trials Facilitation and Coordination Group. Recommendations related to contraception and pregnancy testing in clinical trials. 2020.

Cogle CR. Incidence and burden of the myelodysplastic syndromes. Curr Hematol Malig Rep 2015;10:272-281.

Cortelezzi A, Cattaneo C, Cristiani S, et al. Non-transferrin-bound iron in myelodysplastic syndromes: a marker of ineffective erythropoiesis? Hematol J 2000;1:153-158.

Dammacco F, Silvestris F, Castoldi GL, et al. The effectiveness and tolerability of epoetin alfa in patients with multiple myeloma refractory to chemotherapy. Int J Clin Lab Res 1998;28:127-134.

Dinmohamed AG, Visser O, van Norden Y, et al. Trends in incidence, initial treatment and survival of myelodysplastic syndromes: a population-based study of 5144 patients diagnosed in the Netherlands from 2001 to 2010. Eur J Cancer 2014;50:1004-1012.

Fenaux P, Adès L. How we treat lower-risk myelodysplastic syndromes. Blood 2013;121:4280-4286.

Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374-1403.

Food and Drug Administration. Guidance for Industry: S9 Nonclinical Evaluation for Anticancer Pharmaceuticals. 2010.

Food and Drug Administration. Guidance for Industry: Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals. 2019.

Gallitz I, Lofruthe N, Traeger L, et al. Deficiency of the BMP Type I receptor ALK3 partly protects mice from anemia of inflammation. BMC Physiol 2018;18:3.

Gangat N, Patnaik MM, Begna K, et al. Survival trends in primary myelodysplastic syndromes: a comparative analysis of 1000 patients by year of diagnosis and treatment. Blood Cancer J 2016;6:e414.

Ganz T. Anemia of inflammation. N Engl J Med 2019;381:1148-1157.

Ganz T, Nemeth E. Hepcidin and disorders of iron metabolism. Annu Rev Med 2011;62:347-360.

Goldberg SL, Chen E, Corral M, et al. Incidence and clinical complications of myelodysplastic syndromes among United States Medicare beneficiaries. J Clin Oncol 2010;28:2847-2852.

Goodnough LT. Erythropoietin and iron-restricted erythropoiesis. Exp Hematol 2007;35(suppl 1):167-172.

Ibricevic-Balic L, Icindic-Nakas E, Hasic S, Kiseljakovic E, Sofo-Hafizovic A, Balic S. Dilemma: correlation between serum level of hepcidin and IL-6 in anemic myeloma patients. Med Arch 2016;70:429-432.

INCB000928 Investigator's Brochure. Wilmington, DE: Incyte Corporation.

Jones HB, Björkman JA, Schofield J. Coronary and systemic arterial physiology and immunohistochemical markers related to early coronary arterial lesions in beagle dogs given the potassium channel opener, ZD6169, or the endothelin receptor antagonist, ZD1611. Toxicol Pathol 2013;41:722-735.

Katodritou E, Verrou E, Hadjiaggelidou C, et al. Erythropoiesis-stimulating agents are associated with reduced survival in patients with multiple myeloma. Am J Hematol 2008;83:697-701.

Kelaidi C, Stamatoullas A, Beyne-Rauzy O, et al. Daily practice management of myelodysplastic syndromes in France: data from 907 patients in a one-week cross-sectional study by the Groupe Francophone des Myelodysplasies. Haematologica 2010;95:892-899.

König C, Kleber M, Ihorst G, et al. Prevalence of iron overload vs iron deficiency in multiple myeloma: resembling or different from MDS--and stem cell transplant (SCT)--patients?. Clin Lymphoma Myeloma Leuk 2013;13:671-680.e3.

Kuijpers MH, van de Kooij AJ, Slootweg PJ. The rat incisor in toxicologic pathology. Toxicol Pathol 1996;24:346-360.

Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016;17:e328-e346.

Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003;78:21-33.

Kyle RA, Rajkumar SV. Multiple myeloma [published correction appears in N Engl J Med 2005;352:1163]. N Engl J Med 2004;351:1860-1873.

Kyle RA, Rajkumar SV. Multiple myeloma. Blood 2008;111:2962-2972.

Leyland-Jones B, Bondarenko I, Nemsadze G, et al. A randomized, open-label, multicenter, phase III study of epoetin alfa versus best standard of care in anemic patients with metastatic breast cancer receiving standard chemotherapy. J Clin Oncol 2016;34:1197-1207.

Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. J Clin Oncol 2005;23:5960-5972.

Liu S, Yuan Y. Bayesian optimal interval designs for phase I clinical trials. J R Stat Soc C 2015;64:507-523.

Ma X. Epidemiology of myelodysplastic syndromes. Am J Med 2012;125(suppl):S2-S5.

Ma X, Does M, Raza A, Mayne ST. Myelodysplastic syndromes: incidence and survival in the United States. Cancer 2007;109:1536-1542.

Maes K, Nemeth E, Roodman GD, et al. In anemia of multiple myeloma, hepcidin is induced by increased bone morphogenetic protein 2. Blood 2010;116:3635-3644.

Malcovati L, Della Porta MG, Laarakkers CM, et al. Erythroid activity, transfusion iron overload, and hepcidin levels in patient with myelodysplastic syndrome. Blood 2008;112:2676 [abstr].

Malcovati L, Della Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. J Clin Oncol 2005;23:7594-7603.

Massagué J, Wotton D. Transcriptional control by the TGF-beta/Smad signaling system. EMBO J 2000;19:1745-1754.

McQuilten ZK, Polizzotto MN, Wood EM, Sundararajan V. Myelodysplastic syndrome incidence, transfusion dependence, health care use, and complications: an Australian population-based study 1998 to 2008. Transfusion 2013;53:1714-1721.

Mei S, Wang H, Fu R, et al. Hepcidin and GDF15 in anemia of multiple myeloma. Int J Hematol 2014;100:266-273.

Meynard D, Kautz L, Darnaud V, Canonne-Hergaux F, Coppin H, Roth MP. Lack of the bone morphogenetic protein BMP6 induces massive iron overload. Nat Genet 2009;41:478-481.

Ming Kwan K, Li AG, Wang XJ, Wurst W, Behringer RR. Essential roles of BMPR-IA signaling in differentiation and growth of hair follicles and in skin tumorigenesis. Genesis 2004;39:10-25.

National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017.

Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science 2004;306:2090-2093.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Osterborg A, Boogaerts MA, Cimino R, et al. Recombinant human erythropoietin in transfusion-dependent anemic patients with multiple myeloma and non-Hodgkin's lymphoma--a randomized multicenter study. The European Study Group of Erythropoietin (Epoetin Beta) Treatment in Multiple Myeloma and Non-Hodgkin's Lymphoma. Blood 1996;87:2675-2682.

Ozkurt ZN, Yegin ZA, Suyani E, et al. Factors affecting stem cell mobilization for autologous hematopoietic stem cell transplantation. J Clin Apher 2010;25:280-286.

Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011;364:1046-1060.

Park S, Grabar S, Kelaidi C, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood 2008;111:574-582.

Pullarkat V. Objectives of iron chelation therapy in myelodysplastic syndromes: more than meets the eye? Blood 2009;114:5251-5255.

Rollison DE, Howlader N, Smith MT, et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004: utilizing data from the NAACCR and SEER programs. Blood 2008;112:45-52.

Ross SL, Tran L, Winters A, et al. Molecular mechanism of hepcidin-mediated ferroportin internalization requires ferroportin lysines, not tyrosines or JAK-STAT. Cell Metab 2012;15:905-917.

Sant M, Minicozzi P, Mounier M, et al. Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EUROCARE-5, a population-based study [published correction appears in Lancet Oncol 2014;15:417]. Lancet Oncol 2014;15:931-942.

Santini V. Clinical use of erythropoietic stimulating agents in myelodysplastic syndromes. Oncologist 2011a;16(suppl 3):35 - 42.

Santini V, Girelli D, Sanna A, et al. Hepcidin levels and their determinants in different types of myelodysplastic syndromes. PLoS One 2011b;6:e23109.

Savona MR, Malcovati L, Komrokji R, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. Blood 2015;125:1857-1865.

Sharma S, Nemeth E, Chen YH, et al. Involvement of hepcidin in the anemia of multiple myeloma. Clin Cancer Res 2008;14:3262-3267.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7-30.

Steinbicker AU, Bartnikas TB, Lohmeyer LK, et al. Perturbation of hepcidin expression by BMP type I receptor deletion induces iron overload in mice. Blood 2011a;118:4224-4230.

Steinbicker AU, Sachidanandan C, Vonner AJ, et al. Inhibition of bone morphogenetic protein signaling attenuates anemia associated with inflammation. Blood 2011b;117:4915-4923.

Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th rev ed. Lyon, France: IARC Press, 2017.

Taylor KR, Vinci M, Bullock AN, Jones C. ACVR1 mutations in DIPG: lessons learned from FOP. Cancer Res 2014;74:4565-4570.

Terpos E, Kleber M, Engelhardt M, et al. European Myeloma Network guidelines for the management of multiple myeloma-related complications. Haematologica 2015;100:1254-1266.

Theurl I, Schroll A, Nairz M, et al. Pathways for the regulation of hepcidin expression in anemia of chronic disease and iron deficiency anemia in vivo. Haematologica 2011;96:1761-1769.

Thomas G, Ali S, Hoebers FJ, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. Gynecol Oncol 2008;108:317-325.

Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev 2012;12:CD003407.

University of Washington School of Pharmacy. Drug Interaction Database Program. 2002. http://www.druginteractioninfo.org.

Untch M, von Minckwitz G, Konecny GE, et al. PREPARE trial: a randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel, and CMF versus a standard-dosed epirubicin-cyclophosphamide followed by paclitaxel with or without darbepoetin alfa in primary breast cancer--outcome on prognosis. Ann Oncol 2011;22:1999-2006.

Vanderkerken K, Asosingh K, Croucher P, Van Camp B. Multiple myeloma biology: lessons from the 5TMM models. Immunol Rev 2003;194:196-206.

VanderWall K, Daniels-Wells TR, Penichet M, Lichtenstein A. Iron in multiple myeloma. Crit Rev Oncog 2013;18:449-461.

Vanuytsel T, Senger S, Fasano A, Shea-Donohue T. Major signaling pathways in intestinal stem cells. Biochim Biophys Acta 2013;1830:2410-2426.

Victor M, Evgeniy H, Gergana T, et al. Serum hepcidin levels in multiple myeloma. Clin Lab 2017;63:1273-1277.

Wang Y, Li L, Zheng Y, et al. BMP activity is required for tooth development from the lamina to bud stage. J Dent Res 2012;91:690-695.

Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352:1011-1023.

Zhao N, Zhang AS, Enns CA. Iron regulation by hepcidin. J Clin Invest 2013;123:2337-2343.

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].
  - 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. – transdermal. • Progestogen-only hormonal contraception associated with inhibition of ovulation[d] – oral – injectable – implantable[e] • Intrauterine device[e] • Intrauterine hormone-releasing system[e] • Bilateral tubal occlusion[e] • Vasectomized partner[e,f] • Sexual abstinence[c]

[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. 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 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 with a full glass of water (about 150 mL).
- 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 a dose of INCB000928 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 C. 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 drug.

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

REVIEW AND ASSESSMENT

No later than 3 weeks after the biochemistry abnormality was initially detected and the criteria for PHL were 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. 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 gallbladder 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 CRF if possible.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the standard study processes.
- Have the participant resume study drug as per Protocol guidelines.

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

- Have the participant permanently discontinue study drug and perform EOT 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 D. 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 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 in the eCRF.

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 vaccine (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 E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	17 NOV 2020
Amendment 2	08 APR 2021
Amendment 3	22 DEC 2021
Amendment 4	20 DEC 2022
Amendment 5	06 DEC 2023

Amendment 5 (06 DEC 2023)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to reduce the investigational sampling for participants on the study following the Sponsor's strategic decision to stop further recruitment. Participants will be followed for efficacy and safety while on study but no further PK or PD/translational sampling will occur. Unnecessary assessments or samples have also been removed. Changes are summarized below.

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

   Description of change: Updated the Day 15 hemoglobin assessments to be mandatory only at Cycles 2 to 6.

   Rationale for change: Removal of unnecessary assessments.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.3.5.2, Triplicate 12-Lead ECGs (Table 15: Schedule of Cardiac Function Assessments)**

   Description of change: Removed 12-lead ECG postdose assessment at Cycle 3 Day 1 and Cycle 6 Day 1.

   Rationale for change: Removal of unnecessary assessments.

3. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 8.5.1, Blood Sample Collection (Table 17: Pharmacokinetic Blood Sample Timing); Section 8.6, Pharmacodynamic and Translational Assessments; Section 8.6.1, Blood and Bone Marrow Sample Collection (Table 18: Biomarker/ Translational Sample Timing); Section 8.6.2, Pharmacodynamic and Translational Research Parameters**

   Description of change: Removed the PK and PD/translational samples from Cycles 3 to 6.

   Rationale for change: Removal of unnecessary assessments.

4. **Section 4.3, Study Termination**

   Description of change: Added timing to indicate when the study will be considered closed for data collection for the primary analysis.

   Rationale for change: Clarification.

5. **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 4 (20 DEC 2022)

Overall Rationale for the Amendment:

The rationale for this amendment is to implement changes to clarify the dose-expansion scheme and to allow a more complete exploration of the safety and efficacy of 1 or more RDE(s). Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 4.1.1, Dose Escalation and De-Escalation Algorithm; Section 4.1.3, Expansion Stages; Section 6.5.4, Definition of the Recommended Dose for Expansion; Section 10.1.2, Dose Expansion**

   Description of change: The identification of 1 or more RDE(s) in each disease group and the expansion of each RDE into the dose-expansion stages have been added. As a result, the sample size increased from 80 to 120 participants.

   Rationale for change: The safety and efficacy of INCB000928 in MDS or MM participants will be further explored by expanding 1 or more RDE dose(s).

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.3.5, Cardiac Function Assessments (Table 15: Schedule of Cardiac Function Assessments)**

   Description of change: Added triplicate ECGs to screening and on Cycle 1 Days 1 and 15, and on Cycles 3 and 6 Day 1, to align with the PK or PD sampling schedule. Additional 12-lead ECGs were added to be performed predose on Cycle 2 Day 1 and postdose on Cycles 3 and 6 Day 1.

   Rationale for change: To include cardiac parameter measurements via triplicate ECG to evaluate the effects of the study drug on the cardiac parameters.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.2.1, Efficacy Assessments for All Disease Groups**

   Description of change: Clarified that the recording of Hgb and RBC transfusions are mandatory within 8 weeks prior to Cycle 1 Day 1.

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

4. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 8.5.1, Blood Sample Collection (Table 17: Pharmacokinetic Blood Sample Timing); Section 8.6.1, Blood and Bone Marrow Sample Collection (Table 18: Biomarker/ Translational Sample Timing)**

   Description of change: Additional blood samples that will be collected for PD and PK purposes have been added on to Cycle 3 and Cycle 6 Day 1 between 4 and 8 hours postdose. For plasma PD samples only, clarification was added to state that samples are to be collected until Cycle 24 Day 1.

   Rationale for change: To better assess the PD and PK profiles of the study drug.

5. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 8.6.1, Blood and Bone Marrow Sample Collection (Table 18: Biomarker/Translational Sample Timing)**

   Description of change: Updated to include an additional collection timepoint (Cycle 7 Day 1) for serum biomarkers.

   Rationale for change: To better assess the PD profile of the study drug.

6. **Section 2.3.2, Role of Hepcidin in Myelodysplastic Syndrome– and Multiple Myeloma–Related Anemia; Section 5.1, Inclusion Criteria**

   Description of change: For inclusion criterion 6a, the eligibility criteria regarding definition of anemia was clarified. For inclusion criterion 10, patients with MDS-RS and MDS/MPN overlap syndromes with ring sideroblasts and thrombocytosis are now allowed in the study and as a result the text regarding exclusion from study of participants with MDS-RS and MDS/MPN overlap syndromes with ring sideroblasts and thrombocytosis has been removed.

   Rationale for change: To allow more flexibility to the investigators to enroll study participants.

7. **Section 4.1.1, Dose Escalation and De-Escalation (Table 9: Decision Boundaries)**

   Description of change: A table detailing the decision boundaries in the Dose escalation stages and the definition of the RDE have been added.

   Rationale for change: Clarification of the decision boundaries in the Dose escalation stages and the definition of the RDE.

8. **Section 4.1.3, Expansion Stages**

   Description of change: Added the percentage of transfusion-dependent participants to be enrolled in each expansion cohort.

   Rationale for change: To clarify the percentage of transfusion-dependent participants to be enrolled in each expansion cohort to obtain relevant results.

9. **Section 5.2, Exclusion Criteria (Exclusion Criteria 5 and 9)**

   Description of change: For exclusion criterion 5, the time before first dose of study drug was updated. For exclusion criterion 9, the number of previous years of active invasive malignancy were updated.

   Rationale for change: To allow more flexibility to the investigators to enroll study participants.

10. **Section 5.2, Exclusion Criteria (Exclusion Criterion 12)**

    Description of change: Clarified that only participants with left bundle branch block will be excluded if determined to be clinically significant by investigator.

    Rationale for change: To clarify the eligibility criterion regarding presence of left bundle branch block.

11. **Section 5.2, Exclusion Criteria (Exclusion Criterion 14)**

    Description of change: Clarified that hemochromatosis is to be hereditary.

    Rationale for change: Clarification.

12. **Section 5.2, Exclusion Criteria (Exclusion Criterion 15)**

    Description of change: Revised definitions of hepatitis A, B, and C.

    Rationale for change: Clarification of the definition and harmonization across studies.

13. **Section 5.2, Exclusion Criteria (Exclusion Criterion 25)**

    Description of change: Removed the eligibility criterion for ALP (exclusion criterion 25f). Lowered the thresholds for platelet and ANC values (exclusion criteria 25a and 25b, respectively) to allow enrollment in the study.

    Rationale for change: To allow more flexibility to the investigators to enroll study participants.

14. **Section 5.2 Exclusion Criteria (Exclusion Criterion 25g); Section 8.3.6, Iron Overload Assessment**

    Description of change: 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 no available has been added.

    Rationale for change: Clarified based on request from key investigators.

15. **Section 5.2, Exclusion Criteria (Exclusion Criterion 26)**

    Description of change: Added to allow for iron chelation treatment.

    Rationale for change: To allow more flexibility to the investigators to enroll study participants.

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

    Description of change: Clarified that additional blood samples may be drawn to more precisely characterize a potential DLT event.

    Rationale for change: To allow a better assessment of any potential DLT.

17. **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.

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

    Description of change: Clarified the conditions for intraparticipant dose increase has been added.

    Rationale for change: Clarification.

19. **Section 8.5.1, Blood Sample Collection (Table 17: Pharmacokinetic Blood Sample Timing); Section 8.6.1, Blood and Bone Marrow Sample Collection (Table 18: Biomarker/Translational Sample Timing)**

    Description of change: The 2- and 4-hour postdose PK and transitional blood samples to be drawn on Cycle 1 Day 1 and Cycle 1 Day 15 can be performed with a time-window of ± 15 minutes.

    Rationale for change: To add flexibility to draw PK and translational blood samples as requested by key investigators.

20. **Section 10.4.2.2; Pharmacokinetics; Section 10.4.2.3, Pharmacodynamics; Section 10.4.4; Exploratory Analyses**

    Description of change: [redacted]

    Rationale for change: Clarification.

21. **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 3 (22 DEC 2021)

Overall Rationale for the Amendment:

The rationale for this amendment is to implement changes to clarify the dose-escalation scheme.

1. **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 4.1.1, Dose Escalation and De-Escalation Algorithm; Section 4.1.3, Expansion Stages; Section 6.1, Study Treatment Administered (Table 12: Study Treatment Information); Section 6.5.2.2, Intercohort Dose Increase Algorithm; Section 6.5.4, Definition of the Recommended Dose for Expansion; Section 6.6.5, Criteria and Procedures for Dose Increases of Study Drug; Section 10.1.1, Dose Escalation; Section 10.4.1, Primary Analysis: Safety**

   Description of change: Data from participants in both disease groups will be evaluated together in the dose-escalation stage of the study.

   Rationale for change: To enable the dose-escalation cohorts to be composed of participants from both disease groups.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.2.1, Efficacy Assessments for All Disease Groups; Section 8.3.6, Iron Overload Assessment; Section 8.6.1, Blood and Bone Marrow Sample Collection (Table 19: Biomarker/Translational Sample Timing)**

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

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

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities; Table 4: Schedule of Laboratory Assessments); Section 5.2, Exclusion Criteria (Table 11: Exclusionary Laboratory Values); Section 6.6.3, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 14: 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 potential iron overload. Table 11 and Table 14 were updated to specify the rules for participant eligibility and the rules for study drug interruption/restarting based on the participant's serum ferritin levels.

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

4. **Section 2.3.4, Justification for Starting Dose; Section 2.3.5, Updated Data From Ongoing Clinical Trials**

   Description of change: Updated Section 2.3.4 and added Section 2.3.5 to reflect latest clinical data on INCB000928.

   Rationale for change: To align with latest clinical data.

5. **Section 4.1.2, Exploration of Alternative Administration Schedules; Section 6.1, Study Treatment Administered (Table 12: Study Treatment Information); Section 8.5.1, Blood Sample Collection**

   Description of change: Added the possibility to explore alternative administration schedules and 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.

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

   Description of change: Revised to allow dose escalation after a participant has received only 2 cycles of study drug treatment, instead of 6 cycles, and added that dose escalation can occur if a participant is still receiving RBC transfusions or there is an Hgb increase of < 1.5 g/dL in any of their assessments.

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

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 2 (08 APR 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 4: Schedule of Laboratory Assessments); Section 3, Objectives and Endpoints (Table 10: Objectives and Endpoints); Section 8.6.1, Blood Sample Collection (Table 20: Biomarker/Translational Sample Timing); Section 8.6.2, Pharmacodynamic and Translational Research Parameters; Section 10.2, Populations for Analysis (Table 21: Populations for Analysis); Section 10.4.4, Exploratory Analyses**

   Description of change: [redacted]

   Rationale for change: Clarification and incorporation of clinically relevant PD biomarkers.

2. **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 20: Biomarker/Translational Sample Timing); Section 8.6.2, Pharmacodynamic and Translational Research Parameters; Section 10.4.4, Exploratory Analyses**

   Description of change: [redacted]

   Rationale for change: [redacted]

3. **Section 1, Protocol Summary; Section 8, Study Assessments and Procedures; 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 procedure manual have been replaced with the investigator site file.

   Rationale for change: Clarification.

4. **Section 2.3.4, Justification for Starting 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.

5. **Section 5.1, Inclusion Criteria (Criterion 5); Section 5.2, Exclusion Criteria (Criterion 15); 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**

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

   Rationale for change: Template updated.

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

   Description of change: Clarification of the eligibility thresholds for bilirubin and direct bilirubin values has been added.

   Rationale for change: Clarification.

7. **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: Incorporated guidance for study treatment interruption/restart if a participant enters the study with a high serum ferritin level.

   Rationale for change: Clarification.

8. **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.

9. **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.

10. **Section 8.4, Laboratory Assessments (Table 18: 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.

11. **Section 8.4, Laboratory Assessments (Table 18: Required Laboratory Analytes); Section 8.6.2, Pharmacodynamic and Translational Research Parameters; Section 10.4.2.3, Pharmacodynamics**

    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. In addition, the analyte [redacted].

    Rationale for change: Clarification of laboratory assessments.

12. **Appendix D, 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.

13. **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 (17 NOV 2020)

Overall Rationale for the Amendment:

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

1. **Section 4.3, Study Termination**

   Description of change: Enrollment hold and stopping rules were added that further enrollment of participants will be suspended if 1) more than 1 participant in the first 5 participants enrolled in a specific disease 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 disease group have an AE ≥ Grade 3 that is attributable to the investigational agent.

   Rationale for change: Dosing stopping rules at a population level in dose expansion cohorts were added to the Protocol.

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Approval Task	[redacted] Approver [redacted], Biostatistics 06-Dec-2023 15:19:52 GMT+0000
Approval Task	[redacted] Approver [redacted]of Early Development 06-Dec-2023 15:31:25 GMT+0000
Approval Task	[redacted] Document Preparer [redacted] Clinical Research Scientist 06-Dec-2023 15:48:11 GMT+0000
Approval Task	[redacted] Approver [redacted] Early Clinical Development 06-Dec-2023 17:59:00 GMT+0000
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