Official Title:	**A Randomized Open-Label Phase 1/2 Study of INCB001158 Combined With Subcutaneous (SC) Daratumumab, Compared to Daratumumab SC, in Participants With Relapsed or Refractory Multiple Myeloma**
NCT Number:	NCT03837509
Document Date:	Clinical Study Protocol Amendment 2: 01 December 2021

Clinical Study Protocol

INCB 01158-206

A Randomized Open-Label Phase 1/2 Study of INCB001158 Combined With Subcutaneous (SC) Daratumumab, Compared to Daratumumab SC, in Participants With Relapsed or Refractory Multiple Myeloma

Product:	**INCB001158**
IND Number:	[redacted]
EudraCT Number:	**2018-004076-35**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**25 JAN 2019**
Amendment (Version) 1:	**11 MAR 2019**
Amendment (Version) 1-EU:	**18 MAR 2019**
Amendment (Version) 1-DE:	**16 JUL 2019**
Amendment (Version) 2:	**12 OCT 2020**
Amendment (Version) 3:	**01 DEC 2021**

INVESTIGATOR'S AGREEMENT

I have read the INCB 01158-206 Protocol Amendment 3 (dated 01 DEC 2021) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
[redacted]	[redacted]
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	antibodies to hepatitis B core antigen
anti-HBs	antibodies to hepatitis B surface antigen
AST	aspartate aminotransferase
BID	twice daily
BOIN	Bayesian Optimal Interval
Bregs	regulatory B cells
BUN	blood urea nitrogen
CDC	complement-dependent cytotoxicity
CFR	Code of Federal Regulations
[redacted]	[redacted]
C_{min}	minimum observed plasma or serum concentration over the dose interval
COPD	chronic obstructive pulmonary disease
CR	complete response
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
Dara	daratumumab
DIRA	daratumumab interference reflex assay
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram

Abbreviations and Special Terms	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FFPE	formalin-fixed, paraffin embedded
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte macrophage colony-stimulating factor
[redacted]	[redacted]
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IFE	immunofixation
IFN-γ	interferon gamma
Ig	immunoglobulin
IHC	immunohistochemistry
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IPPI	Investigational Product Preparation Instructions

Abbreviations and Special Terms	Definition
irAE	immune-related adverse event
IRB	institutional review board
IRR	systemic injection-related reaction for SC daratumumab; infusion-related reaction for IV daratumumab
IRT	interactive response technology
IV	intravenous
LDL	low-density lipoprotein
MDSC	myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	modified FOLFOX6 (leucovorin, 5-fluorouracil, and oxaliplatin)
MM	multiple myeloma
M-protein	monoclonal protein
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NGS	next generation sequencing
NK	natural killer
ORR	objective response rate
OS	overall survival
PAD	pharmacologically active dose
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1 receptor
PFS	progression-free survival
PI	proteasome inhibitor
[redacted]	[redacted]
PMN	polymorphonuclear neutrophils
PO	per os

Abbreviations and Special Terms	Definition
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
PPoS	posterior probability of success
PR	partial response
QW	once every week
QXW	once every X weeks
RAR	response adaptive randomization
RBC	red blood cell
rHuPH20	recombinant human hyaluronidase
RNA	ribonucleic acid
RNA-seq	ribonucleic acid sequencing
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SC	subcutaneous
sCR	stringent complete response
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIPPM	Site Investigational Product and Procedures Manual
SmPC	summary of product characteristics
[redacted]	[redacted]
SoA	schedule of activities
SOP	standard operating procedure
SPD	sum of the products of the maximal perpendicular diameters of measured lesions
SPEP	serum M-protein quantitation by electrophoresis
study drug	INCB001158
study treatment	This term refers to all medications that the participant is required to receive as part of this study.
T1DM	Type 1 diabetes mellitus
TAM	tumor-associated macrophages
TCR	T-cell receptor

Abbreviations and Special Terms	Definition
TEAE	treatment-emergent adverse event, AEs reported for the first time or worsening of a pre-existing event after first dose of study treatment
[redacted]	[redacted]
TSH	thyroid-stimulating hormone
TTR	time to response
ULN	upper limit of normal
UPEP	urine M-protein quantitation by electrophoresis
[redacted]	[redacted]
VGPR	very good partial response
WBC	white blood cell

1. PROTOCOL SUMMARY

Protocol Title: A Randomized Open-Label Phase 1/2 Study of INCB001158 Combined With Subcutaneous (SC) Daratumumab, Compared to Daratumumab SC, in Participants With Relapsed or Refractory Multiple Myeloma

Protocol Number: INCB 001158-206

Objectives and Endpoints:

Table 1 presents the primary objectives and endpoints.

Table 1: Primary Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1: To determine the safety, tolerability, and RP2D of INCB001158 in combination with daratumumab SC.	Safety and tolerability determined by monitoring the frequency, duration, and severity of AEs.
Phase 2: To compare the ORR of the RP2D of INCB001158 in combination with daratumumab SC to daratumumab SC monotherapy.	ORR, defined as the proportion of participants with a documented response PR or better, as per IMWG criteria.

Overall Design:

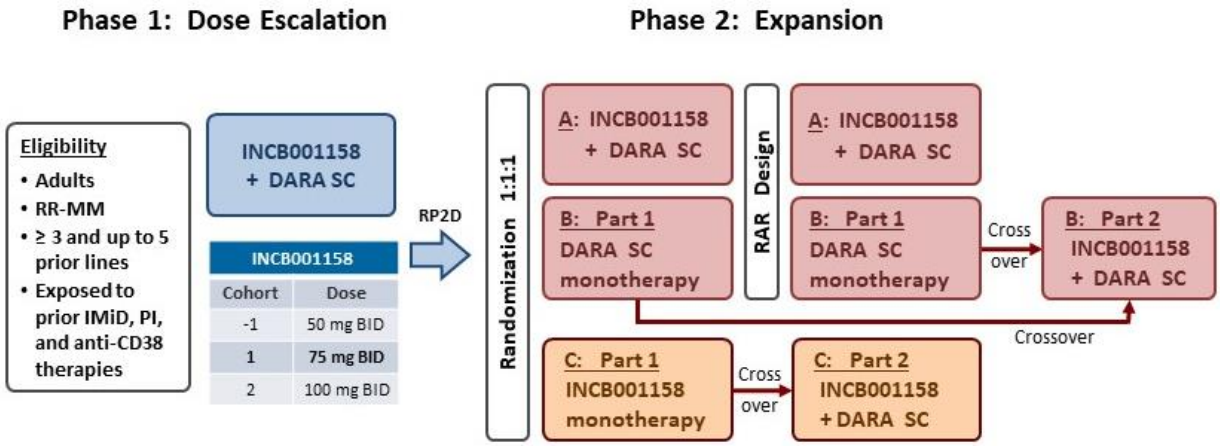
This study will evaluate the safety and efficacy of INCB001158 in combination with daratumumab SC in participants with relapsed or refractory MM, based on the hypothesis that INCB001158 in combination with daratumumab SC will improve response rates compared with daratumumab SC alone.

Table 2 presents the key study design elements. Further details are presented after the table in the study design schema (see Figure 1).

Table 2: Key Study Design Elements

Study Phase	Phase 1/2
Clinical Indication	Multiple myeloma
Population	Male and female participants ≥ 18 years of age who have relapsed or refractory MM.
Number of Participants	Phase 1: Approximately up to 18 evaluable participants will be enrolled. Phase 2: Approximately up to 80 evaluable participants will be enrolled.
Study Design	Open-label, dose-escalation Phase 1 and randomized Phase 2 study.
Estimated Duration of Study Participation	Up to 28 days for screening, continuous treatment in consecutive 28-day cycles as long as participants are receiving benefit and have not met any criteria for study withdrawal, and every 8 to 12 weeks for follow-up. *NOTE:* As of Protocol Amendment 3, no further disease status and survival follow-up assessments will be required beyond the last safety follow-up visit.
Coordinating Principal Investigator	[redacted], MD

Figure 1: Study Design Schema



Treatment Groups and Duration:

The study consists of 2 parts: 1) a Phase 1 dose escalation to define the RP2D of INCB001158 in combination with daratumumab SC, and 2) a Phase 2 expansion to assess the clinical benefit of the RP2D of INCB001158 in combination with daratumumab SC compared with daratumumab SC alone, or as monotherapy.

In Phase 1 eligible participants will receive continuous treatment of INCB001158 at escalating dose levels in combination with daratumumab SC, as long as participants are receiving benefit and have not met any criteria for study withdrawal. Daratumumab SC treatment will consist of subcutaneous injections of 1800 mg once weekly for Cycles 1 and 2, once every 2 weeks for Cycles 3 to 6, and once every 4 weeks thereafter (28-day treatment cycle). At the discretion of the sponsor, up to 6 additional "backfill" participants may be enrolled at any tolerable dose level to further investigate safety, efficacy [redacted].

In Phase 2 eligible participants will be initially equally randomized (1:1:1) into 3 treatment groups of 10 participants per group:

- Treatment Group A: continuous treatment of the RP2D of INCB001158 in combination with daratumumab SC, as long as participants are receiving benefit and have not met any criteria for study withdrawal.
- Treatment Group B: daratumumab SC alone (Treatment Group B – Part 1), as long as participants are receiving benefit and have not met any criteria for study withdrawal. At the time of confirmed disease progression participants will cross over to INCB001158 + daratumumab SC (Treatment Group B – Part 2) and continue treatment until PD, or unacceptable toxicity, or any criteria for study withdrawal.
- Treatment Group C: continuous treatment of INCB001158 alone at the RP2D determined in Phase 1, for at least 2 cycles if the participants are not progressing, and beyond Cycle 2 only if they are receiving clinical benefit and have not met any criteria for study withdrawal (Treatment Group C – Part 1). At the time of confirmed disease progression participants will then cross over to INCB001158 + daratumumab SC (Treatment Group C – Part 2) and continue treatment until PD, or unacceptable toxicity, or any criteria for study withdrawal.

After the equal randomization period, an RAR design will be used to compare the ORR of Treatment Groups A and B with adjustments to the randomization rate based on the observed ORR. Evaluation of the safety and tolerability of the 3 treatment groups will be performed periodically throughout the study. Details of the randomization method and model for response are provided in the Statistical Methods section. Participants will be analyzed for efficacy based on the treatment group in which they were randomized.

Table 3 and Table 4 present the SoA for study site visit assessments prior and post-crossover respectively. Table 5 and Table 6 present the schedule of laboratory assessments prior and post-crossover respectively. As of Protocol Amendment 3, only the SoA presented in Table 7 will be used. Table 22 presents the safety laboratory analytes to be evaluated. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

NOTE: As of Protocol Amendment 3, no further disease status and survival follow-up assessments will be required beyond the last safety follow-up visit.

Table 3: Schedule of Activities for Participants in Phase 1, Phase 2, Treatment Group A, Treatment Group B – Part 1 (Prior to Crossover), and Treatment Group C – Part 1 (Prior to Crossover)

	Screening	Treatment (28-day Cycles)							EOT	Follow-Up			
		Cycles 1 and 2				Cycles 3 to 6		Cycles 7+		Safety	Disease Status	Survival	
Visit Day (Range)	Days -28 to -1	D1	D8 (± 2d)	D15 (± 2d)	D22 (± 2d)	D1 (± 3d)	D15 (± 3d)	D1 (± 3d)	+ 7d	28-35d After EOT	Q8W After EOT ± 7d	Q12W After EOT ± 7d	Notes
Administrative procedures													
Informed consent	X												See Section 8.1.1.
Contact IRT	X	X	X	X	X	X	X	X	X				See Section 8.1.3.
Inclusion/exclusion criteria	X	X											See Section 5.
General and medical history	X												See Section 8.1.5.
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X			See Section 6.8.
Distribute reminder cards		X	X	X	X	X	X	X					See Section 8.1.4.
Assess study treatment compliance		X*				X		X	X				* C2D1 only. See Section 6.4.
Study treatment													
Dispense/administer INCB001158 (participants receiving INCB001158 monotherapy or in combination with daratumumab SC)		X	X	X	X	X	X	X					In clinic, should be given just before administration of daratumumab SC (if applicable). See Section 6.1, Appendix B, and refer to the Pharmacy Manual.
Administer daratumumab SC (participants receiving daratumumab SC monotherapy or in combination with INCB001158)		X	X	X	X	X	X	X					In clinic, should be administered after INCB001158 (if applicable). See Section 6.1, Appendix C, and refer to the Pharmacy Manual.

Table 3: Schedule of Activities for Participants in Phase 1, Phase 2, Treatment Group A, Treatment Group B – Part 1 (Prior to Crossover), and Treatment Group C – Part 1 (Prior to Crossover) (Continued)

	Screening	Treatment (28-day Cycles)							EOT	Follow-Up			
		Cycles 1 and 2				Cycles 3 to 6		Cycles 7+		Safety	Disease Status	Survival	
Visit Day (Range)	Days -28 to -1	D1	D8 (± 2d)	D15 (± 2d)	D22 (± 2d)	D1 (± 3d)	D15 (± 3d)	D1 (± 3d)	+ 7d	28-35d After EOT	Q8W After EOT ± 7d	Q12W After EOT ± 7d	Notes
Safety assessments													
AE assessments	X	X	X	X	X	X	X	X	X	X			See Section 8.3.1.
Forced expiratory volume test (participants with COPD or asthma)	X												See Section 8.3.2.
Physical examination, weight, height	X*	X	X	X	X	X		X	X	X			*Comprehensive examination and height at screening only, targeted physical examination thereafter. See Section 8.3.3.
Vital signs	X	X	X	X	X	X	X	X	X	X			See Section 8.3.4.
Electrocardiogram	X	X*				X**				X			* Predose and 2-4 h after morning dose. ** Predose on C3D1 and C6D1 only. See Section 8.3.5.
ECOG performance status	X	X	X	X	X	X	X	X	X	X			See Section 8.3.6.
Subsequent therapy status									X	X	X	X	See Section 8.8.2.
Survival status												X	See Section 8.8.3.
Efficacy/disease assessments (blood/urine) – samples to be sent to central laboratory													
Serum β2-microglobulin	X												See Section 8.2.1.4.
Quantitative Ig (IgA, IgM, IgG, IgD, IgE)	X					X*		X*	X				* Every 3 months during treatment (window of ± 1 month). See Section 8.2.1.2.
SPEP	X	X				X		X	X	X	X		SPEP and UPEP are to be performed within 14 days before Cycle 1 Day 1 and on the scheduled assessment days (± 3 d). See Section 8.2.1.2.
UPEP (24 h urine sample)	X	X				X		X	X	X	X		

Table 3: Schedule of Activities for Participants in Phase 1, Phase 2, Treatment Group A, Treatment Group B – Part 1 (Prior to Crossover), and Treatment Group C – Part 1 (Prior to Crossover) (Continued)

	Screening	Treatment (28-day Cycles)							EOT	Follow-Up			
		Cycles 1 and 2				Cycles 3 to 6		Cycles 7+		Safety	Disease Status	Survival	
Visit Day (Range)	Days -28 to -1	D1	D8 (± 2d)	D15 (± 2d)	D22 (± 2d)	D1 (± 3d)	D15 (± 3d)	D1 (± 3d)	+ 7d	28-35d After EOT	Q8W After EOT ± 7d	Q12W After EOT ± 7d	Notes
Serum calcium corrected for albumin	X	X				X		X	X	X	X		See Section 8.2.1.3.
Serum FLC & serum/urine immunofixation	X	X*				X*		X*	X*	X*	X*		To be performed when CR is suspected or maintained. * For participants with light chain only disease, serum FLC to be performed on Day 1 of each cycle, at EOT, and at safety and disease status follow-up. See Section 8.2.1.2.
Efficacy/disease assessments (other)													
Bone marrow aspirate/biopsy for assessment of MRD [redacted]	X*	Samples are requested at the time of suspected CR to confirm CR/sCR and to evaluate MRD. [redacted]							X**				Bone marrow samples to be collected at screening (up to 42 d before C1D1). *In the event a fresh screening biopsy will not be collected, use non-decalcified diagnostic tissue (ie, bone marrow aspirate slides or FFPE tissue). ** If feasible, collect at disease progression for participants who achieved PR/CR. See Sections 8.5.8 and 8.2.1.6.
Skeletal survey	X*	As clinically indicated											*For screening, up to 42 d before C1D1. See Section 8.2.1.7.
Assess extramedullary plasmacytomas	X*	Measurable sites every 4 weeks (if applicable; for physical examination) and every 12 weeks** (for radiologic examination) for participants with a history of plasmacytomas, or as clinically indicated for others.											*For screening, up to 42 d before C1D1. ** At 18 months after the participant's first dose, the timing of radiologic assessment of extramedullary plasmacytomas should follow the standard of care. See Section 8.2.1.8.

Table 4: Schedule of Activities for Participants in Phase 2, Treatment Group B – Part 2 and Treatment Group C – Part 2 (Who Cross Over)

	Treatment (28-day Cycles)								Follow-Up			
	Cycles 1 and 2				Cycles 3 to 6		Cycles 7+	EOT	Safety	Disease Status	Survival	
Visit Day (Range)	D1	D8 (± 2d)	D15 (± 2d)	D22 (± 2d)	D1 (± 3d)	D15 (± 3d)	D1 (± 3d)	+ 7d	28-35d After EOT	Q8W After EOT ± 7d	Q12W After EOT ± 7d	Notes
Administrative procedures												
Review criteria for crossover	X											
Concomitant medications	X	X	X	X	X	X	X	X	X			See Section 6.8.
Distribute reminder cards	X	X	X	X	X	X	X					See Section 8.1.4.
Assess study treatment compliance	X*				X		X	X				* C2D1 only. See Section 6.4.
Study treatment												
Dispense/administer INCB001158	X	X	X	X	X	X	X					In clinic, should be given just before administration of daratumumab SC. See Section 6.1, Appendix B, and refer to the Pharmacy Manual.
Administer daratumumab SC	X	X	X	X	X	X	X					In clinic, should be administered after INCB001158. See Section 6.1, Appendix C, and refer to the Pharmacy Manual.
Safety assessments												
AE assessments	X	X	X	X	X	X	X	X	X			See Section 8.3.1.
Vital signs	X	X	X	X	X	X	X	X	X			See Section 8.3.4.
Electrocardiogram	X*				X**				X			* Predose and 2-4 h after morning dose. ** Predose on C3D1 and C6D1 only. See Section 8.3.5.
ECOG performance status	X	X	X	X	X	X	X	X	X			See Section 8.3.6.
Subsequent therapy status								X	X	X	X	See Section 8.8.2.
Survival status											X	See Section 8.8.3.

Table 4: Schedule of Activities for Participants in Phase 2, Treatment Group B - Part 2 and Treatment Group C - Part 2 (Who Cross Over) (Continued)

	Treatment (28-day Cycles)								Follow-Up			
	Cycles 1 and 2				Cycles 3 to 6		Cycles 7+	EOT	Safety	Disease Status	Survival	
Visit Day (Range)	D1	D8 (± 2d)	D15 (± 2d)	D22 (± 2d)	D1 (± 3d)	D15 (± 3d)	D1 (± 3d)	+ 7d	28-35d After EOT	Q8W After EOT ± 7d	Q12W After EOT ± 7d	Notes
Efficacy/disease assessments (blood/urine) – samples to be sent to central laboratory												
Quantitative Ig (IgA, IgM, IgG, IgD, IgE)	X*				X**		X**	X				* Does not need to be repeated if collected at EOT prior to crossover ** Every 3 months during treatment (window of ± 1 month). See Section 8.2.1.2.
SPEP	X*				X		X	X	X	X		SPEP and UPEP are to be performed within 14 days before Cycle 1 Day 1 and on the scheduled assessment days (± 3 d). * Does not need to be repeated if collected at EOT prior to crossover See Section 8.2.1.2.
UPEP (24 h urine sample)	X*				X		X	X	X	X		
Serum calcium corrected for albumin	X*				X		X	X	X	X		* Does not need to be repeated if collected at EOT prior to crossover See Section 8.2.1.3.
Serum FLC & serum/urine immunofixation	X*				X**		X**	X**	X**	X**		To be performed when CR is suspected or maintained. * Does not need to be repeated if collected at EOT prior to crossover ** For participants with light chain only disease, serum FLC to be performed on Day 1 of each cycle, at EOT, and at safety and disease status follow-up. See Section 8.2.1.2.

Table 4: Schedule of Activities for Participants in Phase 2, Treatment Group B - Part 2 and Treatment Group C - Part 2 (Who Cross Over) (Continued)

	Treatment (28-day Cycles)								Follow-Up			
	Cycles 1 and 2				Cycles 3 to 6		Cycles 7+	EOT	Safety	Disease Status	Survival	
Visit Day (Range)	**D1**	**D8 (± 2d)**	**D15 (± 2d)**	**D22 (± 2d)**	**D1 (± 3d)**	**D15 (± 3d)**	**D1 (± 3d)**	**+ 7d**	**28-35d After EOT**	**Q8W After EOT ± 7d**	**Q12W After EOT ± 7d**	**Notes**
Efficacy/disease assessments (other)												
Skeletal survey	As clinically indicated											See Section 8.2.1.7.
Assess extramedullary plasmacytomas	Measurable sites every 4 weeks (if applicable; for physical examination) and every 12 weeks** (for radiologic examination) for participants with a history of plasmacytomas, or as clinically indicated for others.											** At 18 months after the participant's first dose, the timing of radiologic assessment of extramedullary plasmacytomas should follow the standard of care. See Section 8.2.1.8.

Table 5: Schedule of Laboratory Assessments for Participants in Phase 1, Phase 2, Treatment Group A, Treatment Group B – Part 1 (Prior to Crossover), and Treatment Group C – Part 1 (Prior to Crossover)

	Screening	Treatment (28-day Cycles)					EOT	Follow-Up	
		Cycles 1 and 2				Cycles 3+			
Visit Day (Range)	Days -28 to -1	D1	D8 (± 2d)	D15 (± 2d)	D22 (± 2d)	D1 (± 3d)	+ 7d	28-35d After EOT	Notes
Local laboratory assessments									
Blood type assessment	X								Record on participant's identification wallet card. See Section 8.3.7.1.
Chemistries	X	X*	X	X	X	X	X	X	* Does not need to be repeated if the screening assessment was performed within 7 days before C1D1, unless a clinically significant change is suspected. See Section 8.3.7.
Hematology	X	X*	X	X	X	X	X	X	
Lipid panel	X	X*				X	X	X	
Urinalysis	X	X*				X			
Thyroid panel	X	X*				X			
Pregnancy testing	X	X				X	X		All female participants of childbearing potential. Serum at screening and urine at Day 1 of each cycle, at EOT, and as medically indicated or per country or institutional requirements. See Section 8.3.7.5.
Serology	X/X*	X*							* For participants positive for anti-HBs or anti-HBc, HBV DNA testing must be performed at screening, every 12 weeks during treatment, at EOT, and Q12W for up to 6 months after the last dose of study treatment. See Section 8.3.7.6.
Blood sample for plasma ammonia levels	X	X*	X*	X*		X*			Collect during screening. If plasma ammonia is above ULN, repeat screening sample to confirm value. * Additional samples may be collected as clinically indicated according to urine orotic acid elevations. See Section 8.3.7.4.
Central laboratory assessments									
Urine sample for orotic acid		X	X*/**	X*		X			See Table 23 for sample collection times. * Cycle 1 only. ** C1D8 only for participants enrolled in Phase 1. Additional samples may be collected as clinically indicated. See Section 8.3.7.3.

Table 5: Schedule of Laboratory Assessments for Participants in Phase 1, Phase 2, Treatment Group A, Treatment Group B – Part 1 (Prior to Crossover), and Treatment Group C – Part 1 (Prior to Crossover) (Continued)

	Screening	Treatment (28-day Cycles)					Follow-Up	
		Cycles 1 and 2				Cycles 3+	EOT	
Visit Day (Range)	Days -28 to -1	D1	D8 (± 2d)	D15 (± 2d)	D22 (± 2d)	D1 (± 3d)	+ 7d	28-35d After EOT	Notes
Central laboratory assessments (continued)									
[redacted]									

Table 5: Schedule of Laboratory Assessments for Participants in Phase 1, Phase 2, Treatment Group A, Treatment Group B – Part 1 (Prior to Crossover), and Treatment Group C – Part 1 (Prior to Crossover) (Continued)

	Screening	Treatment (28-day Cycles)					EOT	Follow-Up	
		Cycles 1 and 2				Cycles 3+			
Visit Day (Range)	Days -28 to -1	D1	D8 (± 2d)	D15 (± 2d)	D22 (± 2d)	D1 (± 3d)	+ 7d	28-35d After EOT	Notes
[redacted]									

Table 6: Schedule of Laboratory Assessments for Participants in Phase 2, Treatment Group B – Part 2 and Treatment Group C – Part 2 (Who Cross Over)

	Treatment (28-day Cycles)					EOT	Follow-Up	
	Cycles 1 and 2				Cycles 3+			
Visit Day (Range)	**D1**	**D8 (± 2d)**	**D15 (± 2d)**	**D22 (± 2d)**	**D1 (± 3d)**	**+ 7d**	**28-35d After EOT**	**Notes**
Local laboratory assessments								
Chemistries	X*	X	X	X	X	X	X	* Does not need to be repeated if the EOT assessment prior to crossover was performed within 7 days before C1D1, unless a clinically significant change is suspected. See Section 8.3.7.
Hematology	X*	X	X	X	X	X	X	
Lipid panel	X*				X	X	X	
Urinalysis	X*				X			
Thyroid panel	X*				X			
Pregnancy testing	X				X	X		All female participants of childbearing potential. Urine at Day 1 of each cycle, at EOT, and as medically indicated or per country or institutional requirements. See Section 8.3.7.5.
Serology	X*							* For participants positive for anti-HBs or anti-HBc, HBV DNA testing must be performed every 12 weeks during treatment, at EOT, and Q12W for up to 6 months after the last dose of study treatment. See Section 8.3.7.6.
Blood sample for plasma ammonia levels	X*	X*	X*		X*			* Additional samples may be collected as clinically indicated according to urine orotic acid elevations. See Section 8.3.7.4.
Urine sample for orotic acid	X	X*	X*		X			See Table 23 for sample collection times. * Cycle 1 only. Additional samples may be collected as clinically indicated. See Section 8.3.7.3.
[redacted]								

Table 7: Schedule of Activities for All Participants (as of Protocol Amendment 3)

Procedure	Protocol Section	Treatment (28-Day Cycle)	EOT + 7 d	Safety Follow-Up 28-35 d After EOT	Notes
Informed consent	8.1.1	X			Participants will sign a new ICF as per Protocol Amendment 3.
Contact IRT	8.1.3	X	X		
Concomitant medications	6.8	X	X	X	Review to ensure no prohibited medications are being used. Provide data to sponsor about medications used for SAEs and AESIs only.
Distribute reminder cards	8.1.4	X*	X		*On the clinic days for the next visit.
Assess study treatment compliance	6.4	X*	X		*Day 1 of each cycle.
Dispense/administer INCB001158 (participants receiving INCB001158 monotherapy or in combination with daratumumab SC)	6.1	X			On clinic day, INCB001158 should be given just before administration of daratumumab SC (if applicable). See Appendix B and Pharmacy Manual.
Administer daratumumab SC at site (participants receiving daratumumab SC monotherapy or in combination with INCB001158)	6.1	X			In clinic, daratumumab SC should be administered after INCB001158. See Appendix C and Pharmacy Manual.
AE assessments	8.3.1	X	X	X	All SAEs and AESIs must be recorded in the eCRFs, regardless of the causal relationship.
Efficacy/disease assessments (blood/urine/other)	8.2.1	X	X		As of Protocol Amendment 3, the disease assessments are only required to be performed as per standard of care guidelines for the participant's condition and monitoring.
Pregnancy testing	8.3.7.5	X*	X		All female participants of childbearing potential. *Urine at Day 1 of each cycle, at EOT, and as medically indicated or per country or institutional requirements.
Post-treatment anticancer therapy status	8.8.2			X	If a participant is scheduled to begin a post-treatment anticancer therapy before the end of the safety follow-up period, then the safety follow-up visit should be performed before post-treatment anticancer therapy is started.

2. INTRODUCTION

2.1. Background

2.1.1. Multiple Myeloma and Progressive Disease

Multiple myeloma is the second most common type of blood cancer (Siegel et al 2012). Despite recent developments with PIs, IMiDs, and novel therapeutic agents, management of MM remains challenging, as relapses and disease progression occur even after complete remission (Palumbo and Anderson 2011). Relapsed and PD associated with genetic alterations and resistances are frequently observed, causing gradually shorter DOR and leading to relapsed/refractory MM (Chim et al 2018). The bone marrow microenvironment plays a critical role in MM pathogenesis and progressive immune dysfunction (Kawano et al 2015).

2.1.2. Targeting Myeloid-Derived Suppressor Cells and Arginase in Multiple Myeloma

The inflammatory milieu in the bone marrow of MM patients support the growth of immunosuppressive cells such as MDSCs, TAMs, and Tregs (Kumar et al 2016). These immune suppressor cells correlate with clinical outcomes and are involved in the "immune escape" that favors myeloma progression. MDSCs have been shown to promote MM progression via a number of different mechanisms, including promotion of angiogenesis, chemoresistance, and immunosuppression in the bone marrow microenvironment (Herlihy et al 2017). MDSCs and neutrophils accumulate in the blood and bone marrow and promote tumor growth while inducing T cell immunosuppression (Görgün et al 2013, Ramachandran et al 2013). In MM, MDSCs and neutrophils secrete high levels of arginase, and disease progression is associated with increased levels of circulating MDSCs (Romano et al 2018).

2.1.3. INCB001158

INCB001158 is an orally bioavailable small molecule shown to be a potent and selective inhibitor of arginase and developed for cancer indications. Upon stimulation by factors within the tumor microenvironment (eg, proinflammatory cytokines, such as interleukin-8 and tumor necrosis factor-alpha), arginase is released into the tumor microenvironment via degranulation, resulting in substantial local depletion of the amino acid arginine. Arginine is a key factor for T cell and NK cell proliferation and increases the survival of effector T cells as well as their antitumor activity (Steggerda et al 2017, Geiger et al 2016). Arginine depletion prevents the activity of effector T cells in tumors by decreasing the production of IFN-γ, as well as the expression of TCR ζ-chain and T cell proliferation (Timosenko et al 2017). In the tumor microenvironment, arginase 1 is expressed and released extracellularly by immunosuppressive myeloid cells, including MDSCs and neutrophils.

INCB001158 inhibits arginase activity and restores arginine levels in the tumor microenvironment, resulting in antitumor effects in immunocompetent mice implanted with mouse tumors. INCB001158 has additive activity when administered in combination with PD-1 checkpoint inhibitors, IDO1 inhibitor, or chemotherapy agents in mouse tumor models (refer to the INCB001158 IB).

As of 21 JUL 2018, INCB001158 is being investigated in participants with advanced or metastatic solid tumors, as monotherapy and in combination with the anti–PD-1 monoclonal antibody pembrolizumab (Study INCB 01158-101), or in combination with chemotherapy (mFOLFOX6, gemcitabine/cisplatin, and paclitaxel) in Study INCB 01158-203. Preliminary data obtained in participants receiving INCB001158 monotherapy and in combination with pembrolizumab indicate that INCB001158 inhibits arginase activity and increases arginine levels in participant plasma (refer to the INCB001158 IB).

Among the 164 participants with advanced cancer exposed to INCB001158, the most frequently (≥ 10%) reported TEAEs overall were fatigue, nausea, anemia, constipation, hyperglycemia, decreased appetite, hyponatremia, abdominal pain, and diarrhea. Among the 83 participants receiving INCB001158 monotherapy, TEAEs occurred in 72 participants (86.7%), with the most frequent TEAEs being anemia (n = 17, 20.5%) and constipation and fatigue (n = 15 each, 18.1%). There has been no pattern of clinically significant urea cycle inhibition, hemodynamic effects, or immune-related AEs, which are potential on-target safety concerns associated with INCB001158 administration.

For the most comprehensive nonclinical and clinical information regarding INCB001158, refer to the latest version of the INCB001158 IB.

2.1.4. Daratumumab

Daratumumab (JNJ-54767414) is a recombinant human IgG monoclonal antibody immunotherapy that binds with high affinity to CD38, a transmembrane glycoprotein, expressed on tumor cells, and induces tumor cell death through multiple mechanisms of action, including CDC, ADCC, ADCP, and direct cytotoxicity by induction of apoptosis by FcγR-mediated crosslinking of the tumor cells bound by the monoclonal antibodies. Daratumumab treatment decreases $CD38^+$ Tregs, $CD38^+$ MDSCs, and $CD38^+$ Bregs (Krejcik et al 2016). The elimination of these immunosuppressive cells, modulation of CD38 enzymatic activity, and destruction of the malignant myeloma cells is thought to lead to the clonal expansion of $CD8^+$ and $CD4^+$ T cells (Chiu et al 2016).

Daratumumab by IV infusion, and by SC injection, has been approved in the United States and the European Union in different settings as monotherapy and in combination with standards of care therapies (such as PIs and immunomodulatory agents), for the treatment of patients with MM (Darzalex® and Darzalex FASPRO™ Prescribing Information and Darzalex® SmPC).

Daratumumab SC is composed of daratumumab co-formulated with a recombinant human hyaluronidase (rHuPH20), which enables manual SC injection in a few minutes. For the most comprehensive nonclinical and clinical information regarding daratumumab SC, refer to the latest version of the daratumumab IB.

Recombinant human hyaluronidase (rHuPH20) is the active ingredient of Hylenex® recombinant (hyaluronidase human injection), which was approved in the United States in DEC 2005 as an adjuvant to increase the dispersion and absorption of other injected drugs (Hylenex® Prescribing Information). rHuPH20 is also approved in combination with protein therapeutics for SC administration, such as HyQvia (immune globulin infusion 10% [human] with rHuPH20) in the United States and EU, as well as anticancer medications such as trastuzumab (Herceptin® SC in

the EU) and rituximab (MabThera® SC in the European Union, Rituxan Hycela® SC in the United States).

2.2. Study Rationale

2.2.1. Rationale for Study Design

Arginase is expressed by bone marrow myeloid and granulocytic MDSCs in relapsed and refractory MM patients (Görgün et al 2013, Giallongo et al 2016). INCB001158 is an oral small molecule that inhibits arginase and increases arginine levels and promotes antitumor immune function of NK and T cells (refer to the INCB001158 IB). Daratumumab is an anti-CD38 immunotherapy for MM approved as monotherapy or in combination with standards of care for the treatment of MM, such as immunomodulatory agents or PIs. Daratumumab has direct antitumor activity as well as immunomodulatory action by decreasing regulatory T and B cells (Krejcik et al 2016).

INCB001158 in vitro studies show that T cells from patients receiving daratumumab treatment or who are daratumumab-naïve, and cocultured with autologous PMNs and MDSCs, do not respond to anti-CD3/CD28 stimulation, demonstrating pronounced arginase-mediated anergy (M. Munder et al, unpublished data). Upon treatment with INCB001158, this anergic state is reversed, and T cells show a hyper-response in proliferation in cocultures from both daratumumab-naïve and daratumumab-exposed patients, providing evidence to support the evaluation of INCB001158 as a potential single agent and in combination with daratumumab for the treatment of multiple myeloma.

The study will investigate whether the combination of the anti-CD38 immunotherapy daratumumab with the arginase inhibitor INCB001158 will result in improved clinical benefit in participants with relapsing or refractory MM after at least 3 prior treatment lines (including IMiD, PI, and anti-CD38 therapies) but not more than 5 prior treatment lines.

This is an open-label, dose-escalation Phase 1 and randomized Phase 2 study in participants with relapsed or refractory MM. The objective of the study is to evaluate the safety and efficacy of INCB001158 given in combination with daratumumab SC and to compare the RP2D of INCB001158 in combination with daratumumab SC to daratumumab SC monotherapy, using a RAR design. At the time of confirmed disease progression participants treated with daratumumab SC monotherapy (Treatment Group B – Part 1) will cross over to INCB001158 + daratumumab SC (Treatment Group B – Part 2). The safety, efficacy, [redacted] effects of INCB001158 monotherapy will be also evaluated for 2 cycles, provided that the participants are not progressing. This selected timeframe is based on the mechanism of action and preliminary clinical data obtained in other cancer indications (refer to the INCB001158 IB), to allow safe clinical and translational assessments. Beyond Cycle 2, participants will continue treatment with INCB001158 monotherapy only if they are receiving clinical benefit and have not met any criteria for study withdrawal, followed by a crossover to INCB001158 in combination with daratumumab SC at the time of confirmed disease progression.

2.2.2. Combination of INCB001158 and Daratumumab

In patients with MM, efficacy of the CD38-targeting antibody daratumumab can be improved by adding a partner drug with a different mode of action, such as an IMiD. Further improvement may be achieved by combining daratumumab with an agent that is able to enhance or complement the immunomodulatory effect of daratumumab and/or host–antitumor T-cell immunity, and re-challenge can be used (Orlowski and Lonial 2016, van de Donk and Usmani 2018).

Therefore, combining the anti-CD38 immunotherapy daratumumab with the arginase inhibitor INCB001158 to reduce immunosuppression and restore antitumor activity may improve treatment efficacy for relapsing and refractory MM patients.

2.2.3. Justification for the Dose

In the Phase 1 dose escalation, the starting dose of INCB001158 will be 75 mg BID, which is 1 dose level below the RP2D and 2 dose levels below the highest dose of INCB001158 that was shown to be tolerable as a monotherapy in Study INCB 01158-101 (refer to the INCB001158 IB). The second dose level that will be tested is 100 mg BID, which was well-tolerated as monotherapy and in combination with pembrolizumab or with chemotherapy and was selected as the RP2D in INCB 01158-101 (for both monotherapy and combination with pembrolizumab) and INCB 01158-203 (combination with chemotherapy) studies in advanced cancer (refer to the INCB001158 IB). In case of INCB001158-related toxicity, the dose may be reduced by 1 dose level, from 75 mg to 50 mg BID and from 100 mg to 75 mg BID (see Sections 4.1.1 and 6.7.1).

Daratumumab SC is a co-formulated product of daratumumab and rHuPH20, which allows for the SC administration of daratumumab in 3 to 5 minutes compared with 4 to 7 hours for an IV infusion of daratumumab. Daratumumab SC has similar efficacy and safety with fewer infusion-related reactions compared with the IV formulation. Daratumumab SC has been approved in US and Europe for the treatment of patients with multiple myeloma (refer to the daratumumab IB, Darzalex and Darzalex FASPRO Prescribing Information and SmPC). The approved 1800 mg dose of daratumumab SC will be used in this study.

2.3. Benefit/Risk Assessment

Immunomodulatory agents and PIs among others are established treatments of MM. Daratumumab and new immune therapies inducing direct tumor cell killing and/or blocking immunosuppression have been approved or are in clinical development (Kumar et al 2016). INCB001158 is in early phase development and although the safety profile has not been fully evaluated, INCB001158 has been generally well-tolerated in 164 advanced or metastatic solid tumor participants. The main toxicity risks of arginase inhibition by INCB001158 are linked to potential urea cycle inhibition, hemodynamic effects, and immune-related AEs (refer to the INCB001158 IB).

Daratumumab SC was well-tolerated in relapsed/refractory MM patients with low rates of IRRs and no new safety signals compared with daratumumab IV. Daratumumab SC enabled dosing in 3 to 5 minutes and improves patient convenience. The most commonly reported AEs from rHuPH20 in combination with protein therapeutics for SC administration have been mild

injection site reactions. Pre- and post-administration medications are administrated with daratumumab SC (co-formulated with rHuPH20) to reduce the risk of IRRs.

Combining therapies with different mechanism of actions is an effective approach for the treatment of MM. Inhibition of arginase may decrease the immunosuppressive microenvironment driven by myeloid suppressive cells. Combining the arginase inhibitor INCB001158 with the anti-CD38 antibody daratumumab (SC formulation) may improve treatment efficacy with a manageable safety profile in participants with relapsed or refractory MM.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of INCB001158 and daratumumab SC may be found in their respective IBs, Darzalex and Darzalex FASPRO Prescribing Information and SmPC. For rHuPH20, refer to the Hylenex® Prescribing Information.

3. OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are presented in Table 8.

Table 8: Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1: To determine the safety, tolerability, and RP2D of INCB001158 in combination with daratumumab SC.	Safety and tolerability determined by monitoring the frequency, duration, and severity of AEs.
Phase 2: To compare the ORR of the RP2D of INCB001158 in combination with daratumumab SC to daratumumab SC monotherapy.	ORR, defined as the proportion of participants with a documented response PR or better, as per IMWG criteria.
Secondary	
Phase 1: To determine the efficacy of INCB001158 in combination with daratumumab SC.	ORR, defined as the proportion of participants with a documented response PR or better, as per IMWG criteria.
Phase 2: To determine the safety and tolerability of INCB001158 monotherapy at RP2D, and to compare the safety and tolerability and RP2D of INCB001158 in combination with daratumumab SC to daratumumab SC monotherapy.	Safety and tolerability determined by monitoring the frequency, duration, and severity of AEs.

Table 8: Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary (continued)	
Phase 1: To determine the efficacy of INCB001158 in combination with daratumumab SC. **Phase 2:** To estimate the efficacy of INCB001158 monotherapy, and to compare the efficacy of INCB001158 in combination with daratumumab SC to daratumumab SC monotherapy.	• TTR, defined as the time from the first dose of study drug to the first documented response PR or better, as per IMWG criteria. • DOR, defined as time from first documented response PR or better, as per IMWG criteria, until date of disease progression or death, whichever occurs first. • PFS, defined as the duration from the date of first dose of study drug until either PD, as per IMWG criteria, or death, whichever occurs first. • MRD, defined as the percentage of MRD-negative participants. • OS, defined as the time from the first dose of study drug to death from any cause.
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, dose-escalation Phase 1 and randomized Phase 2 study, to evaluate the safety and antitumor activity of INCB001158 in combination with daratumumab SC, compared with daratumumab SC alone, in participants with relapsed or refractory MM who have received at least 3 prior lines (including IMiD, PI, and anti-CD38 therapies) but not more than 5 prior lines of therapy.

Phase 1 will consist of dose-escalation using a BOIN design and will determine the RP2D of INCB001158 in combination with daratumumab SC; efficacy will also be explored.

Phase 2 will consist of a randomized expansion phase to compare the RP2D of INCB001158 in combination with daratumumab SC to daratumumab SC alone using a RAR design. INCB001158 monotherapy will also be explored.

The study design schema is presented in Figure 1, and the SoA in Table 3 and Table 4 for study visit assessments prior to and post-crossover, respectively.

NOTE: As of Protocol Amendment 3, see only Table 7 for the SoA for all participants.

4.1.1. Phase 1: Dose Escalation of INCB001158 + Daratumumab SC

In Phase 1, INCB001158 in combination with daratumumab SC will be administrated in 28-day treatment cycles, and study treatment is summarized in Table 9.

Table 9: Study Treatment for Participants in Phase 1 Dose Escalation

Study Treatment	INCB001158	Daratumumab SC
	50-100 mg PO BID continuous dosing until disease progression, unacceptable toxicity, or discontinuation from study treatment for any other reason.	1800 mg SC co-formulated with rHuPH20 (2000 U/mL). Administration is once weekly for Cycles 1 and 2, once every 2 weeks for Cycles 3 to 6, and then once every 4 weeks until disease progression, unacceptable toxicity, or discontinuation from study treatment for any other reason.

BID = twice daily; IV = intravenous; PO = orally; SC = subcutaneous.

Dose escalation of INCB001158 will begin at a starting dose 75 mg BID, which is 1 dose level below the RP2D for both monotherapy and combination with PD-1 inhibitor (per study INCB 01158-101) and for combination with chemotherapy (per study INCB 01158-203) in participants with advanced/metastatic solid tumors. The starting dose of 75 mg BID is also 2 dose levels below the highest dose (150 mg BID) tested in the INCB 01158-101 study, while the MTD has not been reached (see Section 2.2.3).

The doses of INCB001158 to be evaluated and scenarios for dose escalation and de-escalation are summarized in Table 10.

Table 10: INCB001158 Dose Levels

INCB001158 Dose Level	INCB001158 Dose
-1	50 mg BID
1 (starting dose)	**75 mg BID[a]**
2	100 mg BID

BID = twice daily.
[a] If INCB001158 75 mg BID is not tolerated, INCB001158 50 mg BID may be evaluated.

Dose escalation and de-escalation in Phase 1 will follow the BOIN design algorithm (Yuan and Liu 2016). Given the target DLT rate of 33% for INCB001158 in combination with daratumumab SC, the dose escalation and de-escalation rules are shown in Table 11. The BOIN design also includes an elimination rule. When ≥ 3 participants have been treated, if the probability that the estimated toxicity rate that is above the target DLT rate is > 95% at a certain dose level, then this dose level and higher dose levels are assumed to be too toxic and will be eliminated. If the lowest dose level is eliminated, then the whole dose escalation will be terminated. Table 11 (in the bottom row) provides the elimination rules. Based on this algorithm, a minimum of 3 evaluable participants and a maximum of 9 evaluable participants will be enrolled at each tested dose level. The dose escalation will continue, based on the rules in Table 11, until at least 1 of the following occurs:

- Enrollment of additional participants at a dose level that already has 9 evaluable participants.
- Dose escalation to a dose level that has already been eliminated.
- Dose escalation above 100 mg BID.

At that point, the dose escalation will be stopped.

Table 11: Dose Escalation, De-Escalation, and Elimination Boundaries for Target DLT Rate of 33% in Phase 1

	Number of Evaluable Participants Treated at the Current Dose								
Action	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[a]**
Escalate if # of DLTs ≤	0	0	0	1	1	1	1	2	2
De-escalate if # of DLTs ≥	1	1	2	2	2	3	3	4	4
Elimination if # of DLTs ≥	N/A	N/A	3	3	4	4	5	5	6

DLT = dose-limiting toxicity; N/A = not applicable.
[a] If 9 evaluable participants are enrolled at a dose level, and 3 of those participants experience a DLT, then the medical monitor and the investigators will review the entirety of the data and decide whether to escalate the dose level, de-escalate the dose level, or stop at that dose level.

The INCB001158 dose will be escalated using an open-label BOIN design and a PAD or the MTD will be determined, or the maximum dose of INCB001158 (100 mg BID) will be reached.

A PAD of INCB001158 is defined as a dose that achieves a C_{min} of INCB001158 at steady state of ≥ 1 μM that is equivalent to the IC_{90} for arginase 1. The MTD is the maximum tolerated or tested dose of INCB001158, such that fewer than 33% of the participants receiving the combination experience a DLT during the first 28 days on study drug. After the dose escalation is completed, one of the INCB001158 dose levels that is pharmacologically active and tolerable in combination with daratumumab SC (ie, MTD or lower), will be selected as the RP2D.

Dose interruptions and/or modifications may be implemented based on toxicity. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor. Intraparticipant dose escalation is not permitted. At the discretion of the sponsor, up to 6 additional "backfill" participants may be enrolled at any tolerable dose level to further investigate safety, efficacy [redacted].

4.1.2. Phase 2: Expansion

An initial 1:1:1 randomization of 30 participants between the RP2D of INCB001158 in combination with daratumumab SC (Treatment Group A), daratumumab SC monotherapy (Treatment Group B – Part 1), and INCB001158 monotherapy at the RP2D determined in Phase 1 (Treatment Group C – Part 1) will be conducted. Participants in Treatment Groups A and B will receive continuous treatment until disease progression or unacceptable toxicity, or discontinuation from study treatment for any other reason. At the time of confirmed disease progression, participants in Treatment Group B (Part 1) will cross over to INCB001158 + daratumumab SC (Treatment Group B – Part 2) and continue combination treatment as long as they are receiving clinical benefit and have not met any criteria for study withdrawal. Participants in Treatment Group C will receive continuous treatment with INCB001158 for at least 2 cycles if they are not progressing, and beyond Cycle 2 only if they are receiving clinical benefit and have not met any criteria for study withdrawal (Treatment Group C – Part 1), and then they will cross over to INCB001158 + daratumumab SC at the time of confirmed disease progression (Treatment Group C – Part 2). Stopping rules for unacceptable toxicity based on Grade 4 or higher treatment-related AEs will be used as indicated in Section 10.5.2.

After the equal randomization period, an RAR design will be used to compare the ORR of Treatment Groups A and B with adjustments to the randomization rate based on the observed ORR. Evaluation of the safety and tolerability of the 3 treatment groups will be performed periodically throughout the study. Participants will be analyzed for efficacy based on the treatment group in which they were randomized. Details of the randomization method and model for response are provided in the statistical methods Section 10.4.

Participants will be assigned to the randomization Treatment Groups A, B, or C:

- Treatment Group A: INCB001158 + daratumumab SC
- Treatment Group B: daratumumab SC monotherapy (Part 1), then crossover to INCB001158 + daratumumab SC (Part 2)
- Treatment Group C: INCB001158 monotherapy (Part 1), then crossover to INCB001158 + daratumumab SC (Part 2)

Treatments will be administrated in 28-day cycles for Treatment Groups A, B and C and are summarized in Table 12.

Table 12: Treatments for Treatment Groups A, B, and C

Treatment Group A	**INCB001158**	**Daratumumab SC**
	RP2D PO continuous dosing until disease progression, unacceptable toxicity, or discontinuation from study treatment for any other reason.	1800 mg SC co-formulated with rHuPH20 (2000 U/mL). Administration is once weekly for Cycles 1 and 2, once every 2 weeks for Cycles 3 to 6, and then once every 4 weeks until disease progression, unacceptable toxicity, or discontinuation from study treatment for any other reason.
Treatment Group B Part 1	**Daratumumab SC monotherapy**	
	1800 mg SC co-formulated with rHuPH20 (2000 U/mL). Administration is once weekly for Cycles 1 and 2, once every 2 weeks for Cycles 3 to 6, and then once every 4 weeks until disease progression, unacceptable toxicity, or discontinuation from study treatment for any other reason. At the time of confirmed disease progression, participants will cross over to Treatment Group B - Part 2, and continue with combination treatment as indicated below	
Treatment Group B Part 2	**INCB001158**	**Daratumumab SC**
	RP2D PO continuous dosing until disease progression, unacceptable toxicity, or discontinuation from study treatment for any other reason.	1800 mg SC co-formulated with rHuPH20 (2000 U/mL). Administration is once weekly for Cycles 1 and 2, every 2 weeks for Cycles 3 to 6, and then every 4 weeks until disease progression, unacceptable toxicity, or discontinuation from study treatment for any other reason.
Treatment Group C Part 1	**INCB001158 monotherapy**	
	RP2D PO continuous dosing for at least 2 cycles if participants are not progressing, and beyond Cycle 2 only if they are receiving clinical benefit and have not met any criteria for study withdrawal. The participants will then cross over to Treatment Group C - Part 2 at the time of confirmed disease progression, and continue with combination treatment as indicated below.	
Treatment Group C Part 2	**INCB001158**	**Daratumumab SC**
	RP2D PO continuous dosing until disease progression, unacceptable toxicity, or discontinuation from study treatment for any other reason.	1800 mg SC co-formulated with rHuPH20 (2000 U/mL). Administration is once weekly for Cycles 1 and 2, every 2 weeks for Cycles 3 to 6, and then every 4 weeks until disease progression, unacceptable toxicity, or discontinuation from study treatment for any other reason.

BID = twice daily; IV = intravenous; PO = orally; RP2D = recommended Phase 2 dose; SC = subcutaneous.

Bone marrow aspirate and biopsy will be performed at screening for clinical staging, to establish baseline MM clonality to monitor for MRD, and to perform molecular subtyping to monitor treatment activity in high-risk molecular subgroups.

[redacted]

4.2. Overall Study Duration

The study begins when the first participant signs the ICF. The end of the study is defined as the date of last scheduled procedure shown in the SoA for the last participant in the study globally.

A participant is considered to have completed the study if he/she has completed all parts of the study including the last scheduled procedure shown in the SoA.

If there have been ≤ 5 participants on study for more than 6 months, a database lock of the study may occur to allow the analysis of the study data. Any remaining participants may continue to receive study treatment and be seen by the investigator per usual standard of care for this population. The investigator will be expected to monitor for and report any SAEs, AESIs, and pregnancies, as detailed in Section 9. The remaining participants are considered to be on study until a discontinuation criterion is met.

NOTE: As of Protocol Amendment 3, no further disease status and survival follow-up assessments will be required beyond the last safety follow-up visit.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively if, for example, required by regulatory decision or upon review of emerging data. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. Ability to comprehend and willingness to sign a written ICF for the study.
2. Men or women aged 18 years or older.
3. Prior diagnosis of MM according to IMWG diagnostic criteria (Rajkumar et al 2014).
4. Has measurable disease at screening, as defined by the following:
   - Serum M-protein level ≥ 1.0 g/dL, or
   - Urine M-protein level ≥ 200 mg/24 hours, or
   - Serum Ig FLC ≥ 10 mg/dL and abnormal serum Ig kappa to lambda FLC ratio.
5. Has received at least 3 prior lines (including PI, IMiD, and anti-CD38 therapies) but not more than 5 prior lines of MM treatment.
   a. Has received last dose of prior anti-CD38 therapy at least 3 months before initiation of study treatment.
   b. Has achieved a response (MR or better), based on investigator's evaluation of response by IMWG criteria, to prior anti-CD38 therapy.
   c. Has documented evidence of PD as defined by the IMWG criteria on or after their last regimen.
6. ECOG performance status of 0 or 1.
7. Willing to avoid pregnancy or fathering children based on the criteria below:
   a. Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and at least 51 years of age).
   b. Woman of childbearing potential who has a negative serum pregnancy test at screening and before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening until 3 months after the last dose of the last component of study treatment and must refrain from donating eggs (ova, oocytes). Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participant and their understanding confirmed.

c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening until 3 months after the last dose of the last component of study treatment and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participant and their understanding confirmed.

8. Willing to provide fresh and archival bone marrow aspiration and biopsy tissue during screening and on study.

5.2. Exclusion Criteria

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

1. Receipt of any of the following treatment within the indicated interval before the first administration of study drug:
   a. Anti-myeloma treatment within 2 weeks or 5 half-lives (whichever is longer).
      – Exception: Washout of immune checkpoint inhibitor therapy is NOT required.
   b. Investigational drug (including investigational vaccines) or invasive investigational medical device within 4 weeks.
   c. Autologous stem cell transplant within 12 weeks, or allogeneic stem cell transplant at any time.
   d. Plasmapheresis within 4 weeks.
   e. Radiation therapy within 2 weeks.
   f. Major surgery within 2 weeks, or inadequate recovery from an earlier surgery, or surgery planned during the time the participant is expected to participate in the study or within 2 weeks after the last dose of study treatment.
2. Toxicity ≥ Grade 2 from previous anti-myeloma therapy except for stable chronic toxicities (≤ Grade 2) not expected to resolve, such as stable Grade 2 peripheral neuropathy.
3. Known additional malignancy (other than MM) that is progressing or requires active treatment, or history of other malignancy within 2 years of study entry with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy, or cancers from which the participant has been disease-free for > 1 year, after treatment with curative intent.
4. Known meningeal involvement of MM.
5. Participants with laboratory values at screening defined in Table 13.

Table 13: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	< 75 × 10^9/L for participants in whom < 50% of bone marrow nucleated cells are plasma cells; otherwise < 50 × 10^9/L (transfusions are not permitted to reach this level)
b	Hemoglobin	< 7.5 g/dL (transfusions are not permitted to reach this level)
c	ANC	< 1.0 × 10^9/L (prior growth factor support is not permitted within 10 days before initiation of therapy)
d	Corrected serum calcium	> 14.0 mg/dL (3.5 mmol/L)
Hepatic		
e	ALT	> 2.5 × ULN
f	AST	> 2.5 × ULN
g	Total bilirubin	> 1.5 × ULN OR > 3.0 mg/dL for participants with documented Gilbert's syndrome.
Renal		
h	Measured or calculated creatinine clearance	< 40 mL/minute

6. Significant concurrent, uncontrolled medical condition, including but not limited to the following:
    a. Known COPD (defined as a FEV1 < 50% of predicted normal), persistent asthma, or history of asthma within the past 2 years. Participants with known or suspected COPD or asthma must have a FEV1 test during screening.
    b. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment.
    c. Acute diffuse infiltrative pulmonary disease.
    d. Clinically significant or uncontrolled cardiac disease, including the following:
        – Unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy unless approved by medical monitor.
        – History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. A screening QTcF interval > 470 ms is excluded.
    e. Inability of the participant to swallow and retain oral medication.

7. Any of the following:
    a. Known to be seropositive for hepatitis B (defined by a positive test for HBsAg). Participants with resolved infection (ie, participants who are HBsAg-negative but positive for antibodies to anti-HBc and/or anti-HBs) must be screened using real-time PCR measurement of HBV DNA levels. Those who are PCR-positive will be excluded.
        – Exception: Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR.
    b. Known to be seropositive for hepatitis C. Participants who have had definitive treatment for HCV are permitted if HCV RNA is undetectable at screening visit.
    c. Known to be seropositive for HIV. HIV testing is not required unless mandated by the local health authority.
8. Plasma cell leukemia, Waldenström's macroglobulinemia, POEMS syndrome, or amyloidosis.
9. Prior treatment with an arginase inhibitor for any indication.
10. Known or suspected defect in the function of the urea cycle, including a known deficiency of carbamoyl phosphate synthetase I, ornithine transcarbamylase, argininosuccinate synthetase, argininosuccinate lyase, N-acetyl glutamate synthetase, or arginase.
11. Current use of any prohibited medication as described in Section 6.8.2.
12. Known hypersensitivity or severe reaction to INCB001158, daratumumab, hyaluronidase, monoclonal antibodies, human proteins, or their excipients (refer to the INCB001158 IB, daratumumab IB, Prescribing Information and SmPC, and Hylenex® Prescribing Information).
13. Women who are pregnant or breastfeeding.
14. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
15. Candidates for autologous or allogenic transplantation (for participants enrolled at sites in Germany only).

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

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

Tests with results that fail eligibility requirements may be repeated during screening. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Replacement of Participants

In Phase 1, any participant who withdraws from study treatment before the completion of the DLT observation period for any reason other than a DLT (eg, not evaluable for DLT) may be replaced to ensure a minimum number of evaluable participants.

In Phase 2, any participant who withdraws consent before the first administration of study treatment may be replaced to ensure a minimum number of evaluable participants.

6. STUDY TREATMENT

6.1. Study Treatment(s) Administered

In this Protocol, the term "study drug" refers to INCB001158 only, and "study treatment" refers to INCB001158, daratumumab SC, or the combination of INCB001158 and daratumumab SC.

Table 14 presents the study treatment information.

Table 14: Study Treatment Information

Study treatment name:	**INCB001158**	**Daratumumab SC**
Dosage formulation:	25 mg and 100 mg tablets	120 mg/mL daratumumab + 20 µg/mL rHuPH20 solution
Unit dose strength(s) /dosage level(s):	50 mg BID 75 mg BID 100 mg BID	1800 mg
Route of administration:	PO	SC
Administration instructions:	Administrated PO BID, in the morning and evening, approximately 12 hours apart, without respect to food (see Appendix B).	Administered SC by manual push over 3-5 minutes (see Appendix C and daratumumab IPPI).
Packaging and labeling:	INCB001158 will be provided as 25 mg and 100 mg tablets packaged in bottles, respectively. No preparation is required. Each bottle will be labeled as required per country requirement.	Daratumumab SC will be provided in glass vials containing daratumumab at a concentration of 120 mg/mL and rHuPH20 at a concentration of 2000 U/mL (~20 µg/mL). It will be supplied to the site/pharmacy as open-label supply. Each vial will be labeled as required per country requirement.
Storage:	Ambient conditions 15°C to 30°C (59°F to 86°F).	Under refrigeration 2°C-8°C (36°F-46°F). Protect from light.

6.2. Preparation, Handling, and Accountability

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

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

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

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

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

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a randomized, open-label, Phase 1/2 study. In Phase 2, all participants will be centrally assigned to study treatment using an IRT system. The first 30 participants will be randomized 1:1:1 between the Treatment Groups A (RP2D of INCB001158 in combination with daratumumab SC), B (daratumumab SC monotherapy followed by crossover to

INCB001158 + daratumumab SC at the time of confirmed disease progression), or C (RP2D of INCB001158 as monotherapy with crossover to INCB001158 + daratumumab SC at the time of confirmed disease progression). After the initial equal randomization period, a RAR design will be used to randomize participants between Treatment Groups A and B. The system will update the randomization rates in Treatment Groups A or B based on the observed ORR by investigator assessment at the time each participant is enrolled. See Section 10.5.2 for details regarding the algorithm used for RAR design.

The IRT system will track participant visits, randomize according to the defined parameters, and manage study drug inventory. Periodic reconciliation of responses between the IRT system and the clinical database will be performed. Study treatment will be dispensed at the study visits summarized in the SoA (see Table 3 and Table 4 for study site visit assessments prior to and post-crossover, respectively, and Table 7 for the SoA for all participants as of Protocol Amendment 3).

6.4. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with INCB001158 will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Participants will be instructed to bring all unused INCB001158 tablets with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

Compliance with daratumumab SC administration will be calculated by the sponsor based on drug accountability and administration records documented by the site staff and monitored by the sponsor/designee. The details of each administration will be recorded in the eCRF.

6.5. Guidelines for Prevention and Management of Injection-Related Reactions

6.5.1. Prevention of Injection-Related Reactions Due to Daratumumab SC

6.5.1.1. Pre-Administration Medication

In an effort to prevent IRRs, all participants will receive the following medications 1 to 3 hours before each daratumumab SC administration:

- An antipyretic: paracetamol (acetaminophen) 650 to 1000 mg PO.
- An antihistamine: diphenhydramine 25 to 50 mg PO, or equivalent. Avoid IV use of promethazine (see Appendix D for a list of antihistamines that may be used).
- Administer 20 mg dexamethasone or equivalent before every administration.

If necessary, all mandatory PO pre-administration medications may be administered outside of the clinic on the day of the injection, provided they are taken within 1 to 3 hours before the injection.

Predose administration of a leukotriene inhibitor (montelukast 10 mg PO or equivalent) is optional on Cycle 1 Day 1 and can be administered up to 24 hours before the injection according to investigator discretion.

6.5.1.2. Post-Administration Medication

For participants at higher risk of respiratory complications (eg, participants with mild asthma or participants with COPD developing FEV1 < 80% during the study without any medical history), the following post-administration medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- A short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for participants with asthma; long-acting bronchodilators such as tiotropium or salbutamol ± inhaled corticosteroids for participants with COPD)

In addition, these at-risk participants may be hospitalized for monitoring for up to 2 nights after daratumumab SC administration. If participants are hospitalized, then an improvement in FEV1 should be documented before discharge. If these participants are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all daratumumab SC administrations. If the participant has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as an SAE. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event that a bronchospasm occurs after participants are released from the hospital/clinic. If an at-risk participant experiences no major IRRs, then these post-administration medications may be waived after 4 doses at the investigator's discretion. Any post-administration medication will be administered after the administration has completed.

6.5.2. Management of Injection-Related Reactions

6.5.2.1. Local Injection Site Reactions

In Study MMY1004, SC administration of daratumumab in abdominal subcutaneous tissue was associated with local injection site reactions such as induration and erythema in some participants. The reactions usually resolved within 60 minutes. Local injection site reactions should be managed according to institutional standards.

6.5.2.2. Systemic Injection-Related Reactions

Participants should be observed carefully during daratumumab SC administration. Trained study staff at the clinic should be prepared to intervene in case of any IRRs, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available.

If an IRR develops, then daratumumab SC administration should be temporarily interrupted, as indicated in Table 15. Please refer to the daratumumab IPPI for further details. Participants who experience AEs during daratumumab SC administration must be treated for their symptoms. Participants should be treated with acetaminophen, antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, participants may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, participants may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab SC should be discontinued, and no additional daratumumab SC should be administered to the participant.

Table 15: Recommendations for the Management of Systemic Injection-Related Reactions

IRR	Action
Grade 1 or 2	Daratumumab SC administration should be interrupted. When the participant's condition is stable, daratumumab SC administration may be restarted at the investigator's discretion. For instructions for restarting administration, refer to the daratumumab IPPI.
≥ Grade 2 laryngeal edema, or ≥ Grade 2 bronchospasm that does not respond to systemic therapy and resolve with 6 hours from onset	Participant must be discontinued from daratumumab SC treatment.
≥ Grade 3 (other than laryngeal edema or bronchospasm)	Daratumumab SC administration must be interrupted. Monitor participants carefully until resolution or return to Grade 1. Daratumumab SC administration may be restarted at the investigator's discretion.
If the intensity of the IRRs returns to ≥ Grade 3 after restart of the daratumumab SC administration	Participant must be discontinued from daratumumab SC treatment.
Grade 4	Daratumumab SC administration must be stopped and the participant discontinued from daratumumab SC treatment.
Grade 3 (or ≥ Grade 2 laryngeal edema or bronchospasm) recurrence during or within 24 hours after a subsequent daratumumab SC administration	Participant must be discontinued from daratumumab SC treatment.

6.6. Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose and/or Pharmacologically Active Dose of INCB001158

6.6.1. Definition of a Dose-Limiting Toxicity

A DLT will be defined as the occurrence of any of the toxicities in Table 16 occurring from the start of study treatment up to and including Day 28, 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 criteria. Participants who receive at least 42 of 56 (≥ 75%) doses of study drug at the level assigned or have a DLT will be considered evaluable for determining tolerability of the dose. Participants who do not meet these criteria may be replaced to obtain sufficient evaluable participants to be able to assess that dose level using the BOIN design, as outlined in Table 11.

Clear evidence of urea cycle inhibition (eg, an increase in fasting urinary orotic acid to > 10 × ULN or any orotic acid value of > 40 × ULN, accompanied by plasma ammonia elevation ≥ 2 × ULN and ≥ 2 × baseline, or symptomatic hyperammonemia) would be considered a dose-limiting event and will be treated the same as a DLT with regard to the dose-escalation rules and definition of the MTD described in Section 4.1.1. Refer to the INCB001158 IB for an explanation of the orotic acid thresholds.

Individual participant dose reductions may be made based on events observed at any time during treatment with study drug; however, for the purposes of dose level escalation/de-escalation, expanding a dose level, and for determining the MTD of INCB001158, decisions will be made based on events that are 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.

Table 16: Definition of a Dose-Limiting Toxicity

Toxicity	Definition
Nonhematologic	• Any ≥ Grade 3 nonhematologic toxicity EXCEPT the following: – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. – Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 72 hours. – Fatigue or asthenia that was present at baseline or that lasts for < 7 days. – An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity.
Hematologic	• Grade 3 thrombocytopenia with clinically significant bleeding (requires hospitalization, transfusion of blood products, or other urgent medical intervention). • Grade 4 hematologic toxicity, except for Grade 4 lymphopenia. • Febrile neutropenia (ANC < 1.0×10^9/L and fever > 101°F/38.5°C).

6.6.2. 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 (whenever possible).

6.6.3. 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, unless the participant discontinues study treatment, in which case, the participant will be followed for 28 days after last dose of study treatment or 90 days for irAEs (see Section 9). During follow-up, participants should be seen as often as medically indicated to assure safety.

6.6.4. Procedures for Dose Level Review and Dose Escalation

Telephone conferences with study investigators will be scheduled by the sponsor in order to review dose level–specific data and overall safety data, to agree on dose escalation, to adjudicate individual high-grade AEs as potentially dose-limiting, and to guide other major study decisions.

6.7. Dose Modifications

Selections and modifications to the study treatment regimen are planned for dose-escalation. Dose interruptions and modifications also may occur for individual study participants. The identification of DLTs will define the doses used in planned dose levels (see Section 4.1.1). Further, the occurrence of DLTs and other toxicities (related or unrelated to study drug) will guide decisions for treatment interruptions and discontinuation for individual participants. Intraparticipant dose escalation for any study drug is not permitted.

6.7.1. Dose Modifications of INCB001158

For participants in Phase 1, dose reductions of INCB001158 will be permitted during the first 28 days only if a participant experiences a DLT or a toxicity that may herald a DLT. If a participant experiences a DLT, treatment continuation at a lower dose of INCB001158 will be permitted as long as the toxicity has returned to ≤ Grade 1 or baseline within 28 days. When INCB001158 is held or discontinued, daratumumab SC may be continued, at the investigator's discretion. Upon recovery, participants may restart at 1 INCB001158 dose level lower. Participants who do not recover within 28 days will not be eligible for resumption of study treatment without approval from the medical monitor. See also Table 17.

6.7.2. 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.

As described in Section 2.3, INCB001158 has the potential to cause toxicity related to the inhibition of arginase 1 in the hepatic urea cycle. Table 17 provides guidance for INCB001158 dose modifications and participant management if there is evidence of urea cycle inhibition.

Dose modification and toxicity management for potential irAEs associated with INCB001158 should be managed as follows.

Adverse events (both nonserious and serious) associated with INCB001158 exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue INCB001158 and administer corticosteroids.

Table 17 summarizes the AE dose modification actions for INCB001158. Of note, when indicated by Table 17 to mitigate irAEs, the dose of INCB001158 must be reduced using the dosing levels outlined in Table 11. Once reduced, re-escalation of INCB001158 is not permitted.

Table 17: Guidelines for Interruption and Restarting of Study Drug

Adverse Event	Toxicity Grade or Conditions (CTCAE v5)	Action Taken	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Evidence of urea cycle inhibition	• Fasting urinary orotic acid > 2 × and ≤ 10 × ULN • Any urinary orotic acid > 2 × and ≤ 40 × ULN	• Continue.	• None.	• Retest 1 week later. If still abnormal, withhold INCB001158 and retest every week until orotic acid returns to normal level, then consider restarting (at a lower dose) in consultation with medical monitor.
	• Ammonia 2 × ULN and 2 × baseline (repeated measurements or with symptoms) • Fasting urinary orotic acid > 10 × ULN • Any urinary orotic acid > 40 × ULN • BUN < 50% LLN	• Withhold. • Consider restarting (at a lower dose) in consultation with medical monitor.	• See Section 6.7.3 for management of hyperammonemia.	
Pneumonitis	Grade 2	• Withhold until Grade 0-1. Restart at full dose.	• Administer corticosteroids (initial dose of 1-2 mg/kg/day prednisone or equivalent) followed by taper.	• Monitor participants for signs and symptoms of pneumonitis. • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. • Add prophylactic antibiotics for opportunistic infections.
	Grade 3 or 4, or recurrent Grade 2	• Withhold until Grade 0-1. Consider rechallenge at next dose level lower.		

Table 17: Guidelines for Interruption and Restarting of Study Drug (Continued)

Adverse Event	Toxicity Grade or Conditions (CTCAE v5)	Action Taken	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Diarrhea/colitis	Grade 2 or 3	• Withhold until Grade 0-1. • Grade 2: Restart at same dose level. • Grade 3: Restart at next dose level lower.	• Administer corticosteroids (initial dose of 1-2 mg/kg/day prednisone or equivalent) followed by taper.	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	• Withhold until Grade 0-1. Consider rechallenge at next dose level lower.		
AST/ALT elevation or increased bilirubin[a]	Grade 2	• Withhold until Grade 0-1. Restart at same dose level.	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper.	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returns to baseline or is stable).
	Grade 3 or 4	• Withhold until Grade 0-1. Consider rechallenge at next dose level lower.	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	
T1DM or hyperglycemia[b]	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	• Withhold until Grade 0-1. • Grade 2: Restart at same dose level. • Grade 3: Restart at next dose level lower.	• Initiate insulin replacement therapy for participants with T1DM. • Administer antihyperglycemic in participants with hyperglycemia.	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	• Withhold until Grade 0-1. Restart at same dose level.	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
	Grade 3 or 4	• Withhold until Grade 0-1. • Grade 3: Restart at same dose level. • Grade 4: Consider rechallenge at next dose level lower.		

Table 17: Guidelines for Interruption and Restarting of Study Drug (Continued)

Adverse Event	Toxicity Grade or Conditions (CTCAE v5)	Action Taken	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Hyperthyroidism[b]	Grade 2	• Continue.	• Treat with nonselective β-blockers (eg, propranolol) or thionamides as appropriate.	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	• Withhold until Grade 0-1. Consider rechallenge at next dose level lower.		
Hypothyroidism[b]	Grade 2-4	• Continue.	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	• Withhold until Grade 0-1. Restart at same dose level.	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function.
	Grade 3 or 4	• Withhold until Grade 0-1. • Grade 3: Restart at same dose level. • Grade 4: Consider rechallenge at next dose level lower.		
Rash	Grade 1 or 2	• Continue.	• Manage with topical steroids with or without drug interruption.	
	Grade 3[c]	• Withhold until Grade 0-1. • Restart at same dose level.	• Consider dermatology consultation and biopsy for confirmation of diagnosis. • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	• If toxicity does not resolve within 12 weeks of last dose, or cannot taper below 10 mg or less of prednisone or equivalent within 12 weeks, must permanently discontinue.
	Grade 4	• Withhold until Grade 0-1. Consider rechallenge at next dose level lower.	• Dermatology consultation and consideration of biopsy and clinical dermatology photograph. • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	

Table 17: Guidelines for Interruption and Restarting of Study Drug (Continued)

Adverse Event	Toxicity Grade or Conditions (CTCAE v5)	Action Taken	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Asymptomatic[d] amylase or lipase increased	Grade 3	• May continue treatment with medical monitor approval.		• Permanently discontinue if clinical signs and symptoms of pancreatitis develop (abdominal pain, nausea, vomiting). • If toxicity does not resolve within 12 weeks of last dose after an interruption, must permanently discontinue unless approved by the medical monitor to continue. • If Grade 4 lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, study drug administration dosing may continue with medical monitor approval.
	Grade 4	• Withhold until Grade 0-1. Restart at same dose level.		
All other irAEs	Grade 3, or intolerable/persistent Grade 2	• Withhold until Grade 0-1. Consider rechallenge at next dose level lower.	• Based on severity of AE, administer corticosteroids.	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	• Withhold until Grade 0-1. Consider rechallenge at next dose level lower.		

General Instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and should be continued over at least 4 weeks.
2. For situations where INCB001158 has been withheld, INCB001158 can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. INCB001158 should be permanently discontinued if AE does not resolve within 12 weeks of last dose or if corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

AE = adverse event; ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); BUN = blood urea nitrogen; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; irAE = immune-related adverse events; LLN = lower limit of normal; T1DM = Type 1 diabetes mellitus; ULN = upper limit of normal.

[a] Participants with radiographically documented liver metastases should withhold at > 5 × ULN.

[b] For participants with Grade 3 or 4 immune-related endocrinopathy where withholding of INCB001158 is required, INCB001158 may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

[c] Participants with Grade 3 rash in the absence of desquamation, with no mucosal involvement, that does not require systemic steroids, and that resolves to Grade 1 within 14 days do not have to hold study medication and may be treated similar as Grade 1 events.

[d] If Grade 4 lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, then study drug administration dosing may continue (with or without dose reduction) with medical monitor approval.

6.7.3. Management of Hyperammonemia

Participants receiving INCB001158 as monotherapy or in combination with daratumumab SC should be monitored for elevated venous plasma ammonia. Asymptomatic clinically significant drug-related elevations in ammonia (eg, a repeatable elevation in ammonia > 2 × ULN AND > 2 × baseline) should be managed by interrupting INCB001158 and monitoring to resolution. For symptomatic elevations (ie, significant ammonia elevation associated with nausea, vomiting, severe anorexia, mental status changes, seizure, or other symptoms associated with hyperammonemia), participants should be admitted for management according to the local institutional protocol for hyperammonemia, including 1) sending appropriate laboratory samples (ammonia [on ice, measured immediately], plasma amino acid profile, liver function tests, electrolytes, bicarbonate, BUN or urea, creatinine, glucose, and urine orotic acid), 2) IV hydration with dextrose-containing fluids, 3) discontinuation of protein intake, 4) implementing therapy to reduce ammonia levels (oral lactulose/lactitol, IV Ammonul®), and 5) identifying and treating any potential triggers (eg, discontinue corticosteroids, treat infections).

6.7.4. Dose Delays and Dose Modification of Daratumumab SC

Dose modification of daratumumab SC is not permitted. Dose delay is the primary method for managing toxicities related to daratumumab SC.

On the first day of each new treatment cycle and before each daratumumab SC administration, the participant will be evaluated by the treating physician for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to CTCAE v5. Dose delays will be made based on the toxicity experienced during the previous cycle of therapy or newly encountered on Day 1 of a cycle.

For all daratumumab SC doses in a treatment cycle except the first dose, if daratumumab SC administration does not commence within the prespecified window (see Table 3 and Table 4 for study site visit assessments prior to and post-crossover, respectively, and Table 7 for all participants as of Protocol Amendment 3) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up. The minimal time interval between daratumumab SC doses should be 4 days.

Daratumumab SC treatment must be held if any of the following criteria below are met, to allow for recovery from toxicity, regardless of relationship to INCB001158 or daratumumab SC.

- Grade 4 hematologic toxicity, except for Grade 4 lymphopenia
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia
- Neutropenia with infection, of any grade
- Grade 3 or higher nonhematologic toxicities, *with the following exceptions*:
  - Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days

- Grade 3 fatigue that was present at baseline or that lasts for < 7 days after the last administration of daratumumab SC
- Grade 3 asthenia that was present at baseline or that lasts for < 7 days after the last administration of daratumumab SC.

Administration of daratumumab SC may be restarted (as indicated in Table 18) upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered.

Table 18: Daratumumab SC–Related Toxicity Management

Cycles	Frequency	Dose Held	Dosing Re-Start at
1 and 2	QW	> 3 days	Next planned QW dosing date
3 to 6	Q2W	> 7 days	Next planned Q2W dosing date
7+	Q4W	> 14 days	Next planned Q4W dosing date

The cycles may be delayed up to 4 weeks (Cycle 1 to Cycle 6) or up to 6 weeks (Cycle 7 and beyond). If Day 1 of a cycle is delayed, Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should not be adjusted. [redacted]

When daratumumab SC is held, INCB001158 may be continued, at the investigator's discretion with approval of the medical monitor.

6.7.5. Daratumumab SC Interruption or Missed Doses

A daratumumab SC dose that is held for more than the permitted time (see Table 18) from the per-Protocol administration date for any reason other than toxicities suspected to be related to daratumumab SC should be brought to the attention of the sponsor at the earliest possible time. Participants whose dose was delayed for more than 4 weeks (Cycle 1 to Cycle 9) or 2 consecutive planned doses (after Cycle 9) should have daratumumab SC discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

6.8. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 30 days before the first dose of study treatment and 30 days after the last dose of the last study treatment, 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 treatment should be recorded for SAEs as defined in Section 9.4. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

NOTE: As of Protocol Amendment 3, use of concomitant medications should be monitored for participants to verify that they are not taking any concomitant medication prohibited per Protocol; however, concomitant medications no longer need to be collected in the eCRF, except for concomitant medications in relation with SAEs or AESIs.

6.8.1. Permitted Medications and Procedures

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage frequency, route, and date will also be included on the eCRF.

6.8.1.1. Bisphosphonate Therapy

Bisphosphonate therapy is strongly recommended for all participants with evidence of lytic destruction of bone or with osteopenia. Bisphosphonate therapy is recommended to be continued according to treatment guidelines (NCCN 2014). Commercially available IV bisphosphonates (pamidronate and zoledronic acid) are preferred when available and should be used according to the manufacturer's recommendations, as described in the prescribing information, for participants with osteolytic or osteopenic myelomatous bone disease. Oral bisphosphonates may be used as alternatives if IV bisphosphonates are not available at the study site. It is preferred that investigators use the same route of bisphosphonate therapy for all participants at their sites. Participants who are using bisphosphonate therapy when they enter the study should continue the same treatment. Participants with evidence of lytic destruction of bone or with osteopenia who are not using a bisphosphonate at the time of administration of study treatment should start a bisphosphonate as soon as possible during Cycle 1 or 2 of treatment. Investigators should not start bisphosphonate therapy during the study, unless it has been agreed with the sponsor that there is no sign of disease progression.

6.8.1.2. Therapy for Tumor Lysis Syndrome

Participants should be monitored for symptoms of tumor lysis syndrome. Management of tumor lysis syndrome, including dehydration and abnormal laboratory test results such as hyperkalemia, hyperuricemia, and hypocalcemia, are highly recommended. It is also recommended that high-risk participants (ie, those with a high tumor burden) should be treated prophylactically in accordance with local standards (eg, rehydration, diuretics). Xanthine oxidase inhibitors (eg, allopurinol) are not allowed (see Section 6.8.2), as they cause an accumulation of orotic acid in the urine, which would confound assessment of safety in these participants. Participants will receive prophylactic therapy to prevent IRRs during the treatment period, as described in Section 6.5.1.

6.8.1.3. Management of Hepatitis B Virus Reactivation

For participants who are diagnosed with HBV reactivation while on treatment, daratumumab SC should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, daratumumab SC may be resumed with concomitant antiviral prophylaxis as per local standard of care and in consultation with the medical monitor.

6.8.2. Prohibited Medications and Procedures

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

Participants are prohibited from receiving the following therapies during the screening and treatment of this study:

- Investigational treatments or commercially available agents with activity against or under investigation for MM.
- Live vaccines within 30 days before the first dose of study treatment, while participating in the study, and until 3 months after the last dose of study treatment.
  - Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, nasal seasonal flu, nasal H1N1 flu, rabies, Bacillus Calmette-Guérin, and typhoid.
- Except for erythropoietin or darbepoetin alpha (Aranesp®), use of growth factors (G-CSF, GM-CSF, etc) is not permitted in the first treatment cycle unless the participant experiences a hematologic DLT.
- Typically, IV contrast is not used in CT scanning of participants with secretory MM because of the risk to the kidney. If administration of IV contrast is necessary, then adequate precautions including hydration are indicated.
- Concomitant treatment with valproic acid/valproate-containing therapies is not permitted, as hyperammonemia is a well-described toxicity of valproic acid, particularly at high exposures, potentially through inhibition of the urea cycle (Verrotti et al 2002, Wadzinski et al 2007).
- Concomitant treatment with allopurinol or other xanthine oxidase inhibitors is not allowed. Xanthine oxidase inhibitors (eg, allopurinol) cause an accumulation of orotic acid in the urine, which would confound the assessment of safety in these participants.
- Prolonged therapy with systemic glucocorticoids (> 7 days) for any purpose other than to modulate symptoms from an AE, SAE, or event of clinical interest, or for use as pre- and post-administration medications. Brief, limited use of systemic corticosteroids (≤ 7 days) are permitted where such use is considered standard of care.
  - Replacement doses of steroids (for example, prednisone 5 to 7.5 mg daily) are permitted while on study, as is the use of local steroids.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from treatment but should continue in the study for assessment of disease status and survival.

There are no prohibited therapies during the post-treatment follow-up period.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- The participant has an unacceptable toxicity or a toxicity that does not recover in 6 weeks. Investigators who wish to continue treatment after a treatment delay of 4 weeks should consult with the sponsor's medical monitor for approval.
- An AE requiring more than 2 dose reductions of INCB001158.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be withdrawn from study treatment.
- If a participant is noncompliant with study procedures or study treatment administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 3 and Table 4 (SoA prior and post-crossover respectively), and Table 5 and Table 6 (for laboratory assessments prior and post-crossover respectively). As of Protocol Amendment 3, see only Table 7 for the SoA for all participants.

The last date of the last dose of study treatment and the reason for discontinuation of study treatment will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the participant's medical record and the primary reason for withdrawal must be included in the eCRF.
- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the IRT.
- Participants must be followed for safety until the time of the 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 treatment and actively withdraws consent for collection of follow-up data (safety or disease status follow-up), then no additional data collection should occur; however, participants will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments.

NOTE: As of Protocol Amendment 3, no further disease status and survival follow-up assessments will be required beyond the last safety follow-up visit.

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 (SoA prior and post-crossover respectively), and Table 5 and Table 6 (laboratory assessments prior and post-crossover respectively) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

NOTE: As of Protocol Amendment 3, see only Table 7 for the SoA and laboratory assessments for all participants.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF(s) 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.

[redacted] Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

8.1.2. Screening Procedures

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

Procedures conducted as part of the participant's routine clinical management (eg, blood count, imaging study) and obtained before signing of 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 Cycle 1 Day 1). For participants who are enrolled in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before treatment assignment will be used to determine eligibility. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes there has been a change in eligibility status (eg, after recovery from an infection).

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 system to obtain the participant ID number during screening. Upon determining that the participant is

eligible for study entry, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT system will be contacted at each regular study visit to update the study drug supply. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Reminder Cards and Diaries

Participants will be provided with a reminder card at each visit. The reminder card will indicate the date/time of the next visit and will also remind the participant that they should not take their morning dose of INCB001158 before visiting the clinic on those days, as they will take them after blood draws for safety evaluation have been completed.

Participants will also be provided with diaries to record dates, times, and doses of INCB001158 that they take between clinic visits.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include year of birth/age, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment within the last 10 years that are considered to be clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

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

8.2. Efficacy Assessments

NOTE: As of Protocol Amendment 3, the disease assessments are only required to be performed as per the site standard of care guidelines for the participant's condition and monitoring. Participants must be withdrawn from the study if, in the opinion of the investigator, the disease has progressed and the participant is no longer having clinical benefit from the study treatment.

8.2.1. Evaluations

8.2.1.1. Responses Categories

Assessment of tumor response and disease progression will be conducted in accordance with the IMWG response criteria. Disease evaluations will include measurements of myeloma proteins, bone marrow examinations, skeletal surveys, assessment of extramedullary plasmacytomas, and measurements of serum calcium corrected for albumin.

Efficacy/disease evaluations must be performed at each treatment cycle as specified in the SoA (see Table 3 and Table 4; as of Protocol Amendment 3, see Table 7 for all participants). The sponsor may request that the disease assessments be sent for central independent review. Disease evaluations scheduled for treatment days should be collected before study treatment is administered. Disease evaluations will be performed by a central laboratory (unless otherwise

specified) until disease progression or the EOT. This study will use the IMWG consensus recommendations for MM treatment response criteria (Durie et al 2006, Kumar et al 2016, Rajkumar et al 2011) presented in Table 19. Per IMWG uniform response criteria, all response categories and PD require 2 consecutive assessments except for radiographic or bone marrow assessments. For quantitative Ig at baseline, M-protein, IFE, and FLC measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory. For participants with suspected daratumumab interference on SPEP and IFE, a reflex assay will be performed (see Appendix E). Participants with confirmed daratumumab interference who meet all other clinical criteria for CR or sCR will be considered CR/sCR.

Table 19: International Uniform Response Criteria Consensus Recommendations

Response	Response Criteria
Stringent complete response (sCR)	• CR as defined below, plus • Normal FLC ratio, and • Absence of clonal PCs by immunohistochemistry, immunofluorescence,[a] or 2- to 4-color flow cytometry.
Complete response (CR)[b]	• Negative immunofixation on the serum and urine, and • Disappearance of any soft tissue plasmacytomas, and • < 5% PCs in bone marrow.
Very good partial response (VGPR)[b]	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, or • ≥ 90% reduction in serum M-protein plus urine M-protein < 100 mg/24 hours.
Partial response (PR)	• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours. • If the serum and urine M-protein are not measurable, a decrease of ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in bone marrow PCs is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%. • In addition to the above criteria, if present at baseline, a ≥ 50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.
Minimal response (MR)	• ≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50% to 89%. • In addition to the above criteria, if present at baseline, 25% to 49% reduction in the size of soft tissue plasmacytomas is also required. • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, MR, or PD.

Table 19: International Uniform Response Criteria Consensus Recommendations (Continued)

Response	Response Criteria
Progressive disease (PD)[c]	Increase of 25% from lowest response value in any one of the following: • Serum M-component (absolute increase must be ≥ 0.5 g/dL), • Urine M-component (absolute increase must be ≥ 200 mg/24 hours), • Only in participants without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL). • Only in participants without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥ 10%). • Bone marrow plasma cell percentage: the absolute percentage must be > 10%. • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas (SPD). • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the PC proliferative disorder.

FLC = free light chain; PC = plasma cell; SPD = sum of the products of the maximal perpendicular diameters of measured lesions.

Note: All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

Note: Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

[a] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.

[b] Clarifications to IMWG criteria for coding CR and VGPR in participants in whom the only measurable disease is by serum FLC levels: CR in such participants indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such participants requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

[c] Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in participants without measurable disease by M-protein and by FLC levels; "25% increase" refers to M-protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia, and the "lowest response value" does not need to be a confirmed value.

8.2.1.2. Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples for M-protein measurements will be sent to and analyzed by a central laboratory. Only 1 serum and one 24-hour urine sample at each timepoint are required by the central laboratory to perform the following tests:

- Serum quantitative Igs
  - All participants will be evaluated for IgG, IgA, IgM, IgE, and IgD as indicated in Table 3 and Table 4.
- SPEP

- Serum IFE at screening and thereafter when M-protein is nonquantifiable
- Serum FLC assay
- 24-hour UPEP
- Urine IFE at screening and thereafter when a M-protein is nonquantifiable

Blood and 24-hour urine samples will be collected as specified in the SoA (see Table 3 and Table 4; see Table 7 for the SoA for all participants as of Protocol Amendment 3) until the development of confirmed disease progression. If the 24-hour urine collection (UPEP) began before informed consent was obtained as part of routine patient care, the sample can be used in this study as long as it was sent to the central laboratory for analysis after the informed consent was obtained. Disease progression based on one of the laboratory tests alone must be confirmed by at least 1 repeat investigation performed 1 to 3 weeks later. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed. Serum and urine IFE and serum FLC assay will be performed at screening and thereafter when a CR is suspected or maintained (when serum or 24-hour urine M-protein electrophoresis [by SPEP or UPEP] are 0 or nonquantifiable). For participants with light chain MM, both serum and urine IFE test will be performed routinely.

Serum IFE assay samples will be split into 2 aliquots, with 1 reserved for potential follow-on testing if daratumumab interference with IFE is suspected. As daratumumab is a monoclonal IgG antibody, additional serum samples may be used to monitor for potential daratumumab interference with the IFE.

Previous studies have demonstrated potential interference of therapeutic monoclonal antibodies with detection of endogenous myeloma M-protein on serum IFE (McCudden et al 2015). For participants with suspected daratumumab interference on SPEP, serum IFE, or both, a follow-up test will be run using anti-idiotype antibodies against daratumumab to remove antibody interference.

Participants who meet all other IMWG criteria for CR or sCR, and whose positive IFE is confirmed to be daratumumab, will be considered as having a CR or sCR.

8.2.1.3. Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected and analyzed centrally (as specified in Table 3 and Table 4; see Table 7 for the SoA for all participants as of Protocol Amendment 3). During the treatment period, development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or > 2.8 mmol/L) can indicate disease progression or relapse if it is not attributable to any other cause (see disease response criteria, Table 19). Calcium binds to albumin, and only the unbound (free) calcium is biologically active; therefore, the serum calcium level must be adjusted for abnormal albumin levels ("corrected serum calcium"). Measurement of free ionized calcium is an acceptable alternative to corrected serum calcium for determining hypercalcemia. Free ionized calcium levels greater than the ULN (local laboratory reference ranges) are considered as having achieve a CR or sCR.

8.2.1.4. β2-microglobulin and Albumin

Blood samples for β2 microglobulin and albumin are to be collected at screening and will be analyzed by the central laboratory. The central laboratory values will be used for the International Staging System calculation.

8.2.1.5. Bone Marrow Examination

Bone marrow assessments to be performed locally and centrally are summarized in Table 20.

Table 20: Bone Marrow Testing

	Local Testing	Central Testing
Screening	Disease characterization (morphology and either immunohistochemistry or immunofluorescence or flow cytometry). Cytogenetics by conventional karyotype or FISH.	MRD assessment: a portion of the bone marrow aspirate collected at screening will be sent to the central laboratory (see Section 8.2.1.6). A fresh bone marrow aspirate is preferred, but if a fresh bone marrow aspirate is not performed at screening because a sample is available within 42 days before administration of study treatment, obtain non-decalcified slides (bone marrow aspirate, touch preparation, or clot selection) or FFPE block (clot section only, no bone marrow biopsy).
CR, sCR	For response confirmation, additional bone marrow aspirates or biopsies (or both) will be performed locally to confirm sCR or CR. Response characterization (morphology by immunohistochemistry or immunofluorescence or flow cytometry). For sCR: Detection of kappa/lambda ratio by 2-4 color flow cytometry is strongly preferred. If flow cytometry is not available at site, either immunohistochemistry or immunofluorescence can be done; however, kappa/lambda ratio from analysis of ≥ 100 plasma cells is required to confirm sCR. If sCR is not met, repeat local testing for sCR with subsequent bone marrow examinations will be performed.	MRD assessment: a portion of the bone marrow aspirate collected for confirmation of CR/sCR will be sent to the central laboratory for MRD assessment. For participants who achieve CR and remain on study, an additional bone marrow aspirate will be obtained as indicated in Table 3.

CR = complete response; FFPE = formalin-fixed, paraffin-embedded; FISH = fluorescence in situ hybridization; MRD = minimal residual disease; sCR = stringent complete response.

8.2.1.6. Minimal Residual Disease Assessment

Bone marrow aspirate will be collected for MRD analysis, when bone marrow samples are obtained at screening, confirmation of CR/sCR, and subsequent timepoints after the first dose (see Table 20). Baseline bone marrow aspirate samples will be subjected to DNA sequencing to establish a MM clone for MRD monitoring. A fresh bone marrow aspirate at screening is required, if possible. By exception, non-decalcified diagnostic tissue slides (bone marrow aspirate, touch preparation or clot selection) or FFPE block (clot selection only, no bone marrow biopsy) may be supplied for MRD assessment. For participants who achieve a CR, bone marrow aspirates will be used for assessment of MRD by NGS of Ig heavy and light chains. If this methodology is unavailable, or determined to be scientifically inferior, then alternative methods for MRD assessment may be used.

8.2.1.7. Assessment of Lytic Disease

A complete skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) is to be performed and evaluated by the local laboratory by roentgenography (or the local standard of care imaging, eg, low-dose whole body CT) during the screening period. Please note that the same methodology used at screening should be used throughout the study for comparison purposes. During the treatment period and before disease progression is confirmed, imaging should be performed whenever clinically indicated based on symptoms or to document response or progression. Magnetic resonance imaging is an acceptable method for evaluation of bone disease and may be included as an additional assessment at the discretion of the investigator (see the disease response criteria in Table 19).

Participants may show disease progression manifested by symptoms of pain due to bone changes. Therefore, disease progression may be documented, in these cases, by skeletal survey or other radiographs, depending on the symptoms that the participant experiences. If the diagnosis of disease progression is obvious by radiographic investigations, then no repeat confirmatory imaging is necessary. In instances where changes may be subtler, repeat imaging may be performed in 1 to 3 weeks according to investigator discretion.

8.2.1.8. Assessment of Extramedullary Plasmacytomas

Sites of known extramedullary plasmacytomas must be documented during the screening period. Clinical examination or MRI may be used to document extramedullary sites of disease. Computed tomography scan evaluations are an acceptable alternative if there is no contraindication to the use of IV contrast. Positron emission tomography scan alone (ie, without a CT) or ultrasound tests are not acceptable to document the size of extramedullary plasmacytomas.

Extramedullary plasmacytomas should be assessed for all participants with a history of plasmacytomas or if clinically indicated at screening, by clinical examination or radiologic imaging. For participants with a history of plasmacytomas assessed by physical examination, physical examination should be repeated on Cycle 1 Day 1 if not done within 14 days before administration of study treatment. Assessment of measurable sites of extramedullary disease will be performed and evaluated locally approximately every 4 weeks by physical examination or approximately every 12 weeks by imaging (if required) for participants with a history of

plasmacytomas or as clinically indicated during treatment for other participants, until development of confirmed CR or confirmed disease progression. For every participant, the methodology used for evaluation of each disease site should be consistent across all visits. Irradiated or excised lesions will be considered not measurable and will be monitored only for disease progression.

To qualify for PR, the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have decreased by at least 50%, and new plasmacytomas must not have developed (see the disease response criteria in Table 19). To qualify for disease progression, either the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have increased by at least 50% or a new plasmacytoma must have developed. In the cases where not all existing extramedullary plasmacytomas are reported, but the sum of products of the perpendicular diameters of the reported plasmacytomas have increased by at least 50%, this will also qualify as disease progression.

8.2.2. Health Economics

Not applicable.

8.3. Safety Assessments

See Section 6.7 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

NOTE: As of Protocol Amendment 3, safety assessments are only required to be performed as per the site standard of care guidelines for the participant's condition and monitoring. Only SAEs, AESIs, and pregnancy will be collected in the eCRF.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 28 days after the last dose of study drug. Immune-related AEs will be collected until 90 days after the last dose of study drug. 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 treatment/procedures, or that caused the participant to discontinue the study treatment. 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, and nonserious AESIs (as defined in Section 9.5), 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. Forced Expiratory Volume Test

Participants with known or suspected COPD or asthma must have an FEV1 test during screening. See Section 6.5.1.2 for details on participants with higher risk of respiratory complications.

8.3.3. Physical Examinations

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

8.3.3.1. Comprehensive Physical Examination

At the screening visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include height and body weight, and assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination.

8.3.3.2. Targeted Physical Examination

The targeted physical examination will be a symptom-directed evaluation. The targeted physical examination will include body weight and assessment(s) of the body systems or organs, as indicated by participant symptoms, AEs, or other findings.

8.3.4. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests), include blood pressure, pulse, respiratory rate, body temperature. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Weight will also be assessed at each study visit. Abnormal vital sign results identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug.

8.3.5. Electrocardiograms

Electrocardiograms (triplicate 12-lead ECGs) will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All

12-lead ECGs will be performed in triplicate (within approximately 15 minutes) with the participant in a recumbent or semirecumbent position after 5 minutes of rest. Whenever possible, ECGs should be performed immediately before chemistry [redacted] assessments.

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

8.3.6. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status will be used to evaluate the effect of the disease status on the activities of daily living according to the criteria in Table 21. When scheduled, ECOG performance status assessments should be obtained before any other study procedures planned for the same day whenever possible.

Table 21: ECOG Performance Status

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

Source: Oken et al 1982.

8.3.7. Laboratory Assessments

See Table 22 for the list of clinical laboratory tests to be performed and the Schedule of Laboratory Assessments (see Table 5 and Table 6) for the timing and frequency. A certified laboratory local to the investigative site will perform most of the clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, lipid panel, thyroid panel, and urinalysis). All local laboratory assessments should be performed using standard procedures on the days indicated in Table 5 and Table 6. Table 22 lists the specific laboratory analytes required for each test. Some additional tests (ie, [redacted] urinary orotic acid; see Table 23) will be conducted by 1 or more central laboratories, on the days indicated in Table 5 and Table 6. The investigative site will enter the laboratory results and laboratory normal ranges into the eCRF. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment (or until start if a new anticancer therapy) should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

Screening laboratory assessments must be performed within 7 days of Cycle 1 Day 1. If performed more than 7 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study treatment administration on Cycle 1 Day 1. Laboratory samples collected on study Day 1 must be performed before study treatment administration. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study treatment administration (within the study windows indicated in Table 3 and Table 4; Table 5 and Table 6; see Table 7 for the SoA for all participants as of Protocol Amendment 3), and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

NOTE: As of Protocol Amendment 3, laboratory assessments should be performed in accordance with the standard of care of the investigational site for the participant's condition. Laboratory results do not need to be reported in the eCRF, but all laboratory results corresponding with an SAE or an AESI will be reported on the SAE form. In addition, pregnancy testing will continue to be performed for all participants as per the SoA in Table 7.

Table 22: Required Laboratory Analytes

Chemistries	Hematology	Urinalysis With Microscopic Examination	Serology[a]
Albumin Alkaline phosphatase ALT Ammonia Amylase [redacted] AST Bicarbonate or CO_2 BUN or urea Calcium Chloride Creatinine Glucose Lactate dehydrogenase Lipase [redacted] Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • White blood cell count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils Absolute values must be provided for: • WBC differential laboratory results • Blood type test[c]	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Orotic acid[b] Protein	Hepatitis B surface antigen Hepatitis B surface antigen antibody Hepatitis B core antibody HBV DNA HCV antibody HCV RNA HIV RNA (if required by local regulations)
		Lipid Panel	**Pregnancy Testing**
		Total cholesterol Triglycerides LDL HDL	Female participants of childbearing potential require a serum pregnancy test at screening and a urine pregnancy test on Day 1 of every cycle, at EOT, and as medically indicated or per country or institutional requirements. Pregnancy tests (serum or urine) should be repeated if required by local regulations.
		Thyroid panel	
		TSH FT4 FT3/T3	

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data.

[a] Hepatitis B and C viral loads by PCR assay only need to be assessed when respective serology results are positive. Hepatitis B virus DNA does not need to be performed if the surface antibody is the only positive result.

[redacted]

[c] For participants receiving daratumumab SC (monotherapy or in combination with INCB001158) only.

8.3.7.1. Blood Type Assessment

A blood type test will be performed as outlined in Table 22. CD38 is expressed on erythrocytes to a minor extent. Hemolysis could occur after the administration of daratumumab SC, which would confound the blood type assessment. To be cautious and in case of urgent need for blood transfusion, the participant's blood type will be assessed before administration of daratumumab SC, and it is recommended that the participants carries a card with the blood type during the study at all times.

8.3.7.2. Chemistries

[redacted]

See Table 5 and Table 6 for sampling time points and the Laboratory Manual for details of how to process, store, and ship the samples to the certified central laboratory or laboratories for sample analysis.

8.3.7.3. Urinalysis

Standard urinalysis will be performed as outlined in Table 22, and urinary orotic acid, which is a marker of urea cycle inhibition that is a potential side effect of INCB001158 (refer to the IB), will be assessed as outlined in Table 23. Participants must fast at least 8 hours before each clinic visit and void their bladder in the morning before providing the predose urine sample at the clinic.

Table 23: Sample Collection Times for Assessments of Urinary Orotic Acid

Study Visit	Time
C1D1	Predose and 6 h (± 1 h) postdose
C1D8[a]	Predose
C1D15	Predose and 6 h (± 1 h) postdose
C2D1 and D1 of all subsequent cycles	Predose

Note: Additional samples may be collected as clinically indicated.
[a] The C1D8 sample will be collected only for participants enrolled in Phase 1.

8.3.7.4. Plasma Ammonia

Plasma ammonia levels are to be tested during screening (see Table 5 and Table 6). If above the ULN, repeat the sample to confirm the value. If the participant experiences an elevation in urine orotic acid (> 10 × ULN fasted or > 40 × ULN of any value) while on study treatment or during the follow-up period, monitor plasma ammonia levels each time the urine orotic acid is tested, at least until orotic acid levels have returned to normal, at the investigator's and medical monitor's discretion.

8.3.7.5. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening. Urine pregnancy tests will be performed locally as outlined in Table 5 and Table 6, as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement (note that country-required urine pregnancy testing will be outlined and communicated to investigational sites under separate cover). If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

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

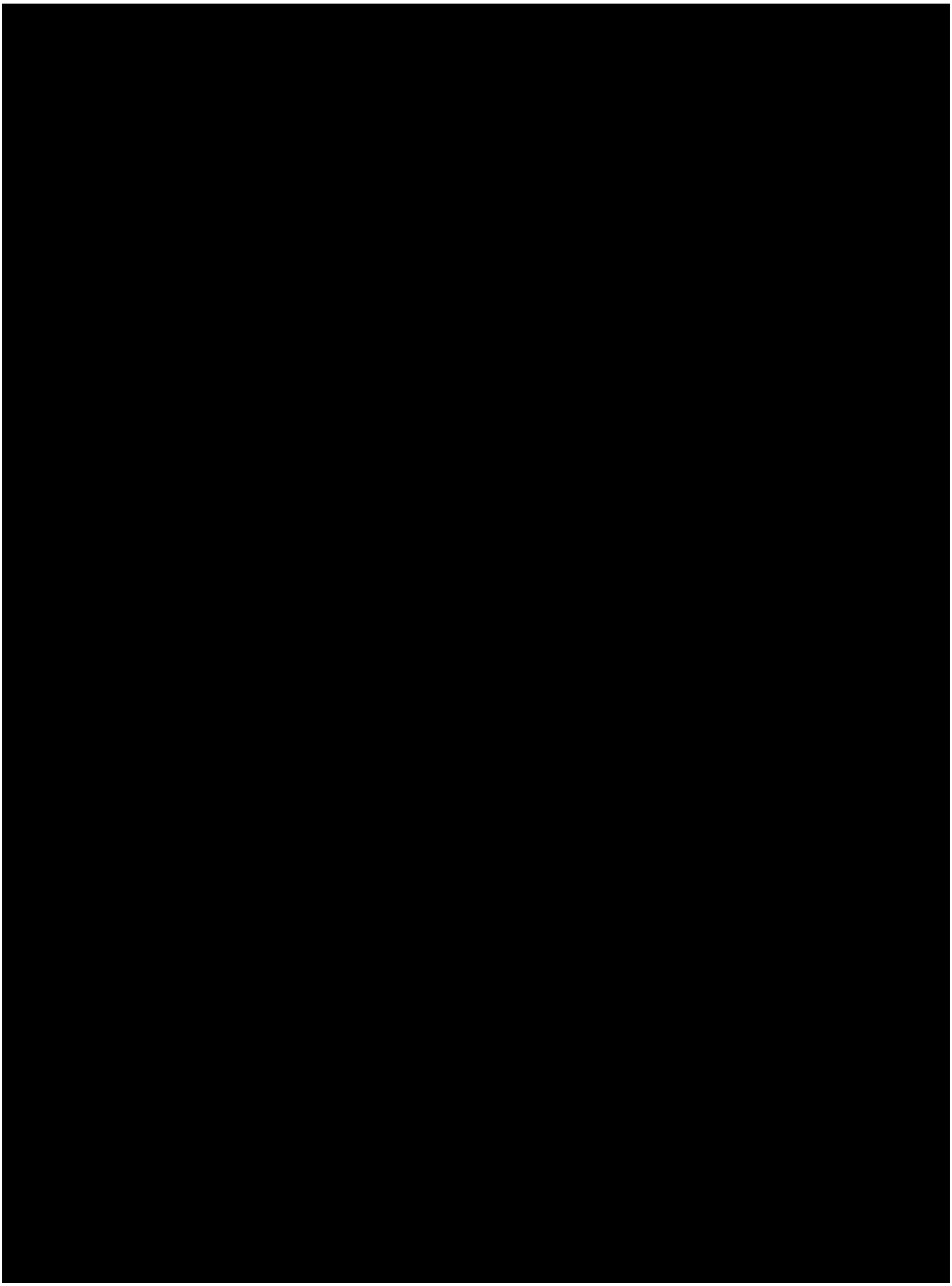
If a pregnancy is confirmed by a serum pregnancy test, see Section 9.7 for reporting requirements.

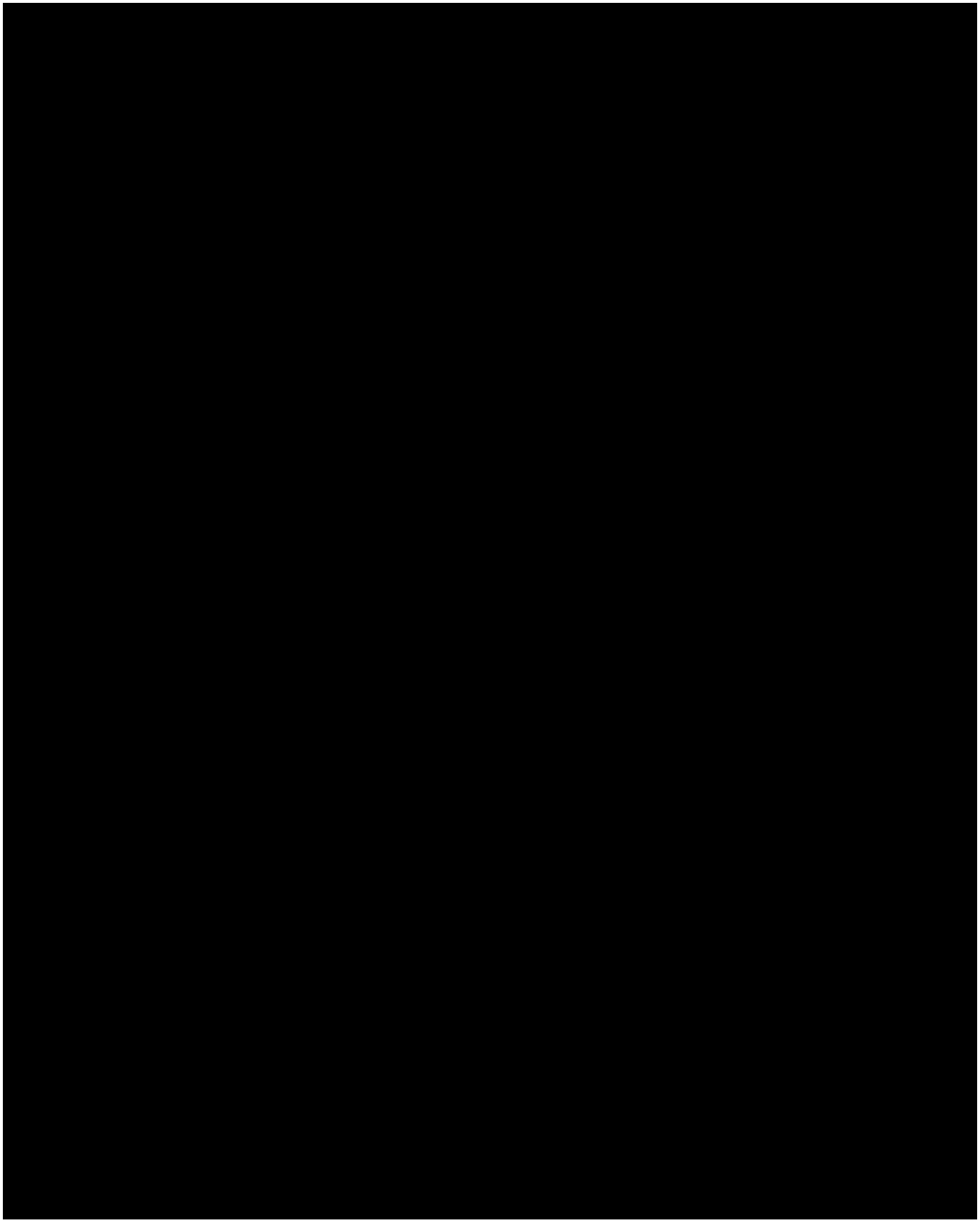
8.3.7.6. Serology

Hepatitis and HIV screening assessments will be performed at the screening visit (see Table 5) to rule out hepatitis and HIV infection, respectively; required analytes are shown in Table 22.

Participants who are positive for anti-HBs or anti-HBc will undergo testing for HBV DNA by PCR as specified in Table 5 and Table 6. Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR.

Generally, hepatitis and HIV 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.





8.6. Unscheduled Visits

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

8.7. End of Treatment and/or Early Termination

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

8.8. Follow-Up

8.8.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 28 to 35 days after the EOT visit (or after the last dose of study treatment if the EOT visit was not performed). Adverse events and SAEs must be reported up

until 1) at least 28 days after the last dose of study treatment and 90 days for irAEs or the start of a new anticancer therapy or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period. If the participant cannot return to the site for the safety follow-up visit, the participant should be contacted by telephone for assessment of AEs and SAEs, and this contact should be documented in the source.

If a participant is scheduled to begin a new anticancer therapy before the end of the 28- to 35-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 survival follow-up period.

NOTE: As of Protocol Amendment 3, data will only be collected for SAEs, AESIs, and pregnancy. Once a new anticancer therapy has been initiated, the participant will no longer be followed for survival follow-up beyond the last safety follow-up visit.

8.8.2. Disease Status Follow-Up

Participants who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up period and should be assessed every 8 weeks ± 7 days after EOT to monitor disease status. Every effort should be made to collect information regarding disease status until:

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

NOTE: As of Protocol Amendment 3, disease status follow-up visits for participants who discontinue study treatment for a reason other than disease progression are no longer required beyond the safety follow-up visit. The last disease status follow-up data will be recorded in the eCRF at the time of the safety follow-up visit. The last study visit will be the safety follow-up visit.

8.8.3. Survival Follow-Up

Once a participant has received the last dose of study drug, has confirmed disease progression, or starts a new anticancer therapy, the participant moves into the survival follow-up period and should be contacted by telephone, email, or visit at least every 12 weeks following EOT to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

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

NOTE: As of Protocol Amendment 3, the survival follow-up visits for participants who discontinue study treatment for a reason other than disease progression are no longer required beyond the safety follow-up visit. The last survival follow-up data will be recorded in the eCRF at the time of the safety follow-up visit. The last study visit will be the safety follow-up visit.

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

NOTE: As of Protocol Amendment 3, the only safety data that will be collected will be related to SAEs, AESIs, and pregnancy. The safety follow-up visits may be completed remotely (such as by televisit).

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
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 treatment. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal lab result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after study treatment administration are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from dosing errors of a study 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. • 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, and the procedure is to be documented as well. 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 (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 invasive or malignant cancers (excluding the disease under study), intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse, or suspected transmission of an infectious agent via a medicinal product. Secondary malignancies should always be considered SAEs. Suspected transmission of an infectious agent via a medicinal product is also to be considered an SAE.

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

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Event Form in the eCRF. Conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the AE eCRF page.
- There may be 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 on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the Study Reference Manual or as per SAE completing guidelines.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

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

- The 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 treatment (including INCB001158 and/or daratumumab SC): 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 INCB001158 and/or daratumumab SC 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 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 1 of the following categories:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.

- **Grade 2:** Moderate; minimal, local, or noninvasive treatment indicated; limiting age appropriate activities of daily living.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4:** Life-threatening consequences; urgent treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. If appropriate, the relationship to the combination may be assessed as well.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- The investigator will also consult the Reference Safety Information in the respective INCB001158 and daratumumab IBs, or Darzalex/Darzalex FASPRO Product Information, in making his/her assessment.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality 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 send a follow-up SAE report with the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- 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 treatment, the interventions required to treat the event, and the outcome.
- Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (either via email/fax if paper SAE form is used or in the SAE EDC CRF) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study treatment, or study procedure[s]), all SAEs occurring after the participant has signed the ICF through 28 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) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Serious AEs that are irAEs must be reported until 90 days after the last dose of study drug. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. If the investigator learns of any SAE, including death, at any time during this period, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AESIs (as defined in Section 9.5), 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 a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

If the SAE is not documented in the Reference Safety Information in the respective INCB001158 and daratumumab IBs, or Darzalex/Darzalex FASPRO Product Information (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 expedited reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

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

Investigator safety reports must be prepared for suspected unexpected adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

NOTE: As of Protocol Amendment 3, all SAEs regardless of causality relationship will continue to be reported in the eCRF.

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 SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available. The contact information for Incyte Pharmacovigilance by email/fax is listed in the Study Reference Manual 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 or Study Reference Manual for details and for the email address or fax number). • Follow-up information is recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study treatment because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

9.5. Adverse Events of Special Interest

Adverse events that are potentially immune-related or related to urea cycle inhibition will be assessed as AESIs that must rapidly be communicated to Incyte for further evaluation. Adverse events of special interest may be laboratory abnormalities or clinical AEs.

The description of the AESI should generally include the following:

- The definition of the event
- Whether it is a measurable quantity. If so, how will the measurement be done?
- Whether it is a clinical event. If so, how will it be confirmed?

Adverse events of special interest should be captured in the eCRF, and/or be provided as expedited reporting from investigators to Incyte's Pharmacovigilance department.

NOTE: As of Protocol Amendment 3, all AESIs will continue to be reported in the eCRF.

9.6. Emergency Unblinding of Treatment Assignment

Not applicable.

9.7. Pregnancy

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

- The study treatment must be interrupted immediately (female participants only).
- If the female participant is no longer pregnant and meets the treatment continuation criteria within 28 days of the scheduled start of a cycle, study treatment may be resumed after approval has been received from the sponsor medical monitor.
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

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

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

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

NOTE: As of Protocol Amendment 3, pregnancy will continue to be reported in the eCRF.

9.8. 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.

9.9. 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.

9.10. Treatment of Overdose

Overdose, as defined for this study, refers to the use of study treatment in doses exceeding those specified in the protocol.

Incyte does not recommend specific treatment of overdose. Treatment of overdose should consist of general supportive measures. In the event of an overdose with INCB001158, the participant should be observed closely for signs of toxicity.

Daratumumab SC is provided as a single vial for administration by a health care professional. Thus, the risk of overdose with daratumumab SC is negligible. There is no known specific antidote for daratumumab overdose. In the event of an overdose of daratumumab SC, the participant should be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment should be instituted immediately.

10. STATISTICS

10.1. Sample Size Determination

10.1.1. Sample Size for Phase 1

In Phase 1, the BOIN design will be used to determine the RP2D of INCB001158 given in combination with daratumumab SC, in participants with relapsed or refractory MM. Dose escalation and de-escalation will follow the BOIN design algorithm. Based on this algorithm, a minimum of 3 evaluable participants and a maximum of 9 evaluable participants will be enrolled at each tested dose level, so up to 18 evaluable participants will be enrolled in Phase 1. The details of the dose escalation, de-escalation, and elimination rules according to the BOIN design are provided in Section 4.1.1.

10.1.2. Sample Size for Phase 2

In Phase 2, the sample size will be guided by the RAR design based on a Bayesian beta-binomial model, which will include within individual treatment groups early termination rules for efficacy and early stopping rules for safety. The proposed RAR design has an expected frequentist 1-sided Type I error of approximately 10% and power of 78% to detect an improvement in response from 20% to 45%. The response rates for each treatment group will be estimated with 90% Bayesian credible intervals.

The expected number of participants accrued each month is 4, and the expected number of months between treatment and assessment of response is 3. The simulation results for various Treatment Group A response rates are presented in Table 26.

Table 26: Estimates of Operating Characteristics for Response Adaptive Design

True Response Rate: Treatment Group A	True Response Rate: Treatment Group B	Probability to Reject Null Hypothesis (Early Termination)	Expected Sample Size in Treatment Groups A, B, and C (Treatment Group A)	Average Study Duration in Months
20%	20%	9.8% (1.2%)	79.7 (34.7)	22.9
35%	20%	50.1% (12.1%)	76.6 (41.4)	21.8
40%	20%	65.7% (19.8%)	74.5 (41.5)	21.0
45%	20%	78.7% (30.0%)	71.7 (40.6)	20.0

Note: For each simulated study replication, the first 30 participants were equally randomized among Treatment Groups A, B, and C, and the next 50 participants were randomized among Treatment Groups A and B using RAR. Sample size and study duration estimates were based on projected enrollment of 4 participants per month and the time to response of 3 months. Estimates were based on simulation of 300,000 study replications.

Descriptive statistics for the ORR, DOR, and other efficacy parameters for Treatment Group C will be provided.

10.2. Populations for Analysis

Table 27 presents the populations for analysis.

Table 27: Populations for Analysis

Population	Description
Enrolled	All participants who sign the ICF.
FAS	All participants enrolled in the study who received at least 1 dose of study treatment (INCB001158 or daratumumab SC). Participants will be analyzed according to the treatment that they were assigned to. The FAS will be used for the summary of demographics, baseline characteristics, and disposition.
IMWG response evaluable	All participants enrolled in the study who have received at least 1 dose of study treatment (INCB001158 or daratumumab SC), completed a baseline disease assessment, and meet at least 1 of the following criteria: • ≥ 1 postbaseline disease assessment • Been on the study for a minimum of 35 days of follow-up • Discontinued from treatment
DLT evaluable	All participants who receive at least 42 of 56 doses for the 28-day cycle regimen (representing ≥ 75% of the dose planned) of INCB001158 at the level assigned or who have a DLT.
[redacted]	[redacted]

10.3. Level of Significance

The test for the primary efficacy analysis in Phase 2 has approximately a 1-sided 10% Type I error level. Other secondary [redacted] endpoints will be compared using a 2-sided, 5% significance level but are not considered alpha-controlled hypotheses.

10.4. Statistical Analyses

10.4.1. Efficacy Analyses

10.4.1.1. Primary Efficacy Analyses

The primary endpoint of the Phase 2 portion of the Protocol is ORR, defined as the proportion of participants with CR, VGPR, or PR, according to IMWG Criteria in the randomized IMWG response evaluable population. Participants will be summarized by treatment group assignment in Phase 2.

The primary analysis of ORR in Phase 2 will compare Treatment Groups A and B modeling the ORR of each treatment group with a Beta (0.5,0.5) prior, calculating the probability that the posterior distribution of the ORR for Treatment Group A exceeds that of the posterior distribution the ORR for Treatment Group B. If x_1 (n_1) is the number of responders (evaluable participants) in Treatment Group A and x_2 (n_2) correspond to the same for Treatment Group B, the resulting posterior distribution will be

$$f_i(\gamma_i|x_i,n_i) = \frac{\Gamma(n_i+1)}{\Gamma(x_i+0.5)\Gamma(n_i+0.5-x_i)}\gamma_i^{\,x_i+0.5}(1-\gamma_i)^{\,n_i+0.5-x_i}$$

The resulting probability that the ORR for Treatment Group A exceeds that of Treatment Group B, that is, the PPoS, is the quantity

$$\text{PPoS} = \Pr(ORR_A > ORR_B|x_1,n_1,x_2,n_2) = \int_0^1\int_{\gamma_2}^1 f_1(\gamma_1|x_1,n_1)f_2(\gamma_2|x_2,n_2)d\gamma_1 d\gamma_2$$

Objective response rate and its 90% Bayesian credible intervals for each treatment group will be presented.

Interim analyses will be conducted after the 31st participant is randomized and after each subsequent participant is to be randomized to adjust the randomization rate between Treatment Groups A and B and to determine whether the study should be terminated for positive efficacy. See Section 10.5.2.1 for details on the conduct of these interim analyses.

If the study does not terminate for early efficacy, the final analysis will take place once all participants have been randomized and monitored for response for 3 months OR once all participants have discontinued the study. If PPoS > 0.915, then the null hypothesis will be rejected, and Treatment Group A will be considered to be superior (with respect to ORR) to Treatment Group B.

10.4.1.2. Secondary Efficacy Analyses

Objective response rate will be summarized descriptively for Phase 1 IMWG response evaluable participants.

Time to response is defined as the number of days from the randomization in Phase 2 (or first dose of study drug in Phase 1) to the first documented response of PR, VGPR, or CR (as per IMWG criteria). Time to response will be summarized descriptively by assigned treatment group in Phase 2 and by dose level in Phase 1.

Duration of response is defined as the number of days from earliest date of PR, VGPR, or CR (as per IMWG criteria) until the earliest date of disease progression, relapse, or death due to any cause. Duration of response will be summarized descriptively by assigned treatment group in Phase 2 and by dose level in Phase 1.

Progression-free survival is defined as the duration from the date of first dose of study drug until either progressive disease, as per IMWG criteria, or death, whichever occurs first. Progression-free survival will be summarized descriptively by assigned treatment group in Phase 2 and by dose level in Phase 1.

Minimal residual disease rate is defined as the percentage of participants who are considered MRD negative by IMWG criteria at any time after randomization in Phase 2 or first dose of study drug in Phase 1. The MRD rate will be estimated with 95% binomial confidence intervals provided.

Overall survival is defined as the number of days from randomization in Phase 2 (or first dose of study drug in Phase 2) to death due to any cause. Overall survival will be summarized descriptively by assigned treatment group in Phase 2 and by dose level in Phase 1.

10.4.2. Safety Analyses

10.4.2.1. Adverse Events

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class for all events and AESIs, including irAEs and potential inhibition of the urea cycle (based on urinary orotic acid, plasma ammonia and urea/BUN assessments). Severity of AEs will be based on the NCI CTCAE v5 using Grades 1 through 5.

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

Periodic safety stopping rules will be applied in the Phase 2 portion of the study. See Section 10.5.2.2 for details regarding these interim safety analyses.

10.4.2.2. Clinical Laboratory Tests

Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

Laboratory data will be classified into Grades 1 through 5 using CTCAE v5. The following summaries will be produced for the laboratory data:

- Number and percentage of participants with worst postbaseline CTCAE grade (regardless of baseline value). Each participant will be counted only for the worst grade observed postbaseline.
- Shift tables from baseline to the worst postbaseline value using CTCAE grade.

For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value using the low/normal/high classifications based on laboratory reference ranges.

10.4.2.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 28), and participants exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

Table 28: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 beats/min	< 45 beats/min
Temperature	> 38ºC	< 35.5ºC
Respiratory rate	> 24 breaths/min	< 8 breaths/min

10.4.2.4. Electrocardiograms

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

Table 29: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 470 ms	< 295 ms
PR	> 220 ms	< 75 ms
QRS	> 120 ms	< 50 ms
QT	> 500 ms	< 300 ms
RR	> 1330 ms	< 600 ms

QTcF = Fridericia correction.

10.4.2.5. Adverse Events of Special Interest

Adverse events of special interest include irAEs that are seen with immunotherapy and potential inhibition of the urea cycle (based on urinary orotic acid, plasma ammonia, and BUN/urea assessments).

An overall summary of irAEs will include number (%) of participants reporting any irAEs, any Grade 3 or higher irAEs, any treatment-related irAEs, any fatal irAEs, and any irAEs leading to treatment interruption/dose reduction/discontinuation.

10.5. Interim Analysis

The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

10.5.1. Interim Analysis for Phase 1

In Phase 1, the BOIN design will be used to determine the RP2D of INCB001158 in combination with daratumumab SC. For the design parameters, let ϕ denote the target DLT rate. Let ϕ_1 (= 0.6ϕ) denote the highest toxicity probability below the MTD so that dose escalation is

required, and ϕ_2 (= 1.4ϕ) denote the lowest toxicity probability deemed overly toxic so that dose de-escalation is required.

A dose elimination rule is also applied to avoid assigning participants to an overly toxic dose. Let p_j represent the DLT rate, n_j the participants in the treatment group treated at dose level j, and m_j the participants with a DLT at dose level j. If $P_r(p_j > \phi | m_j, n_j) > 0.95$ and $n_j \geq 3$, then dose levels j and higher are eliminated from the dose escalation for the treatment group, and the dose level is terminated if the first dose level is eliminated.

Table 11 (in the bottom row) provides the elimination boundaries for the target DLT rate of 33%, respectively. For example, for the target DLT rate 33%, when the number of participants treated at the current dose $n_j = 4$, we will eliminate that dose and higher doses if 3 or more participants experience toxicity.

Based on the algorithm of the BOIN design, a minimum of 3 evaluable participants will be enrolled in each dose level with a maximum of 9 evaluable participants in each dose level.

10.5.2. Interim Analysis for Phase 2

10.5.2.1. Efficacy Interim Analysis for Phase 2

In Phase 2, a RAR design will be used to adjust randomization between Treatment Groups A and B and to determine if the study should be terminated for superior efficacy. The first 30 participants will be equally randomized (1:1:1) between Treatment Groups A, B and C. From the 31st participant, adaptive randomization will begin based on the PPoS (as defined in Section 10.4.1.1), comparing Treatment Group A to B ORR using posterior probabilities with the probability of assignment to Treatment Group A being

$$\text{Randomization Probability} = \begin{cases} 0.2 & if\ PPoS < 0.2 \\ 0.8 & if\ PPoS > 0.8 \\ PPoS & otherwise \end{cases}$$

If during randomization PPoS > 0.9975, then the study will be terminated for superior efficacy. Properties of the design parameters, including likelihood of early termination for efficacy and expected sample sizes, are provided in Section 10.1.2, Table 26. Stopping rules will also be applied in the event of unacceptable toxicity and are provided in Section 10.5.2.2. Up to 50 participants will be adaptively randomized to expansion Treatment Groups A and B.

10.5.2.2. Safety Interim Analysis for Phase 2

Stopping rules will be applied using the historical rate of Grade 4 or higher AEs for daratumumab monotherapy as the endpoint in question for potential early stopping for safety. The expected proportion of participants experiencing such AEs is approximately 19.2% (30/156) in participants receiving daratumumab monotherapy (see Appendix 3 of the daratumumab IB). Table 30 provides the resulting stopping boundaries for various numbers of evaluable participants and will use the Pocock-type boundary (Ivanova et al 2005).

The boundary was selected using a 10% Type 1 error for stopping when the true rate of Grade 4 or higher AEs is 19.2% assuming a maximum sample size of 55 participants. If 55 participants are to be treated in the INCB001158 + daratumumab treatment group and the treatment group has a true Grade 4 or higher AE rate of 40%, the resulting rule has a 96% probability to halt

enrollment to the study with a probability of approximately 12% if the AE rate is only 20%. If only 40 participants are randomized and treated with INCB001158 + daratumumab, then the rule has an 89% probability to halt enrollment to the study and a probability of approximately 10% if the AE rate is only 20%.

Table 30: Pocock-Like Boundaries for Treatment Group A (INCB001158 + Daratumumab)

Boundaries	**No. of Participants**								
Number of evaluable participants	3-4	5-6	7-9	10-13	14-16	17-20	21-23	24-27	28-31
Halt enrollment if Grade 4 and 5 AEs observed in ≥	3	4	5	6	7	8	9	10	11
Number of evaluable participants	32-35	36-39	40-43	44-47	48-51	52-55			
Halt enrollment if Grade 4 and 5 AEs observed in ≥	12	13	14	15	16	17			

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.

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

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor 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 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.

The sponsor (or designee) will be responsible for:

- The data management of this study including quality checking of the data.
- 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.

The investigator will be responsible for:

- Ensuring participant data relating to the study is recorded in the eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, diary data) or as otherwise specified in the Protocol. The investigator is responsible for 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.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
  - Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.

- Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR). Appropriate consent for collection, use and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

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

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

11.4. Financial Disclosure

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

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

11.5. Publication Policy

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

11.6. Study and Site Closure

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

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

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

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For male participants in the study:

Male participants should use a condom from screening through 90 days after the end of systemic exposure. If the male participant has a partner that is of child-bearing potential, the partner should also use contraception through 90 days after the end of relevant systemic exposure. In addition, male participants must refrain from donating sperm from screening through 90 days after the end of relevant systemic exposure. Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

For female participants in the study:

The following methods 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[a]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - injectable
  - implantable[b]
- Intrauterine device[b]
- Intrauterine hormone-releasing system[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[bc]
- Sexual abstinence[d]

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide[e]
- Cap, diaphragm, or sponge with spermicide[e]
- Tubal ligation

[a] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

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

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

[d] 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.

[e] A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Source: Clinical Trial Facilitation Group 2014.

APPENDIX B. INSTRUCTION TO PARTICIPANTS FOR HANDLING STUDY DRUG (INCB001158)

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

- To store the study drug at room temperature.
- To only remove from the study drug bottle the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- To report any missed doses.
- To take study drug at approximately the same times each day, without respect to food (except on Protocol-defined clinic days when the participant should fast for at least 8 hours before taking study drug) with a full glass of water. The second dose on any given day should be taken approximately 12 hours after the first dose.
- If the participant vomits after taking study drug, the participant should not take another dose. The participants should report the frequency of vomiting occurrences associated with study drug administration to the site. [redacted]
- To keep study drug in a safe place and out of reach of children.
- To bring all used and unused study drug containers to the site at each visit.
- Missed doses of INCB001158 should be skipped. If a participant forgets to take a dose of study drug and he/she is outside of the allotted window period (± 6 h), he/she should be instructed to skip that dose and NOT take extra study drug at their next administration.

On Protocol-defined clinic days (see Table 3 and Table 4; Table 5 and Table 6; see Table 7 for the SoA for all participants as of Protocol Amendment 3) participants should be instructed NOT to take their morning dose of INCB001158 at home. The morning dose must be administered at the clinical site after all predose procedures have been performed. The time of dose administration will be recorded in the clinic. The evening doses will be self-administered by the participant after all postdose activities have been completed.

APPENDIX C. DARATUMUMAB SC DRUG INFORMATION

Detailed information on the composition of the daratumumab SC is in the SIPPM and the daratumumab IPPI.

Physical Description of Daratumumab SC

The daratumumab supplied for SC injection (daratumumab SC) in this study is a colorless to yellow liquid and sterile concentrate of 120 mg/mL daratumumab + 2000 U/mL rHuPH20 as a liquid in vial. The study agent should be essentially free of visible particulate matter at the time of syringe preparation and drug product administration. Refer to the daratumumab IB for a list of excipients.

Packaging

Daratumumab SC is supplied in glass vials containing daratumumab at a concentration of 120 mg/mL and rHuPH20 at a concentration of 2000 U/mL (~20 µg/mL). It will be supplied to the site/pharmacy as open-label supply.

Labelling

Daratumumab SC labels will contain information to meet the applicable regulatory requirements. Each vial will contain a study-specific label with a unique identification number.

Preparation, Handling, and Storage

Daratumumab SC Formulation

Daratumumab SC must be stored in the original carton in a refrigerator at controlled temperatures ranging from 2°C to 8°C until it is removed for dose preparation. Daratumumab SC must not be used after the expiry date printed on the label. Daratumumab SC must be protected from light and must not be frozen. The product does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded. Refer to the IPPI for additional guidance on daratumumab SC preparation, handling, and storage.

Daratumumab SC Preparation

Daratumumab SC is a fixed combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial. Detailed instructions for preparation of SC daratumumab will be supplied in the SIPPM and IPPI.

Daratumumab SC Delivery

Daratumumab SC will be delivered by SC injection given through a syringe and needle by a manual push over approximately 3 to 5 minutes. Each dose will be administered at alternating locations on the abdomen. The volume of the SC solution will be 15 mL for the 1800 mg dose. Refer to the IPPI for additional guidance on SC administration of daratumumab SC. All participants will be observed for at least 6 hours after the end of the SC injection during Cycle 1 Day 1 and, if deemed necessary by the investigator, after consecutive injections.

Participants will receive pre-administration and post-administration medications as detailed in Section 6.5.1. All participants should have vital signs monitored as specified in Table 3 and Table 4. If a participant experiences a significant medical event, then the investigator should assess whether the participant should stay overnight for observation. If the participant has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as an SAE.

APPENDIX D. ANTIHISTAMINES THAT MAY BE USED PREDOSE

The following antihistamines may be used pre-dose, before daratumumab SC injection (including, but not limited to):

- Diphenhydramine
- Cetirizine
- Fexofenadine
- Loratadine
- Clemastine
- Dexchlorpheniramine
- Promethazine*

* The IV use of promethazine should be avoided.

APPENDIX E. INTERPRETATION OF DARATUMUMAB INTERFERENCE REFLEX ASSAY

Background: Clinical response assessment in myeloma relies on SPEP and IFE. As daratumumab is a monoclonal IgG kappa antibody, the SPEP and IFE can be positive for daratumumab at the serum levels anticipated during this protocol.

Implementation: To mitigate this interference, the sponsor has developed the DIRA to distinguish a positive SPEP/IFE due to the presence of daratumumab versus the presence of the underlying (endogenous) monoclonal protein (McCudden et al 2015). The DIRA test will be sent automatically to the central laboratory if a participant with IgG kappa multiple myeloma has an SPEP at or below 0.2 g/dL on 2 or more consecutive cycles. In addition, the DIRA test will be sent automatically to the central laboratory if a participant has an SPEP of 0 but persistently positive IFE for IgG kappa on 2 or more occasions.

Interpretation of Results: The results will be available to the investigator by the central laboratory interface and will be reported as either "POSITIVE" or "NEGATIVE."

- POSITIVE: indicates that the sample is still positive for underlying (endogenous) monoclonal myeloma protein. Therefore, this participant is not in a CR, because the CR response criteria require a negative SPEP and serum IFE.
- NEGATIVE: indicates that the sample is negative for underlying (endogenous) monoclonal myeloma protein. This participant may be in a CR if the other criteria for CR (including negative bone marrow aspiration/biopsy) are achieved.

Source: McCudden et al 2015.

APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1-EU:	18 MAR 2019
Amendment (Version) 1-DE:	16 JUL 2019
Amendment (Version) 2:	12 OCT 2020
Amendment (Version) 3:	01 DEC 2021

Amendment 3 (01 DEC 2021)

Overall Rationale for the Amendment: The primary purpose of this amendment is to provide guidance for the management of ongoing participants, as enrollment has been terminated and sufficient data have been collected for safety analysis.

1. **Protocol Summary (Table 2: Key Study Design Elements; Table 7: Schedule of Activities for All Participants [as of Protocol Amendment 3]; Section 4.1, Overall Design; Section 4.2, Overall Study Duration; Section 6.3, Measures to Minimize Bias: Randomization and Blinding; Section 6.7.4, Dose Delays and Dose Modification of Daratumumab SC; Section 6.8, Concomitant Medications and Procedures; Section 7.1.2, Discontinuation Procedures; Section 7.2, Participant Withdrawal From the Study; Section 8.2, Efficacy Assessments; Section 8.2.1.1, Responses Categories; Section 8.2.1.2, Myeloma Protein Measurements in Serum and Urine; Section 8.2.1.3, Serum Calcium Corrected for Albumin; Section 8.3, Safety Assessments; Section 8.3.7, Laboratory Assessments; Section 8.8.1, Safety Follow-Up; Section 8.8.2, Disease Status Follow-Up; Section 8.8.3, Survival Follow-Up; Section 9, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting; Section 9.4, Reporting of Serious Adverse Events; Section 9.5, Adverse Events of Special Interest; Section 9.7, Pregnancy; Appendix B, Instruction to Participants For Handling Study Drug (INCB001158)**

   Description of change: Study assessments for all participants remaining on study treatment have been limited to standard of care for the participant's condition. Safety data will only be collected for SAEs and AESIs, and disease status and survival follow-up data will only be collected until the last safety follow-up visit.

   Rationale for change: To update the study assessments for all ongoing participants.

2. **Protocol Summary (Table 2: Key Study Design Elements); Section 11.1.1, Identification of the Coordinating Principal Investigator**

   Description of change: Included the process for identification of the coordinating principal investigator.

   Rationale for change: To update applicable sections as per current protocol template.

3. **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 (12 OCT 2020)

Overall Rationale for the Amendment: The primary purpose of this amendment is to introduce a crossover to INCB001158+Daratumumab after Daratumumab monotherapy.

1. **Section 1, Protocol Summary, Figure 1, Study Design Schema, SoA (Tables 3 and 4), Schedule of Laboratory Assessments (Tables 5 and 6); Section 2.2.1, Rationale for Study Design; Section 4.1, Overall Design; Section 4.1.2, Phase 2: Expansion and Table 11, Treatments for Treatment Groups A, B, and C; Section 6.3, Measures to Minimize Bias: Randomization and Blinding; Section 6.7.4, Dose Delays and Dose Modification of Daratumumab SC; Section 7.1.1, Reasons for Discontinuation; Section 7.1.2, Discontinuation Procedures; Section 7.2, Participant Withdrawal From the Study; Section 8.2.1.1, Responses Categories; Section 8.2.1.2, Myeloma Protein Measurements in Serum and Urine; Section 8.2.1.3, Serum Calcium Corrected for Albumin; Section 8.3.7, Laboratory Assessments; Section 8.3.7.2, Chemistries; Section 8.3.7.4, Plasma Ammonia; Section 8.3.7.5, Pregnancy Testing; Section 8.3.7.6, Serology**

   Description of change: Added a crossover to INCB001158+Daratumumab (Treatment Group B - Part 2) for participants enrolled in Treatment Group B – Part 1. (Daratumumab SC monotherapy) at confirmed PD. Updated SoA and Laboratory Assessments Tables.

   Rationale for change: Introduce a crossover to combination treatment for patient progressing under daratumumab monotherapy, and update the SoA and Schedule of Laboratory Assessments prior to and post-crossover.

2. **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; Section 9.5, Adverse Events of Special Interest; Section 9.7, Pregnancy; Section 9.10 Treatment of Overdose; Appendix B, Instruction to Participants for Handling Study Drug (INCB00158); Appendix C, Daratumumab SC Drug Information**

   Description of change: Updated AE definitions, overdose, and SAE reporting via EDC.

   Rationale for change: Sponsor Pharmacovigilance updated guidance

3. **Section 2.1.4, Daratumumab; Section 2.2.3, Justification for the Dose; Section 2.3, Benefit/Risk Assessment; Section 12, References**

   Description of change: Updated background information in relation to the approval of the daratumumab subcutaneous formulation in United States of America and European Union.

   Rationale for change: To align with FDA and EMA approvals of Daratumumab SC.

4. **Section 1, Protocol Summary, Table 2, Key Study Design Elements; Table 3, Schedule of Activities for Participants in Phase 1, Phase 2, Treatment Group A, Treatment Group B - Part 1 (Prior to Crossover), and Treatment Group C - Part 1 (Prior to Crossover); Table 5, Schedule of Laboratory Assessments for Participants in Phase 1, Phase 2, Treatment Group A, Treatment Group B - Part 1 (Prior to Crossover), and Treatment Group C - Part 1 (Prior to Crossover); Section 8.1.2, Screening Procedures**

   Description of change: Updated the screening period of time from 21 days to up to 28 days.

   Rationale for change: To provide a longer period of time for the screening assessments.

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

   Description of change: Clarified that the participants in Phase 2 may be replaced in case of withdrawal before first administration of study treatment.

   Rationale for change: Clarification on the condition for Phase 2 participant replacement.

6. **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-DE (16 JUL 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is to address change requested by the Federal Institute for Drugs and Medical Devices (BfArM) in Germany.

1. **Section 5.2, Exclusion Criteria**

   Description of change: Added new exclusion criterion #15 to exclude participants who are candidates for autologous or allogenic transplantation.

   Rationale for change: Requested by BfArM.

2. **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-EU (18 MAR 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is to update the study drug formulation with tablets and to incorporate changes from global Amendment 1 requested by the FDA in the United States of America.

1. **Section 6.1, Study Treatment(s) Administrated (Table 11, Study Treatment Information); Section 6.2, Preparation, Handling, and Accountability; Section 6.4, Study Treatment Compliance; Appendix B, Instruction to Participants for Handling Study Drug (INCB001158)**

   Description of change: Clarified that INCB001158 tablet formulation and bottle packaging will be used.

   Rationale for change: Clarification.

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

Changes incorporated from global Amendment 1 (11 MAR 2019):

1. **Section 2.2.1, Rationale for Study Design**

   Description of change: A summary of experimental studies was added to provide evidence to support the biologic rationale for the combination.

2. **Section 1, Protocol Summary; Section 2.2.1, Rationale for Study Design; Section 4.1, Overall Design; Section 4.1.2, Phase 2: Expansion; Section 5.1, Inclusion Criteria**

   Description of change: Updated to allow for 2 cycles of INCB001158 monotherapy instead of 3 cycles in Treatment Group C – Part 1, and to require all participants to have had at least 3 prior treatments (including IMiD, PI, and anti-CD38 therapies).

3. **Section 4.1.2, Phase 2 Expansion; Section 10.1.2, Sample Size for Phase 2; Section 10.4.2.1, Adverse Events; Section 10.5.2, Interim Analysis for Phase 2**

   Description of change: Stopping rules were added for safety in Phase 2.

4. **List of Abbreviations; Section 6.5.2.2, Systemic Injection-Related Reaction**

   Description of change: A revision was made to clarify the definition of injection-related reactions and management of IRRs.

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Approval	[redacted] [redacted]Biostatistician 02-Dec-2021 20:45:11 GMT+0000

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