Official Title: A Randomized, Double-Blind, Placebo-Controlled Study of the PI3Kδ Inhibitor Parsaclisib Plus Ruxolitinib in Participants With Myelofibrosis Who Have Suboptimal Response to Ruxolitinib

NCT Number: NCT04551053

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Clinical Study Protocol

INCB 50465-304

A Randomized, Double-Blind, Placebo-Controlled Study of the PI3Kδ Inhibitor Parsaclisib Plus Ruxolitinib in Participants With Myelofibrosis Who Have Suboptimal Response to Ruxolitinib

Product:	**Parsaclisib (INCB050465)**
IND Number:	**147,207**
EudraCT Number:	**2020-003415-98**
Phase of Study:	**3**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol:	**17 JUL 2020**
Amendment 1:	**07 OCT 2021**
Amendment 2:	**20 OCT 2022**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, applicable Good Clinical Practices, and applicable laws and country-specific regulations in which the study is being conducted.
The information in this document is confidential. No part of this information may be duplicated, referenced, or transmitted in any form or by any means (electronic, mechanical, photocopy, recording, or otherwise) without prior written consent.

INVESTIGATOR'S AGREEMENT

I have read the INCB 50465-304 Protocol Amendment 2 (Version 3 dated 20 OCT 2022) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
AKT	protein kinase B
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
[redacted]	[redacted]
BID	twice daily
CALR	calreticulin
CI	clinical improvement
[redacted]	[redacted]
CMH	Cochran-Mantel-Haenzel
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DIPSS	Dynamic International Prognostic Scoring System
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
[redacted]	[redacted]
EOT	end of treatment
ET	essential thrombocythemia
FDA	Food and Drug Administration

Abbreviations and Special Terms	Definition
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HGB	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1986
HIV	human immunodeficiency virus
HSD	Hwang-Shih-DeCani
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IL	interleukin
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
[redacted]	[redacted]
IXRS	interactive web/voice response system
JAK	Janus kinase
LCM	left costal margin
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MFSAF v4.0	Myelofibrosis Symptom Assessment Form v4.0
MHRA	Medicines and Healthcare products Regulatory Agency
MPN	myeloproliferative neoplasms
[redacted]	[redacted]
MRI	magnetic resonance imaging
MRT	Myeloproliferative Neoplasms Research and Treatment

Abbreviations and Special Terms	Definition
OS	overall survival
PBMC	peripheral blood mononuclear cell
[redacted]	[redacted]
PET-MF	post-essential thrombocythemia myelofibrosis
[redacted]	[redacted]
PI3K	phosphatidylinositol 3-kinase
[redacted]	[redacted]
PJP	*Pneumocystis jirovecii* pneumonia
PMDA	Pharmaceutical and Medical Devices Agency
PMF	primary myelofibrosis
PP	per protocol
PPV-MF	post-polycythemia vera myelofibrosis
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
PV	polycythemia vera
Q12W	every 12 weeks
QD	once daily
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOP	standard operating procedure
STAT	signal transduction and activator of transduction
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TSS	total symptom score
ULN	upper limit of normal
WBC	white blood cell
[redacted]	[redacted]

1. PROTOCOL SUMMARY

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Study of the PI3Kδ Inhibitor Parsaclisib Plus Ruxolitinib in Participants With Myelofibrosis Who Have Suboptimal Response to Ruxolitinib

Protocol Number: INCB 50465-304

Objectives and Endpoints:

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

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate and compare the efficacy of parsaclisib plus ruxolitinib versus placebo plus ruxolitinib on spleen volume at Week 24.	Proportion of participants achieving ≥ 25% reduction in spleen volume from baseline to Week 24 as measured by MRI (or CT scan in applicable participants).
Major/Key Secondary	
To evaluate and compare the effect of parsaclisib plus ruxolitinib versus placebo plus ruxolitinib on participant reports of MF symptoms.	Proportion of participants who have a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MFSAF v4.0 diary. Change in TSS from baseline to Week 24 as measured by the MFSAF v4.0 diary. Time to the first ≥ 50% reduction in TSS as measured by the MFSAF v4.0 diary.
To evaluate and compare the effect of parsaclisib plus ruxolitinib versus placebo plus ruxolitinib with respect to OS.	OS determined from the date of randomization until death due to any cause.
To evaluate and compare the safety and tolerability of parsaclisib plus ruxolitinib versus placebo plus ruxolitinib.	Safety and tolerability will be assessed by monitoring the frequency and severity of AEs, performing physical examinations, and evaluating changes in vital signs, ECGs, and laboratory results.

Overall Design:

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

Table 2: Key Study Design Elements

Study Phase	Phase 3
Clinical Indication	Treatment of patients with primary and secondary MF
Population	Participants with primary or secondary MF who have residual signs and symptoms while on a stable dose of ruxolitinib.
Number of Participants	Approximately 212 participants will be randomized 1:1 to 1 of 2 groups (106 participants per group). Note: Certain countries must meet a minimum enrollment regulatory requirement; therefore, enrollment in these countries may continue after enrollment in other countries ends. Group A: parsaclisib plus ruxolitinib Group B: placebo plus ruxolitinib
Study Design	Randomized, double-blind. Participants will be randomized on Day 1 to Group A or Group B with stratification for baseline platelet count ($\geq 100 \times 10^9$/L versus 50 to $< 100 \times 10^9$/L inclusive) and DIPSS risk category (high vs intermediate-2 vs intermediate-1). If a participant's platelet count has decreased to $< 50 \times 10^9$/L at baseline, the platelet count at screening will be used for stratification/randomization.
Estimated Duration of Study Participation	Screening: Up to 28 days. Baseline: 7 days before first dose of parsaclisib/matching placebo plus ruxolitinib. Treatment period: Begins with the first dose of parsaclisib or matching placebo and ruxolitinib (Day 1). Participants will receive daily doses of parsaclisib or matching placebo of 5 mg together with ruxolitinib. The primary endpoint portion of study treatment is from Day 1 to the end of Week 24. Extension period: After 24 weeks, participants may enter the extension period of the study. Treatment will continue as long as the regimen is tolerated and the participant does not meet discontinuation criteria. Participants who discontinue study treatment will be followed for subsequent MF treatments and survival. When a participant has completed the Week 24 visit with assessments (including imaging), this participant will be unblinded, and if found to have been randomized to the placebo/ruxolitinib group may crossover to treatment with parsaclisib plus ruxolitinib. Early crossover is possible in exceptional circumstances for participants who demonstrate worsening symptomatic splenomegaly. Follow-up period: 30 to 35 days after the last dose of medication is taken. Survival follow-up period: Until death, withdrawal of consent, or the end of the study, whichever occurs first. It is estimated that an individual participant will be in the study for approximately 24 months.
DSMB/DMC	Yes (external)

Table 2: Key Study Design Elements (Continued)

Interim Analyses	Two interim futility analyses will be performed. The first interim analysis will be performed when the first 30% of participants have been randomized to the 2 groups (approximately 32 per group) and have completed Week 12 assessments (including imaging). The second interim analysis will be performed when the first 30% of participants have completed Week 24 assessments (including imaging).
Coordinating Principal Investigator	[redacted], MD, PhD [redacted] [redacted] [redacted], France

Treatment Groups and Duration:

This is a Phase 3, randomized, double blind study of the combination of the PI3Kδ inhibitor parsaclisib or matching placebo and the JAK1/2 inhibitor ruxolitinib in participants with PMF or secondary MF (PPV-MF or PET-MF) who have suboptimal response while receiving ruxolitinib monotherapy. Prospective participants must be on stable doses of ruxolitinib ranging from 5 mg BID to 25 mg BID and will have been on that dose for at least the last 8 weeks. At least 3 months duration of prior ruxolitinib is required. Participants must meet Protocol-defined criteria for suboptimal response to ruxolitinib monotherapy. After participants have been determined to meet all criteria, they will be randomized to 1 of 2 treatment groups and will receive parsaclisib or matching placebo at a dose of 5 mg QD beginning on Day 1. Participants will also continue to receive the stable dose of ruxolitinib they were taking for the 8 weeks prior to Day 1. Both parsaclisib/matching placebo and ruxolitinib dosing will continue for the duration of participation in the study.

Figure 1 presents the study design schema, and Table 3, Table 4, and Table 5 show the SoA for study site visit assessments, post-crossover assessments, and laboratory assessments, respectively. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Figure 1: Study Design Schema

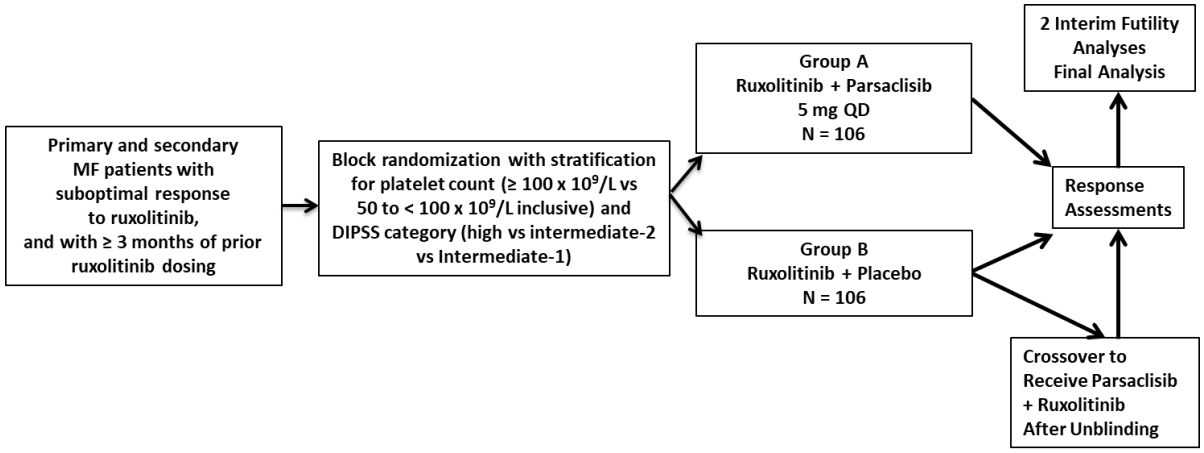


Table 3: Schedule of Activities for Randomized Participants in Group A, Group B, and After Crossover

Visit Day (Range)	Screening Day −35 to Day −8	Baseline Day −7 to Day −1	Day 1	End of Week 2 ± 3 Days	End of Weeks 4, 8, 16, 20 ± 5 Days	End of Week 12 and 24 ± 5 Days	Extension Visits (Q12W After Week 24) ± 7 Days	EOT or ET Visit ± 5 Days	Safety Follow-Up EOT + 30-35 Days	Survival Follow-Up Every 12 Weeks ± 2 Weeks	Notes
Administrative procedures											
Informed consent	X										
Contact IXRS	X		X		X	X	X	X			
Inclusion/exclusion criteria	X	X	X								
General and disease medical history	X										
Prior/concomitant medications	X	X	X	X	X	X	X	X	X		
Dispense parsaclisib/matching placebo			X		X	X	X				
Administer parsaclisib/matching placebo and ruxolitinib at clinic visit			X	X	X	X					
Distribute reminder cards and dosing diary where applicable	X	X	X	X	X	X	X	X			
Collect study drug and review dosing diary					X	X	X	X			
Assess drug compliance					X	X	X	X			
Transfusion history status	X	X	X		X	X	X	X	X		Record of transfusions must include at least 12 weeks prior to screening visit.
Safety assessments											
Record AEs	X	X	X	X	X	X	X	X	X		Body systems with symptoms should be physically examined.
Physical examination	X	X			X	X	X	X	X		Complete physical examination at screening and EOT visits, targeted physical examination at the other visits. Height at screening only.

Table 3: Schedule of Activities for Randomized Participants in Group A, Group B, and After Crossover (Continued)

Visit Day (Range)	Screening Day −35 to Day −8	Baseline Day −7 to Day −1	Day 1	End of Week 2 ± 3 Days	End of Weeks 4, 8, 16, 20 ± 5 Days	End of Week 12 and 24 ± 5 Days	Extension Visits (Q12W After Week 24) ± 7 Days	EOT or ET Visit ± 5 Days	Safety Follow-Up EOT + 30-35 Days	Survival Follow-Up Every 12 Weeks ± 2 Weeks	Notes
Vital signs, weight	X	X			X	X	X	X	X		
12-lead ECG	X					X*		X			*Week 24 only.
PJP		X		X	X	X	X	X	X		PJP prophylaxis can be started anytime beginning at Baseline visit up to Day 1 and will continue through at least 2-6 months beyond the last dose of study treatment.
Efficacy assessments											
Screening Symptom Form	X										
[redacted]											
Bone marrow biopsy and aspirate	X*		[redacted]								*Screening [redacted] Screening [redacted] not required if biopsy from prior 2 months available (report and samples).
MRI/CT scan of the upper and lower abdomen and pelvis		X				X	X				No MRI/CT scan after Week 108.
Dispense and/or bring MFSAF v4.0 diary to visit		X	X		X	X					
MFSAF v4.0 diary		Completed every evening from baseline through Week 24									
ECOG performance status	X					X			X		
[redacted]											

Table 3: Schedule of Activities for Randomized Participants in Group A, Group B, and After Crossover (Continued)

Visit Day (Range)	Screening Day −35 to Day −8	Baseline Day −7 to Day −1	Day 1	End of Week 2 ± 3 Days	End of Weeks 4, 8, 16, 20 ± 5 Days	End of Week 12 and 24 ± 5 Days	Extension Visits (Q12W After Week 24) ± 7 Days	EOT or ET Visit ± 5 Days	Safety Follow-Up EOT + 30-35 Days	Survival Follow-Up Every 12 Weeks ± 2 Weeks	Notes
[redacted]											
Laboratory assessments*	X	X	X	X	X	X	X	X	X		* Participants will also have laboratory-only visits to collect hematology samples at Week 6, Week 10, Week 30 and every 12 weeks thereafter (except where coincident with study visit); see Table 5.
Survival follow-up data collection										X	

Table 4: Schedule of Additional Study Visits for Participants Who Cross Over

Visit Day (Range)	Crossover Visit	4 Weeks Post-Crossover ± 5 Days	Notes
Administrative			
Contact IXRS	X	X	
Review criteria for crossover	X		
Concomitant medications	X	X	
Dispense parsaclisib	X	X	
Distribute reminder cards	X	X	
Collect study drug and review diary cards	X*	X†	*Parsaclisib/matching placebo bottles to be collected. †Parsaclisib bottles to be collected.
Transfusion history/status	X	X	
Safety assessments			
Record AEs	X	X	Body systems with symptoms should be physically examined.
PJP	X	X	Prophylaxis continues from crossover visit through at least 2-6 months beyond the last dose of study treatment.
Efficacy assessments			
[redacted]			
Dispense and/or bring MFSAF v4.0 diary to visit	X	X	Diary continues only for early crossover before Week 24 and ends at Week 24.
MFSAF v4.0 diary	X	X	Diary continues only for early crossover before Week 24 and ends at Week 24.
[redacted]			
ECOG performance status		X	
[redacted]			
Laboratory assessments			
Serum chemistry	X	X	Then follow Table 5.
Hematology	X	X	Then follow Table 5.
[redacted]			

Table 5: Schedule of Laboratory Assessments for All Participants

Window	Screening	Baseline	Day 1	End of Weeks 2, 6, 10, and 30 and Then Q12W	End of Weeks 4, 8, 12, 16, 20, and 24, and Then Q12W	EOT or Early Termination Visit	Safety Follow-Up 30-35 Days After Last Dose of Parsaclisib	Notes
				The window for laboratory-only visits is ± 3 days through Week 10 inclusive, and ± 7 days for laboratory-only visits beginning at Week 30 and Q12W				
Local laboratory assessments								
Serum chemistry	X	X*			X	X	X	*Should be taken as close as possible to Day 1 but may be drawn up to 3 days before first dose. Only 1 sample for baseline/Day 1 is required.
Hematology	X	X*		X	X	X	X	*Should be taken as close as possible to Day 1 but may be drawn up to 3 days before first dose. Only 1 sample for baseline/Day 1 is required. Note that if platelet count is < 50 × 10^9/L at baseline, the platelet count at screening will be used for stratification/randomization. See Section 8.1.3.
Coagulation panel	X				X*	X	X	*Required at Weeks 12 and 24 and Q12W thereafter.
Urine pregnancy test		X			X*	X*		All female participants of childbearing potential. *Pregnancy tests should be repeated if required by local regulations.
Bone marrow biopsy and aspirate analysis	X*		[redacted]					Local pathologist to document findings. *Predose biopsy/aspirate is not required if biopsy has occurred within previous 2 months of screening as long as biopsy/aspirate and data are available for review by investigator and/or sponsor. [redacted]

Table 5: Schedule of Laboratory Assessments for All Participants (Continued)

	Screening	Baseline	Day 1	End of Weeks 2, 6, 10, and 30 and Then Q12W	End of Weeks 4, 8, 12, 16, 20, and 24, and Then Q12W	EOT or Early Termination Visit	Safety Follow-Up 30-35 Days After Last Dose of Parsaclisib	Notes
Window				**The window for laboratory-only visits is ± 3 days through Week 10 inclusive, and ± 7 days for laboratory-only visits beginning at Week 30 and Q12W**				
Central laboratory samples*								*The central laboratory is the sponsor or sponsor's designee.
Lipid panel (requires overnight fast)	X				X*	X		*Required at Weeks 12 and 24 and Q12W thereafter.
Virology and serology (hepatitis and HIV)	X							HBV, HCV, HIV.
Virology - CMV	X				X*			*CMV measured at Weeks 4, 8, and 12 and Q12W thereafter.
Urinalysis	X				X*		X	*Required at Weeks 12 and 24 and Q12W thereafter.
Serum pregnancy test	X						X	All female participants of childbearing potential.
FSH level	X							To document hormonal menopause in relevant participants.
[redacted]								

Table 5: Schedule of Laboratory Assessments for All Participants (Continued)

	Screening	Baseline	Day 1	End of Weeks 2, 6, 10, and 30 and Then Q12W	End of Weeks 4, 8, 12, 16, 20, and 24, and Then Q12W	EOT or Early Termination Visit	Safety Follow-Up 30-35 Days After Last Dose of Parsaclisib	Notes
Window				The window for laboratory-only visits is ± 3 days through Week 10 inclusive, and ± 7 days for laboratory-only visits beginning at Week 30 and Q12W				
[redacted]								

2. INTRODUCTION

Parsaclisib (INCB050465) represents a novel, potent, and selective inhibitor of the Class IA PI3K enzymes, with selectivity for the δ isoform, which is proposed for development for treatment of hematologic malignancies. For a thorough discussion of the pharmacology of INCB054065, refer to the parsaclisib IB. Ruxolitinib, a potent and selective inhibitor of the JAK family of protein tyrosine kinases, JAK1 and JAK2, is approved in multiple jurisdictions for the treatment of MF, with variations on the specific indication language, and is currently in development for the treatment of MPNs, hematologic malignancies, and solid tumors. For a thorough discussion of the pharmacology of ruxolitinib (INCB018424), refer to the ruxolitinib IB and the Jakafi® package insert (Jakafi 2021).

2.1. Overview of Myelofibrosis

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

The median age at diagnosis of MF is approximately 60 to 67 years, and the incidence of PMF has been estimated at 4 to 6 cases per 100,000 people in the United States (Stein et al 2015). Survival in MF varies with the presence or absence of specific risk factors. Analysis of risk factors over the past 20 years has resulted in a number of prognostic scoring systems (for a review, refer to Bose and Verstovsek 2016). A prognostic scoring system based on a time-dependent risk evaluation has been developed: the DIPSS for PMF (Passamonti et al 2010). Age older than 65 years, presence of constitutional symptoms, anemia (hemoglobin < 100 g/L), leukocytosis (WBC count $> 25 \times 10^9$/L), and a circulating blast percentage of $\geq 1\%$ were assessed for their impact on survival when analyzed as time-dependent covariates in a multivariate Cox proportional hazards model. The approach showed that acquisition of anemia over time affects survival with a hazard ratio roughly double that of other parameters, and therefore anemia was assigned a score of 2, while the other 4 factors were assigned scores of 1. Four risk categories with nonoverlapping survival curves are described in Table 6.

Table 6: Risk Categories for Myelofibrosis

Total Risk Score	Risk Category	Median Survival (years)
0	Low	Not reached
1 or 2	Intermediate-1	14.2
3 or 4	Intermediate-2	4
5 or 6	High	1.5

Recent literature has indicated that although the prognostic factors for OS for patients with PET-MF and PPV-MF overlap with those for patients with PMF, the relative importance of these factors and their associated outcomes show differences. Additional improvements in scoring systems that include disease subtypes is warranted (Masarova et al 2017). Although not included in the DIPSS, somatic mutations in PMF, JAK2 V617F point mutations, mutations in exon 9 of the gene encoding CALR, and mutations in the gene encoding the thrombopoietin receptor (MPL) have been examined for impact on DIPSS score, thrombotic risk, and OS and together are grouped as "driver" mutations. These mutations often coexist with several somatic mutations: genes for the epigenetic regulators EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit), ASXL1 (additional sex combs-like 1 transcriptional regulator), the splicing gene SRSF2 (serine/arginine-rich splicing factor), and the genes encoding the Krebs cycle enzymes isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2). These factors have been combined into genetic-based scoring systems, although they are currently restricted to PMF (Tefferi et al 2018).

2.2. Role of Janus Kinase Pathway in Myelofibrosis

In recent years, it was discovered that approximately 95% of patients with PV and approximately 50% of patients with PMF and ET have a somatic gain-of-function mutation in the JAK2 gene resulting in substitution of phenylalanine for valine at position 617 (JAK2 V617F) within the pseudokinase domain of the encoded protein. Janus kinase 2 is 1 of 4 members of the JAK family, along with JAK1, JAK3, and TYK2. The JAKs are responsible for transduction of cell signaling from Type I and II cytokine receptor families, because these receptors do not possess intrinsic kinase activity to activate downstream signal transduction. Under physiologic conditions, the JAKs associate with the intracellular domain of the cytokine receptors in response to cytokine binding. They then undergo autophosphorylation, resulting in conformational changes that enable them to transduce intracellular signaling by phosphorylating and activating transcription factors called STAT proteins. The activated STATs translocate to the nucleus where they regulate transcription of a number of genes involved in cellular activation, proliferation, and survival. JAKs associate with the intracellular domain of the Type I and II cytokine receptors in pairs, which may be homodimers (eg, 2 JAK2s) or heterodimers (eg, a JAK1 and a JAK2). A large number of inflammatory mediators, such as IL-6, interferon-γ, and IL-17, are known to signal primarily through receptors that utilize JAK heterodimers.

It is also apparent that MF, as well as ET and even PV, occur in the absence of the JAK2 V617F mutation. In a minority of patients, other mutations in the JAK-STAT pathway have been identified, but in many patients, the mutations have not been identified yet or may not exist. Regardless, it appears that the majority of patients with MF have overactivation of the JAK-STAT pathway. In MF, excessive cytokine signaling through both JAK1 and JAK2 has been observed both in patients harboring the JAK2V617F mutation and in patients without

known mutations. Therefore, JAK inhibitors have the potential to treat some or all of the manifestations of MF, despite the potential for mechanism-based myelosuppression.

2.3. Role of PI3K/Protein Kinase B Signaling Pathway in Myelofibrosis

Recent evidence suggests that other regulatory pathways in addition to the JAK-STAT pathway are dysregulated in MPNs. Targeting multiple signaling pathways might provide synergistic effects on the overall pathogenic process of MF. The PI3K/AKT pathway is a signal transduction pathway that promotes survival and growth of cells in response to extracellular signals. There are several isoforms of PI3K. When activated, PI3Ks generate the lipid second messenger PIP3, leading to activation of several kinases, including AKT. Activated AKT initiates numerous downstream effects, including on cell survival, proliferation, growth, migration, and metabolism (Thorpe et al 2015, Tzenaki et al 2013). Meadows et al (2013) reported that the primary isoform of PI3K expressed in CD34+ cells obtained from ruxolitinib-treated or -naive patients with MF was PI3Kδ. Bartalucci et al (2013) and Khan et al (2013) demonstrated that inhibition of the PI3K/mTOR pathway in combination with JAK2 inhibition was synergistic in mouse models of MPN as well as in clonogenic assays of hematopoietic progenitors of patients with PMF. Hermouet et al (2015) recently reviewed the multiple pathways activated by inflammatory cytokines and grown factors and affected by MPN-associated mutations. Activators such as granulocyte colony-stimulating factor, erythropoietin, and thrombopoietin stimulate both JAK and PI3K-AKT pathways with considerable overlap and potential for synergistic effects.

2.4. Treatment of Myelofibrosis

The early drug therapies used in MF, including hydroxyurea, busulfan, 6-mercaptopurine, anagrelide, thalidomide, lenalidomide, interferon, corticosteroids, and erythropoiesis-stimulating agents or growth factors, have not been shown to improve survival. Some can increase the risk of leukemic transformation and can be poorly tolerated, and all have limited effectiveness in improving splenomegaly and constitutional symptoms.

Ruxolitinib, a potent and selective inhibitor of JAKs 1 and 2, is approved for use in patients with intermediate- or high-risk MF, including PMF, PPV-MF, and PET-MF. Registration studies showed improvement in spleen size, symptom burden, and OS with ruxolitinib use in this patient population (Cervantes et al 2013, Harrison et al 2012, Mesa et al 2013a, Mesa et al 2013b, Vannucchi et al 2015, Verstovsek et al 2012, Verstovsek et al 2015). Another JAK inhibitor, fedratinib, was approved more recently (August 2019) for intermediate-2 or high-risk MF. Both a significant decrease in spleen volume and reduction in MF-related symptoms were observed in double-blind, placebo-controlled studies (Pardanani et al 2015).

For the subset of patients who are younger (generally younger than 65 years), are otherwise healthy, and have a histocompatible donor, allogeneic stem cell transplantation may provide a curative option, although with a substantial risk of mortality (10%-20%; Deeg et al 2003, Robin et al 2019). Splenectomy, performed in approximately 10% of the patient cohort reported by Cervantes et al (2009), is associated with significant morbidity and mortality. Splenic irradiation is also used to reduce symptoms secondary to splenomegaly, but symptomatic improvement is variable and short-lived; moreover, transient and life-threatening pancytopenia and an approximate 20% treatment-related mortality have been noted.

Currently, there are no approved agents designed specifically for use when response to JAK therapy becomes suboptimal or declining. A number of agents are under investigation in this setting. Results of a limited study examining the effects of the JAK2 inhibitor fedratinib have shown effects on spleen size and symptoms in MF patients previously treated with ruxolitinib (Harrison et al 2017). Preliminary data using buparlisib, a pan-PI3K inhibitor, together with ruxolitinib demonstrated effects on both spleen size and symptoms in patients with MF with or without prior JAK therapy, but these results did not demonstrate synergy, and the anticipated risk/benefit profile was modest (Durrant et al 2019). However, the current studies in ruxolitinib refractory patients is confounded by the way in which refractoriness or ruxolitinib failure has been defined, precluding clear demonstrations of efficacy from newly added agents.

2.5. Study Rationale

Not all MF patients treated with the JAK inhibitor ruxolitinib experience optimal and/or stable response. Targeting additional signaling pathways might have clinically relevant effects on the overall disease burden of MF. The present study compares the impact of added PI3K delta inhibitor, parsaclisib, on signs and symptoms of MF in participants on stable ruxolitinib doses who have suboptimal or declining response to ruxolitinib monotherapy.

2.5.1. Scientific Rationale for Study Design

Despite statistically significant improvements in signs and symptoms of MF and OS rates compared with either placebo or best available therapy demonstrated in the registration studies, ruxolitinib therapy fails to provide optimal response for some patients. For some of these patients, individual genetic or systemic factors may impact the effects of JAK inhibition on overall disease. For other patients, declining hemoglobin levels or platelet counts may preclude optimal ruxolitinib dosages. Regardless of etiology, there is a patient population for whom ruxolitinib monotherapy is insufficient for optimal response (Pardanani and Tefferi 2014).

The persistent activation of the PI3K/AKT pathway in patients with MF suggests that this pathway may also be a driver of MPN diseases. For example, Bartalucci et al (2013) and Khan et al (2013) demonstrated that inhibition of the PI3K/mTOR pathway in combination with JAK2 inhibition was synergistic in mouse models of MPN as well as in clonogenic assays of hematopoietic progenitors of patients with PMF.

An ongoing Phase 2 study in participants with MF, INCB 50465-201, showed that additional alleviation of both symptoms and splenomegaly occurred when the PI3Kδ inhibitor parsaclisib (INCB050465) was added to the regimen of participants with suboptimal response to ruxolitinib monotherapy. Preliminary data showed > 20% reduction in spleen volume after 24 weeks of daily parsaclisib therapy together with continued ruxolitinib along with reductions in symptoms (Yacoub et al 2021).

The present Phase 3 study (INCB 50465-304) will explore the addition of parsaclisib in participants with MF with residual disease-related signs and symptoms while on stable ruxolitinib therapy. The study population is rigorously defined so that activity of the newly added agent (parsaclisib) can be demonstrated. The study design is placebo-controlled, double-blind as a combination of parsaclisib or placebo with ongoing ruxolitinib therapy. The objective measurement of spleen volume at 24 weeks is the primary endpoint. The study is blinded; symptom data will be collected objectively using daily electronic diary entries.

Participants randomized to placebo will have the opportunity to crossover to receive parsaclisib once Week 24 has been reached and all data have been entered and verified for the participant; early crossover will be available to participants who have symptomatic spleen growth meeting Protocol-defined criteria.

2.5.2. Justification for Dose

In the ongoing Phase 2 study in MF (INCB 50465-201), dose-limiting toxicities were not observed with daily doses of parsaclisib of up to 20 mg for 8 weeks followed by weekly dosing at 10 or 20 mg, or with continuous daily dosing of 5 mg, or 20 mg for 8 weeks followed by daily dosing of 5 mg. In the INCB 50465-201 study, AEs frequently reported with first-generation PI3K inhibitors (Coutré et al 2015, Flinn et al 2018), including hepatotoxicity (fatal or serious elevations of liver enzymes), severe and/or fatal diarrhea and colitis, intestinal perforation, and infections such as CMV retinitis, have not been observed (colitis, CMV retinitis, intestinal perforation) or rarely observed (diarrhea, elevated liver enzymes) with either daily or weekly parsaclisib dosing in the MF population. One SAE of diarrhea has been reported (Grade 3), unrelated to study drug, and resolved with drug interruption. This same participant also had Grade 4 elevation of bilirubin; multiple AEs involving the renal, gastrointestinal, and pulmonary system (assessed as unrelated to study medication); and increased peripheral blasts and subsequently died, with a cause of death of disease progression. The present Phase 3 study will use an all daily dose regimen as add-on therapy to a stable ruxolitinib regimen, with 5 mg of parsaclisib or matching placebo being administered QD from Day 1 until a given participant discontinues treatment.

2.6. Benefit/Risk Assessment

The following sections describe risks and benefits of the study drug (parsaclisib) and risks for reference (background) treatment (ruxolitinib).

2.6.1. Risks and Benefits of Parsaclisib

2.6.1.1. Potential Risks of Parsaclisib Based on Preclinical Findings

Based on the nonclinical toxicology studies, the primary potential risk associated with clinical administration of parsaclisib is immunosuppression and associated inflammatory complications and/or infections. Participants receiving parsaclisib should be frequently monitored and appropriate treatment, including but not limited to drug withdrawal, should be considered. Immunosuppressive findings showed evidence of recovery following 4 to 6 weeks of drug withdrawal, confirming the reversibility of immunosuppressive complications.

2.6.1.2. Potential Risks of Parsaclisib Based on Prior and Ongoing Clinical Studies

As of the data cutoff of 30 MAR 2022, 1159 unique individuals have been exposed to parsaclisib monotherapy, including healthy participants and participants with renal or hepatic impairment (N = 69), as monotherapy in oncology indications (N = 592), as monotherapy in inflammation and autoimmunity indications (N = 35), or in combination with other agents in oncology indications (N = 463).

The most common AEs with parsaclisib monotherapy in advanced malignancies (N = 592) have been diarrhea, nausea, cough, fever, and fatigue.

Parsaclisib has effects on the immune system and serious infection events have occurred in patients treated with parsaclisib, including PJP, CMV, and COVID-19. Therefore, participants must be monitored closely for evidence of infections or new cancers, and administration should be discontinued if there is evidence of clinically significant infection or new cancer. All irAEs must be completely resolved to baseline for 2 weeks before starting parsaclisib.

Four cases of PJP have been reported with the use of parsaclisib as monotherapy and another in combination with pembrolizumab. None of these events occurred in the MF population. None of the participants were on PJP prophylaxis at the time of the event. Participants in the present study will receive PJP prophylaxis beginning with the baseline visit.

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

2.6.1.3. Potential Risks of PI3K Inhibition Based on Other Agents in Class

Idelalisib was approved by the FDA in July 2014 for treatment of relapsed/refractory follicular lymphoma and relapsed small lymphocytic lymphoma and for treatment of chronic lymphocytic leukemia in combination with rituximab. Severe toxicities seen with the use of this agent include hepatotoxicity (fatal and/or serious occurring in 16%-18%), fatal and/or serious diarrhea or colitis (14%-20%), intestinal perforation, pneumonitis, and infections (fatal and/or serious occurring in 21%-48%). PJP infection and CMV infection have also been reported (Zydelig® 2018).

Copanlisib was approved in 2017 for the treatment of relapsed follicular lymphoma. Clinically important toxicities observed with this agent include SAEs, including fatal infections (19%), usually pneumonia, Grade 3 or 4 hyperglycemia (41%), and Grade 3 hypertension (26%). Serious PJP occurred in 0.6% of patients treated with copanlisib (Aliqopa® 2019).

Duvelisib was approved in 2019 for the treatment of relapsed or refractory chronic lymphocytic leukemia, small lymphocytic lymphoma, or follicular lymphoma. Clinically important toxicities observed with this agent include fatal and/or serious infections (31%), fatal and/or serious diarrhea or colitis (18%), fatal and/or serious cutaneous reactions (5%), or fatal and/or serious pneumonitis (5%). Serious, including fatal, PJP occurred in 1% of patients taking duvelisib, and CMV reactivation also occurred in 1% of patients taking duvelisib (Copiktra® 2019).

Participants in the present study will be monitored closely for the development of bacterial, fungal, or viral infections and will have treatment interrupted and dose reduced as appropriate. Participants will receive prophylaxis for PJP and will be monitored for CMV viremia during the study.

2.6.1.4. Potential Benefits of Parsaclisib

The ongoing Phase 2 study showed that additional alleviation of both symptoms and splenomegaly occurred when the PI3Kδ inhibitor parsaclisib (INCB050465) was added to participants on a stable ruxolitinib regimen. Specifically, at the time of efficacy data cutoff of 27 AUG 2020, 35 participants had been enrolled to receive all daily dosing regimens (18 dosed with 5 mg QD from Day 1 forward and 17 dosed with 20 mg QD for the first 8 weeks followed

by 5 mg QD going forward). The median reduction in spleen volume at 12 and 24 weeks was 13.0% and 21.8%, respectively. Seven of 23 participants (30%) had at least 25% reduction in spleen volume at Week 24. Thirty percent of participants had 50% reduction in TSS at Week 12 and 19% at Week 24 (Yacoub et al 2021). These preliminary findings suggest the combination of parsaclisib and ruxolitinib may be efficacious in the difficult-to-treat population with suboptimal response to ruxolitinib.

2.6.2. Risks of Ruxolitinib

2.6.2.1. Potential Risks of Ruxolitinib

The primary clinical risks with ruxolitinib treatment are the potential sequelae of decreased hematopoietic proliferation attributable to the inhibition of growth factor pathways associated with JAK inhibition. Dose-dependent, reversible thrombocytopenia has been observed in studies of participants with MF. Anemia and, less frequently, neutropenia have also been observed in studies in participants with MF. Increased rates of infection and anemia are potential risks of myelosuppression, and there are multiple sequelae of anemia, including the burden and risks of transfusion. In healthy volunteers, participants with rheumatoid arthritis, and participants with hormone-refractory prostate cancer with greater bone marrow reserve, the effects on hematopoietic proliferation appear to be less pronounced (ruxolitinib IB, Jakafi 2021, Jakavi® 2022).

2.6.2.2. Potential Risks of Parsaclisib Plus Ruxolitinib

As of the data cutoff date of 30 MAR 2022, 74 participants with MF had received parsaclisib together with continued ruxolitinib in Study INCB 50465-201. The most common AEs observed were thrombocytopenia, diarrhea, nausea, abdominal pain, anemia, fall, and platelet count decreased.

3. OBJECTIVES AND ENDPOINTS

Table 7 presents the objectives and endpoints.

Table 7: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate and compare the efficacy of parsaclisib plus ruxolitinib versus placebo plus ruxolitinib on spleen volume at Week 24.	Proportion of participants achieving ≥ 25% reduction in spleen volume from baseline to Week 24 as measured by MRI (or CT scan in applicable participants).
Secondary	
To evaluate and compare the effect of parsaclisib plus ruxolitinib versus placebo plus ruxolitinib on participant reports of MF symptoms.	Proportion of participants who have a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MFSAF v4.0 diary. Change in TSS from baseline to Week 24 as measured by the MFSAF v4.0 diary. Time to the first ≥ 50% reduction in TSS as measured by the MFSAF v4.0 diary.
To evaluate and compare the effect of parsaclisib plus ruxolitinib versus placebo plus ruxolitinib with respect to OS.	OS determined from the date of randomization until death due to any cause.
To evaluate and compare the safety and tolerability of parsaclisib plus ruxolitinib versus placebo plus ruxolitinib.	Safety and tolerability will be assessed by monitoring the frequency and severity of AEs, performing physical examinations, and evaluating changes in vital signs, ECGs, and laboratory results.
To evaluate and compare the time to onset and duration of response in spleen volume of participants receiving parsaclisib plus ruxolitinib versus placebo plus ruxolitinib.	Time to the first ≥ 25% reduction in spleen volume and duration of maintenance of a ≥ 25% reduction in spleen volume.
[redacted]	

Table 7: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, randomized, double blind study of the combination of the PI3Kδ inhibitor parsaclisib or matching placebo and the JAK1/2 inhibitor ruxolitinib in participants with PMF or secondary MF (PPV-MF or PET-MF) who have suboptimal response while receiving ruxolitinib monotherapy. Prospective participants must be on stable doses of ruxolitinib ranging from 5 mg BID to 25 mg BID and will have been on that dose for at least the last 8 weeks prior to Day 1. At least 3 months duration of prior ruxolitinib is required. Participants must meet Protocol-defined criteria for suboptimal response to ruxolitinib monotherapy. After participants have been determined to be eligible for the study and completed the baseline symptom diary assessment for 7 days, they will be randomized to 1 of 2 treatment groups, with stratification for baseline platelet count ($\geq 100 \times 10^9$/L vs 50 to $< 100 \times 10^9$/L inclusive) and DIPSS risk category (high vs intermediate-2 vs intermediate-1). Note that if a participant's platelet count is $< 50 \times 10^9$/L at baseline, the platelet count at screening will be used for stratification/randomization. Participants will receive study drug or matching placebo at a dose of 5 mg QD beginning on Day 1 and will continue to receive the stable dose of ruxolitinib they were taking for the 8 weeks prior to Day 1. Both parsaclisib/matching placebo and ruxolitinib dosing will continue for the duration of the participation in the study.

Figure 1 (see Section 1) presents the study design schema, and Table 3, Table 4, and Table 5 present the SoA for study site visit assessments, post-crossover assessments, and laboratory assessments, respectively.

4.1.1. Study Schedule/Procedures

There will be study site visits and laboratory-only visits in the study.

Participants will have a regularly scheduled study site visit at screening, baseline, Day 1, and at the end of 2, 4, 8, 12, 16, 20, and 24 weeks of treatment (ie, visits designated Week 2, Week 4, and so on) and then every 12 weeks thereafter if continuing on treatment in the extension period. During these visits, assessments, including blood samples and spleen measurements, will be performed. All serology, lipid profile, and urinalysis laboratory assessments will be analyzed by a central laboratory. Serum chemistry, hematology, and coagulation parameters will be assessed using local laboratories. [redacted]

Participants will have laboratory-only visits to collect hematology laboratory samples at Week 6, Week 10, and, if continuing beyond Week 24, every 12 weeks beginning with Week 30 (except where coincident with study visit). Participants may visit a local laboratory or a location convenient to the participant for these interim hematology assessments provided that the laboratory data and corresponding normal ranges can be scanned and e-mailed to the investigative site; interim laboratory visits at the study site laboratory are preferred. Additional and unscheduled laboratory assessments may be performed at investigator discretion, including following changes in dose, or if laboratory parameters are at Grade 3 or Grade 4 levels based on CTCAE v5.0.

Participants who crossover (defined in the following text) will have 2 additional study site visits: the day of crossover and 4 weeks after crossover. Participants who have crossed over will otherwise remain on the same study schedule they were on prior to crossover. Of note, these crossover participants may not need to have the laboratory visit at Week 30 as this may coincide with the Week 4 post-crossover visit.

Participants will have an MRI of the upper and lower abdomen and pelvis to determine the spleen volume at baseline, Week 12, Week 24, and every 12 weeks thereafter through Week 108.

A CT scan will be substituted for participants who are not candidates for MRI or when MRI is not readily available. [redacted]

Participants will complete an electronic symptom diary (MFSAF v4.0) daily from baseline through the Week 24 visit (total of 25 weeks).

[redacted]

All participants must receive prophylaxis against PJP beginning as early as the baseline visit and no later than Day 1 through at least 2 to 6 months after the last dose of study drug.

After 24 weeks, participants may enter the extension period of the study. Treatment will continue as long as the regimen is tolerated and the participant does not meet discontinuation criteria.

4.1.2. Unblinding and Crossover

When a participant has completed the Week 24 assessments, and the data entered has been verified and cleaned through the Week 24 visit (including imaging), the database for that participant will be frozen through the Week 24 visit. The participant's treatment assignment will then be unblinded and if found to be placebo, the participant will have the opportunity to crossover to begin receiving parsaclisib, together with continued ruxolitinib, as long as hematology parameters are adequate (see Section 6.4 for hematology requirements). If a participant who has completed the Week 24 assessments is found to have been randomized to parsaclisib, treatment with parsaclisib, together with continued ruxolitinib, will be continued as long as the regimen is tolerated and the participant does not meet discontinuation criteria.

4.1.3. Early Unblinding and Crossover

Participants with Protocol-defined spleen growth may be eligible for unblinding and, if found to have been randomized to the placebo group, may be eligible for crossover to parsaclisib, together with continued ruxolitinib, before reaching Week 24.

Participants who show symptomatic spleen growth may be eligible for unblinding and cross over if they meet both of the following criteria:

- Score of 5 or higher on at least 2 of 3 symptoms related to spleen size (abdominal discomfort, pain under the left ribs, early satiety), as assessed by the Worsening Symptomatic Splenomegaly Form (see Appendix B).
- Participants must demonstrate worsening spleen growth measured as an increase of ≥ 25% in spleen volume by MRI (or CT scan in applicable participants) compared with baseline. In addition to the regularly scheduled MRIs (or CT scans in applicable participants) at Week 12 and Week 24, 1 additional MRI (or CT scan in applicable participants) may be conducted between Week 2 and Week 10 and/or between Week 14 and Week 22 provided the participant meets the definition of worsening symptoms above. Only MRI or CT scans performed by the Protocol-qualified facilities and submitted to the central imaging laboratory may be used. No other MRI or CT scans for the purpose of documenting spleen growth are permitted.

[redacted]

Participants who meet both criteria and are unblinded and found to have been randomized to placebo must either cross over or be discontinued from the study treatments (placebo and ruxolitinib) and have an EOT visit scheduled.

Participants with worsening symptomatic spleen growth as described above for early crossover and who are found to have been randomized to parsaclisib must discontinue from the study treatments (parsaclisib and ruxolitinib) and have an EOT visit scheduled.

At any time, once unblinded, a placebo-randomized participant must either cross over or be discontinued from study treatments (placebo and ruxolitinib) and have an EOT visit scheduled. All participants who cross over will continue to take ruxolitinib in addition to parsaclisib.

4.1.4. Early Unblinding/Crossover Process

The site, CRO, central imaging laboratory, and IXRS system will work together to ensure efficient data capture and verification of criteria for unblinding and crossover. The process steps will include the following:

- The investigator will begin to complete the Worsening Symptomatic Splenomegaly Form in the eCRF, with appropriate entries for symptom scores.
- The investigator will send the MRI (or CT scans for applicable participants) to the central imaging laboratory.
- The site will start entering all available data in the eCRF up to the current visit.
- The eCRF system will verify that the data fulfill the symptom criteria, and a notification will be sent to the site and to the central imaging laboratory that the participant has fulfilled the symptom-based criteria for early crossover.

- The central imaging laboratory will process the scan and compare it with the baseline scan. If the on-study scan shows a ≥ 25% increase from baseline, the CRO and IXRS will be notified. The CRO will confirm in the IXRS that the spleen growth-based criteria for early crossover have been met.
- The eCRF system will verify that all data up to the current visit are indeed in the eCRF and are verified and cleaned. The database for that participant will then be frozen through the current visit.
- IXRS will be notified that final conditions have been met.
- An e-mail will be sent to the site, CRO, and sponsor that the participant may be unblinded.

4.1.5. Participant Unblinding/Crossover Process After Completion of the Week 24 Assessments

The site, CRO, central imaging laboratory, and IXRS system will work together to ensure efficient data capture and verification of participant unblinding/crossover timing. The process steps will include the following:

- The site will be advised to continuously enter data into the eCRF and address queries.
- The imaging vendor will communicate to the sponsor and CRO that the Week 24 spleen volume image has been read and verified.
- The eCRF system will verify that all data up to the Week 24 visit are in the eCRF and are verified and cleaned. The database for that participant will then be frozen through the Week 24 visit.
- IXRS will be notified that final conditions have been met.
- An e-mail will be sent to the site, CRO, and sponsor that the participant may be unblinded.

4.2. Overall Study Duration

The study begins when the first participant signs the ICF. Treatment will continue for an individual participant as long as the regimen is tolerated and the participant does not meet discontinuation criteria. The end of the study is defined as the date of the last visit/last contact of the last participant in the study.

4.3. Study Termination

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

The sponsor may terminate the study electively if, for example, required by regulatory decision or upon advice of the DMC. If the study is terminated prematurely, the sponsor will notify the investigators/head of study site (Japan), the IRBs and IECs, and the regulatory bodies of the

decision and reason for termination of the study. The DMC may recommend termination of the study if warranted, as described in Sections 5.6 and 10.5. For Japan, the head of the study site will notify the investigators and IRBs of the decision and reason for termination of the study.

5. STUDY POPULATION

Male or female participants aged 18 years or older (19 years or older in South Korea) who have been diagnosed with PMF or secondary MF (PPV-MF or PET-MF) and who have a suboptimal response while receiving ruxolitinib monotherapy for a period of at least 3 months with a stable ruxolitinib dose regimen for at least 8 weeks before the first administration of parsaclisib/matching placebo.

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. Men and women aged 18 years or older.

   Note: For South Korea, men and women aged 19 years or older.
2. Diagnosis of PMF, PPV-MF, or PET-MF.
3. DIPSS risk category of intermediate-1, intermediate-2, or high (see Table 8 and Table 9).

Table 8: Risk Categories According to DIPSS

Number of Risk Factor Points Present	Risk Category
0	Low
1-2	Intermediate-1
3-4	Intermediate-2
5-6	High

Table 9: Risk Factors and Point Assignments for DIPSS

Risk Factor	Points Assigned
Age older than 65 years	1
Presence of constitutional symptoms	1
Hemoglobin < 10 g/dL	2
WBC count > 25×10^9/L	1
Presence of peripheral blood blasts (laboratory value ≥ 1%)	1

4. Treated with ruxolitinib for ≥ 3 months with a stable dose for at least the last 8 weeks prior to Day 1 (acceptable doses are 5 mg BID to 25 mg BID, split doses are allowed [total daily dose at least 10 mg], QD dosing not allowed).
5. Evidence of suboptimal response to ruxolitinib (both 5a and 5b must be satisfied):
    a. Palpable spleen of ≥ 5 cm below the left subcostal margin on physical examination at the screening visit, AND
    b. Active symptoms of MF at the screening visit as demonstrated by the presence of a TSS of ≥ 10 using the Screening Symptom Form (see Appendix C).
6. Participants with an ECOG performance status score of 0, 1, or 2 (see Appendix D).
7. Screening bone marrow biopsy specimen and pathology report(s) available that was obtained within the prior 2 months or willingness to undergo a bone marrow biopsy at screening/baseline; willingness to undergo bone marrow biopsy at Week 24 and every 24 weeks thereafter. Screening/baseline biopsy specimen must show diagnosis of MF.
8. Life expectancy of at least 24 weeks.
9. Willingness to avoid pregnancy or fathering children based on the criteria below.
    a. Female participants without childbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and at least 50 years of age) are eligible.
    b. Female participants with childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. 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. Male participants with childbearing potential must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 93 days after the last dose of study drug 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.

5.2. Exclusion Criteria

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

1. Prior therapy with any drug that inhibits PI3K (examples of drugs targeting this pathway include but are not limited to INCB040093, idelalisib, duvelisib, buparlisib, copanlisib and umbralisib).
2. Use of experimental drug therapy for MF or any other standard drug used for MF (whether for treatment of MF or another indication), with the exception of ruxolitinib, within 3 months of starting study drug, and/or lack of recovery from all toxicities from previous therapy (except ruxolitinib) to Grade 1 or better.

3. Inability to swallow food or any condition of the upper gastrointestinal tract that precludes administration of oral medications.
4. Recent history of inadequate bone marrow reserve; examples include but are not limited to the following:
   a. Platelet count $< 50 \times 10^9$/L in the 4 weeks before screening or at the screening laboratory assessment; or platelet transfusion(s) within 8 weeks before screening.
   b. Absolute neutrophil count $< 0.5 \times 10^9$/L in the 4 weeks before screening or at the screening laboratory assessment.
   c. Peripheral blood blast count of ≥ 10% at the screening hematology assessment.
5. Inadequate liver function at screening visit, as demonstrated by the following:
   a. Total bilirubin > 2.0 × ULN. Note: if total bilirubin is > 2.0 × ULN, the participant may enroll if the direct bilirubin is < 2.0 × ULN.
   b. ALT or AST > 2.5 × ULN.
6. Inadequate renal function at screening, as demonstrated by creatinine clearance ≤ 50 mL/min estimated based on Cockcroft-Gault formula. The cutoffs for mild, moderate, and severe renal insufficiency based on the Cockcroft-Gault formula are 60 to 90 mL/min, 30 to 59 mL/min, and 0 to 29 mL/min, respectively. If the investigator prefers, he/she may use measured creatinine clearance instead of estimated.
7. Active bacterial, fungal, parasitic, or viral infection that requires therapy. Participants with acute infections requiring treatment should delay screening/enrollment until the course of therapy has been completed and the event is considered resolved. Prophylactic antibiotics or antivirals will be permitted.
8. Active HBV or HCV infection that requires treatment or at risk for HBV reactivation. Hepatitis B virus DNA and HCV RNA must be undetectable upon testing. At risk for HBV reactivation is defined as hepatitis B surface antigen positive or anti–hepatitis B core antibody positive. Cytomegalovirus must be undetectable by polymerase chain reaction.
9. Known HIV infection.
10. Uncontrolled, severe, or unstable cardiac disease that in the investigator's opinion may jeopardize the safety of the participant or compliance with the Protocol.
11. Active invasive malignancy over the previous 2 years except treated basal or squamous carcinomas of the skin, completely resected intraepithelial carcinoma of the cervix, and completely resected papillary thyroid and follicular thyroid cancers. Participants with malignancies with indolent behavior such as prostate cancer treated with radiation or surgery may be enrolled as long as they have a reasonable expectation to have been cured with the treatment modality received.
12. Splenic irradiation within 6 months before receiving the first dose of study drug.
13. Concurrent use of any prohibited medications (see Section 6.8.5 for specific prohibited medications and the associated timeframe over which they are prohibited).

14. Active alcohol or drug addiction that would interfere with the ability to comply with the study requirements.
15. Use of any potent CYP3A4 inhibitors or inducers within 14 days or 5 half-lives (whichever is longer) before the first dose of study drug or anticipated during the study.
16. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
17. Currently breastfeeding or pregnant.
18. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
19. Inability to comprehend or unwilling to sign the ICF.
20. History of Grade 3 or 4 irAEs from prior immunotherapy.
    a. Any irAEs of Grade 1 or 2 must be resolved before receiving the first dose of study drug.
21. Receipt of any live vaccine within 30 days of the first dose of study drug.
22. Unwillingness to receive RBC transfusions to treat low hemoglobin levels.
23. Known hypersensitivity or severe reaction to parsaclisib or ruxolitinib or excipients of parsaclisib/matching placebo or ruxolitinib formulations.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

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

Results from the screening visit evaluations will be reviewed to confirm participant eligibility before enrollment/randomization 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 randomization/treatment assignment will be used to determine participant eligibility.

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 (eg, after recovery from an infection). Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Replacement of Participants

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

5.6. Data Monitoring Committee

Preplanned analyses of safety and efficacy will be provided to an independent DMC as specified in the DMC charter. The process by which the DMC will review data and make recommendations and decisions will be documented in the DMC charter. The external DMC will also conduct the interim analyses (see Section 10.5).

6. STUDY TREATMENT

6.1. Study Treatments Administered

Table 10 presents the study treatment information.

Table 10: Study Treatment Information

	Study Treatment 1	Study Treatment 2	Reference (Background) Treatment
Study treatment name:	Parsaclisib	Placebo	Ruxolitinib
Dosage formulation:	Tablets	Tablets	Tablets
Starting dose:	5 mg QD without regard to food	5 mg QD without regard to food	5 mg BID to 25 mg BID without regard to food Doses of different AM and PM strengths allowed provided total dose is at least 10 mg and no greater than 50 mg.
Start day for dosing	Day 1	Day 1	Continuing from prestudy dosing. Date of Day 1 dose for study will be recorded
Time of dosing	Morning	Morning	Morning/evening, approximately 12 hours apart
Unit dose strength(s)/dosage level(s):	5 mg tablets, 2.5 mg tablets, 1.0 mg tablets	5 mg tablets, 2.5 mg tablets, 1.0 mg tablets	5 mg to 25 mg tablets (all tablet strengths may not be available in all countries)
Route, frequency of administration:	Oral, QD	Oral, QD	Oral, BID
Packaging and labeling:	Parsaclisib will be provided in bottles. Each bottle will be labeled as required per country requirement.	Placebo will be provided in bottles. Each bottle will be labeled as required per country requirement.	Commercially available supplies of ruxolitinib will be used.
Storage conditions	Refer to the Pharmacy Manual.	Refer to the Pharmacy Manual.	Per labeling instructions.
Status of treatment in participating countries:	Experimental	Not applicable	Approved

Note: There is no order for the morning doses of parsaclisib/matching placebo and ruxolitinib. They may be taken together or in any order in the morning.

6.2. Preparation, Handling, and Accountability

The investigator, investigational drug storage manager (for Japan), 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, investigational drug storage manager (for Japan), and authorized site staff.

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

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

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

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

Administration instructions for the participant are provided in Appendix H.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a double-blind, placebo-controlled study. Participants will receive ruxolitinib plus blinded study drug (parsaclisib or placebo). Participants, investigators, and the sponsor will remain blinded to each participant's treatment assignment (Group A or Group B) throughout the study. Emergency unblinding will occur if an AE requires the investigator to be made aware of the participant's treatment assignment (see emergency unblinding procedures in Section 9.6 and the Study Reference Manual).

A sponsor-designated statistician (in-house or contract) who is not part of the study team will be unblinded and will provide summary aggregated data by treatment group to the DMC for scheduled interim analyses or other DMC meetings, but individual participant data will remain blinded.

Block randomization with stratification for baseline platelet count ($\geq 100 \times 10^9$/L vs 50 to $< 100 \times 10^9$/L inclusive) and DIPSS risk category (high vs intermediate-2 vs intermediate-1) will be used. If a participant's platelet count is $< 50 \times 10^9$/L at baseline, the platelet count at screening will be used for stratification/randomization. Participants will be randomly assigned to either Group A or Group B. All participants will be centrally assigned to study treatment using an IXRS. Randomization schedule will be generated by a sponsor-independent statistician and sent directly to the IXRS without provision to the sponsor. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the login information and directions for the IWRS will be provided to each site. Full details will be provided in the IXRS Manual.

The primary endpoint, spleen volume as measured by MRI (or CT scan in applicable participants), will be assessed by a blinded central reader and reviewer.

Study treatment will be dispensed at the study visits summarized in the SoA (see Table 3).

Returned study treatment should not be redispensed to the participants.

6.4. Dose and Requirement to Start Dosing After Crossover

After criteria for crossover have been met (early or at Week 24) and sites have received notification that unblinding and crossover may occur, the crossover visit will be scheduled and dosing with parsaclisib will begin as long as the following hematology criteria are met based on a laboratory visit within 2 weeks of the planned parsaclisib start date:

- Platelet count $\geq 50 \times 10^9$/L.
- ANC $\geq 0.5 \times 10^9$/L.

No more than 3 repeat assessments for platelet count and ANC are allowed. Participants who have received 1 or more platelet transfusions must have a platelet count $\geq 50 \times 10^9$/L at least 7 days after the most recent platelet transfusion to qualify for crossover. Participants in whom the platelet count and/or ANC remain below these thresholds at the time of the later of (a) 4 weeks or (b) the next regularly scheduled study visit, following the date at which it was determined that crossover could occur, will be discontinued from the study, and that visit will constitute the EOT.

The dose of parsaclisib will be 5 mg QD, taken in the morning, without regard to food.

6.5. 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.

Participants will complete a daily dosing diary (electronic or paper) and will bring it with them to each study visit. Compliance with parsaclisib/matching placebo 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 study drug with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

Although commercial supplies of ruxolitinib will be used, compliance with ruxolitinib will also be documented in the medical record and monitored by the sponsor or its designee. Participants will record the doses of ruxolitinib taken on a paper diary issued by the site and collected at each visit.

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

Previously, the Phase 2 study INCB 50465-201 examined daily doses up to 20 mg for 8 weeks followed by doses up to 20 mg weekly or 5 mg daily. Pharmacological activity was observed at all dose combinations with 8 weeks of daily dosing followed by continued daily dosing or weekly dosing, although activity appeared to diminish with time with weekly dosing. Dose-limiting toxicities were not observed in any dosing part of the study, and the maximum tolerated dose was not reached.

6.7. Dose Modifications

6.7.1. Dose Increases for Inadequate Efficacy

Dose increases for parsaclisib: The dose of parsaclisib (or matching placebo) will be 5 mg QD. Dose increases are not allowed at any time during the study. If a dose has been reduced due to AEs, the dose may be increased back to the original starting dose of 5 mg QD once safety has adequately resolved (see Section 6.7.2).

Dose increases for ruxolitinib: Dose increases of ruxolitinib are not allowed. Participants will remain on the stable dose they were taking for the 8 weeks prior to Day 1 throughout the study, unless dose decreases for toxicity are required (see Section 6.7.7).

6.7.2. Dose Decreases of Parsaclisib/Placebo for Toxicity

Parsaclisib or matching placebo should be interrupted/decreased first, with no change to the ruxolitinib dosage. Adjustments to ruxolitinib may be used if interruption/dose adjustment of parsaclisib or matching placebo does not lead to resolution or at least improvement of the AE within a 14-day period (see Section 6.7.7).

Treatment with parsaclisib or matching placebo may be delayed up to 2 weeks (14 days) to allow for resolution of toxicity. Participants may resume treatment if no medical condition or other

circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the case of any participant whose treatment has been delayed for more than 14 days before restarting treatment with parsaclisib or matching placebo and/or ruxolitinib. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules.

Table 11 shows dose-reduction and interruption guidelines for parsaclisib and matching placebo. Because participants may enter the study with extensive pretreatment and/or severe bone marrow infiltration by the primary disease, these dose-reduction rules are provided as guidelines (see Table 11). **Individual decisions regarding dose reduction/interruption should be made using investigator clinical judgment and in consultation with the sponsor's medical monitor in those cases where the guidelines will not be followed, taking into account relatedness of the AE to parsaclisib and the participant's underlying condition**. Available dose strengths for parsaclisib/matching placebo are shown in Table 12.

Table 11: Guidelines for Interruption and Restarting of Parsaclisib/Matching Placebo

Adverse Event	Action Taken
Chemistry	
AST and/or ALT > 5.0 × ULN (Grade 3).	Step 1: Interrupt parsaclisib or matching placebo for up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 except by approval of the medical monitor. Step 2: Restart parsaclisib or matching placebo at the same dose. If assessed as related to parsaclisib or matching placebo, restart parsaclisib or matching placebo at the next lower dose; monitor as clinically indicated.
Hematology	
• ANC < 1.0 × 10^9/L (Grade 3) unless because of underlying disease. Applies only if this represents a worsening grade from baseline. • Platelet count ≥ 25 × 10^9/L and < 40 × 10^9/L. Applies only if this represents a worsening grade from baseline.	**Step 1:** Interrupt parsaclisib or matching placebo for up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 or pretherapy baseline. **Step 2:** Restart parsaclisib or matching placebo at the same dose and monitor as clinically indicated.
• Grade 4 ANC (< 0.5 × 10^9/L) regardless of baseline grade. • ≥ Grade 3 ANC with temperature of at least 38.5°C OR with ≥ Grade 3 infection regardless of baseline grade. • Platelet count is < 25 × 10^9/L (Grade 4), regardless of baseline grade.	**Step 1:** Interrupt parsaclisib or matching placebo for up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 or pretherapy baseline. **Step 2:** Restart parsaclisib or matching placebo at the next lower dose; monitor as clinically indicated. Escalate to original dose with recovery to preinterruption levels of analyte.
Nonhematologic toxicities	
• Diarrhea/colitis (Grade 1)	**Step 1:** Treat with antimotility agents (eg, loperamide) and initiate supportive care (see Section 6.7.3). If not improved after 48 hours, treat per guidance for ≥ Grade 2.

Table 11: Guidelines for Interruption and Restarting of Parsaclisib/Matching Placebo (Continued)

Adverse Event	Action Taken
• Diarrhea/colitis (Grade 2)	**Step 1:** Interrupt parsaclisib or matching placebo. Perform workup for infection (including CMV, *Clostridium difficile*, etc) immediately. Initiate or continue supportive care (see Section 6.7.3). Monitor approximately every 48 hours until resolution. **Step 2:** If improved within 48 hours and/or infection* is confirmed, restart parsaclisib/matching placebo at the **same schedule and dose** after resolved to ≤ Grade 1 and continue to monitor. *For infectious diarrhea/colitis, follow institutional standard of care guidelines and restart parsaclisib/matching placebo according to clinical judgment after resolved to ≤ Grade 1. Consult with medical monitor if needed. **Step 3:** If not improved within 48 hours and infection is ruled out, start oral steroids or consider IV steroids if participant is being given IV fluids. If no improvement with oral steroids, switch to IV steroids. **Step 4:** When diarrhea resolves to ≤ Grade 1, continue supportive care and taper steroids according to institutional standard of care. When taper is complete (eg, no steroid or ≤ 10 mg/day prednisone or equivalent) and diarrhea is ≤ Grade 1, restart parsaclisib/matching placebo at the next lower dose with approval of the medical monitor. **Step 5:** If Grade 2 diarrhea reoccurs, treat per guidance for diarrhea (≥ Grade 3)/noninfectious colitis. **Step 6:** If ≥ Grade 2 diarrhea reoccurs a third time, permanently discontinue parsaclisib/matching placebo.
• Diarrhea (≥ Grade 3) • Noninfectious colitis (any grade; confirmed or suspected)	**Step 1:** Interrupt parsaclisib. Perform workup for infection (including CMV, *C. difficile*, etc) immediately. Initiate or continue supportive care (see Section 6.7.3). Consider colonoscopy with biopsy for diarrhea ≥ Grade 3 and/or if symptoms suggestive of colitis (diarrhea accompanied by abdominal pain and/or mucus or blood in stool). Monitor every 48 hours until resolution. **Step 2:** If infection* is ruled out, start oral steroids or consider IV steroids if participant is being given IV fluids. If no improvement with oral steroids within 48 hours, switch to IV steroids. *For infectious diarrhea/colitis, follow institutional standard of care guidelines and restart parsaclisib according to clinical judgment after resolved to ≤ Grade 1. Consult with medical monitor if needed. **Step 3:** When diarrhea/colitis resolves to ≤ Grade 1, continue supportive care and taper steroids according to institutional standard of care. When taper is complete (eg, no steroid or ≤ 10 mg/day prednisone or equivalent) and diarrhea/colitis is ≤ Grade 1, restart parsaclisib with approval of the medical monitor. Continue to monitor. **Step 4**: If ≥ Grade 3 diarrhea or noninfectious colitis (any grade) reoccurs, permanently discontinue parsaclisib/placebo.
• Pneumonitis (Grade 1)	**Step 1:** Interrupt parsaclisib or matching placebo until the toxicity has resolved. **Step 2:** Restart parsaclisib or matching placebo at the next lower dose. Monitor as clinically indicated.
• Pneumonitis (≥ Grade 2)	Permanently discontinue parsaclisib or matching placebo.
• Skin toxicity (eg, rash, pruritus, etc, unless otherwise specified) (Grade 2-3)	**Step 1:** Interrupt parsaclisib or matching placebo until the toxicity has resolved to ≤ Grade 1. **Step 2:** Restart parsaclisib or matching placebo at the same dose. If assessed as related to parsaclisib or matching placebo, restart at the next lower dose.

Table 11: Guidelines for Interruption and Restarting of Parsaclisib/Matching Placebo (Continued)

Adverse Event	Action Taken
• Exfoliative dermatitis (Grade 1)	**Step 1:** Interrupt parsaclisib or matching placebo until the toxicity has resolved. **Step 2:** Restart parsaclisib or matching placebo at the next lower dose. Monitor as clinically indicated.
• Exfoliative dermatitis (≥ Grade 2)	Permanently discontinue parsaclisib or matching placebo.
• Intestinal perforation (any grade)	Permanently discontinue parsaclisib or matching placebo.
• PJP	Interrupt parsaclisib or matching placebo. Permanently discontinue parsaclisib or matching placebo if PJP is confirmed.
• CMV infection	Participants with CMV viremia without associated clinical signs of CMV infection should be carefully monitored. Consider interrupting parsaclisib or matching placebo for participants with CMV viremia and clinical signs of infection until the infection has resolved. Restart parsaclisib or matching placebo reduced by 1 dose level if approved by the medical monitor.
• Varicella zoster infection	Interrupt parsaclisib or matching placebo. Restart parsaclisib or matching placebo only by approval of the medical monitor.
• Any Grade 1 or Grade 2 toxicity unless otherwise specified.	Continue parsaclisib or matching placebo treatment and treat the toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care unless otherwise specified.	**Step 1:** Interrupt parsaclisib or matching placebo for up to 2 weeks (14 days) until toxicity resolves to ≤ Grade 1. **Step 2:** Restart parsaclisib or matching placebo at the same dose. If assessed as related to parsaclisib or matching placebo, restart at the next lower dose. If interrupted for > 14 days, contact the medical monitor for approval to restart parsaclisib or matching placebo. Monitor as clinically indicated.
• Any recurrent Grade 3 toxicity after 2 dose reductions.	Discontinue parsaclisib or matching placebo administration and follow-up per Protocol. Exceptions require approval of sponsor.
• Any other Grade 4 toxicity.	Discontinue parsaclisib or matching placebo administration and follow-up per Protocol. Exceptions require approval of sponsor.

Table 12: Dose Strengths for Parsaclisib/Matching Placebo

Current Dose Level	Dose After 1 Reduction	Dose After 2 Reductions
5 mg QD	2.5 mg QD	1 mg QD
2.5 mg QD	1 mg QD	Contact medical monitor
1 mg QD	Contact medical monitor	Contact medical monitor

6.7.3. Supportive Care for Diarrhea/Colitis

Participants should be informed to immediately report to the investigator any event of diarrhea. Participants should receive appropriate supportive care measures as deemed necessary by the investigator. For any ≥ Grade 1 diarrhea, participants 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. Participants should try to eat 5 to 6 small meals per day; low-fat, high-protein foods; and cooked instead of raw vegetables. Participants may supplement their diet with bananas, rice, applesauce, and toast to reduce the number of bowel movements and may also try crackers, gelatin, noodles, or oatmeal. Participants should avoid fried, fatty,

greasy, or spicy foods; milk, milk products, and acidic drinks; high-fiber foods and foods that cause gas; and alcohol, caffeine, and herbal supplements (Coutré et al 2015).

For each occurrence, attempts should be made to rule out other causes, such as metastatic disease or bacterial or viral infection (including CMV), which might require additional supportive care.

It may be necessary to perform conditional procedures such as colonoscopy with biopsy as part of evaluation of the event. Note that several courses of steroid tapering may be necessary because symptoms may worsen when the steroid dose is decreased.

Participants should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain or cramping, and blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

6.7.4. Follow-Up for Immune Related Adverse Events

An AE with a potential immunologic etiology, or an irAE, may be defined as an AE consistent with an immune phenomenon associated with study drug exposure after all other etiologies have been eliminated. Immune-related AEs may be expected based on previous experience with parsaclisib and other drugs (eg, idelalisib) that inhibit PI3Kδ. Special attention should be paid to AEs that may be suggestive of potential irAEs. Based on emerging data from the ongoing parsaclisib clinical program (parsaclisib IB), most irAEs occur after the first 9 weeks of study drug administration. However, an irAE could occur at any time. Suspected irAEs should be discussed with the medical monitor when possible.

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of drug-related AEs with potential immunologic etiology are outlined in Table 11. For each AE, attempts should be made to rule out other causes, including but not limited to metastatic disease or bacterial or viral infection, which might require specific supportive care.

6.7.5. COVID-19

Infection with SARS-CoV-2, the coronavirus that causes COVID-19, is more frequent and severe in patients with hematologic dysfunction (Jee et al 2022). The presence of hematologic malignancy, baseline neutropenia and lymphopenia, B-cell depletion, and other factors have been identified as risk factors for loss of humoral immunity to COVID-19, poor vaccine response, viral persistence, and severe disease (Lee et al 2022, Lyudovyk et al 2022, Shree et al 2022). Targeting B-cell function, proliferation, and survival with various therapies are current strategies for improving the outcome of several hematologic malignancies. PI3Kδ inhibition with parsaclisib alone or in combination with other therapies, which may also suppress humoral immunity, has the potential to negatively impact SARS-CoV-2 infection risk, vaccine effectiveness, recovery from COVID-19, and disease severity (Cheson 2022). Investigators and participants in trials of parsaclisib, alone or in combination, need to be aware of these potential risks and consider the local standards of care and available therapies for disease prevention, vaccination, and infection management of COVID-19.

6.7.6. Criteria for Permanent Discontinuation of Parsaclisib/Matching Placebo

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

- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- An AE requiring more than 2 dose reductions.
- Persistent AE requiring a delay of therapy for more than 2 weeks (14 days) unless a greater delay has been approved by the sponsor.

See Section 7.1.2 for discontinuation procedures.

6.7.7. Dose Decreases of Ruxolitinib for Safety

Dose modifications/interruptions of ruxolitinib because of toxicity are not required unless parsaclisib modifications/interruptions have been first implemented for 14 days with no improvement in toxicity grade. Doses of ruxolitinib may be modified/interrupted earlier if the study investigator deems this necessary. Dose interruptions and modifications for ruxolitinib because of hematologic toxicity that continues after interruption of INCB050465 are shown in Table 13.

Table 13: Dose Reductions/Interruptions and Restarts for Hematologic Toxicities That Persist for > 14 Days After Interruption of Parsaclisib

ANC ($\times 10^9$/L)			Platelet Count ($\times 10^9$/L)		
Value	CTCAE Grade		Value	CTCAE Grade	Dose of Ruxolitinib
0.5 to < 1.0	3	or	25 to < 40	Below UL of Grade 3	If Grade 3 cytopenia persists for > 14 days after interrupting parsaclisib/matching placebo or if the primary investigator deems that earlier interruption of ruxolitinib is necessary, then ruxolitinib will be interrupted until the toxicity is resolved to ≤ Grade 1 or pretherapy baseline and then restarted at the current dose. If a Grade 3 event recurs and persists for > 14 days after interrupting parsaclisib/matching placebo or if the primary investigator deems that earlier interruption of ruxolitinib is necessary, then ruxolitinib will be interrupted and the restart dose (after recovery to ≤ Grade 1 or pretherapy baseline) of ruxolitinib will be 1 dose level (5 mg BID less) lower than the dose that resulted in the cytopenia. A participant who was taking 5 mg BID will restart at 5 mg QD.

Table 13: Dose Reductions/Interruptions and Restarts for Hematologic Toxicities That Persist for > 14 Days After Interruption of Parsaclisib (Continued)

ANC ($\times 10^9$/L)			Platelet Count ($\times 10^9$/L)		
Value	CTCAE Grade		Value	CTCAE Grade	Dose of Ruxolitinib
< 0.5	4	or	< 25	4	If Grade 4 thrombocytopenia or neutropenia occurs and persists for > 14 days after interrupting parsaclisib/matching placebo or if the primary investigator deems that earlier interruption of ruxolitinib is **necessary**, then ruxolitinib will be interrupted until toxicity is resolved to ≤ Grade 1 or pretherapy baseline and the restart dose will be 1 dose level (5 mg BID less) lower than the dose that resulted in the cytopenia. A participant who was taking 5 mg BID ruxolitinib will restart at 5 mg QD.
Neutropenic fever					If neutropenia (ANC < 1.0) persists for > 14 days after interrupting parsaclisib/matching placebo or if the primary investigator deems that earlier interruption of ruxolitinib is necessary, then ruxolitinib will be interrupted until recovery of ANC to ≥ 1.0 × 10^9/L, and the restart dose will be 1 dose level (5 mg BID less) lower than the dose that resulted in the cytopenia.

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 to 35 days after the last dose of study treatment, or until the participant begins a new MF 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 the last dose of study treatment should be recorded for SAEs as defined in Section 9.3. Prior medication history for MF should be entered in its entirety, as well as complete ruxolitinib dosing history.

6.8.1. Permitted Medications

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 for conditions other than MF.

6.8.2. *Pneumocystis jirovecii* Pneumonia Prophylaxis

All participants receiving combination study treatment with parsaclisib/matching placebo and ruxolitinib are required to receive a standard PJP prophylaxis regimen determined by the investigator. Examples of standard PJP prophylaxis therapies for this population include trimethoprim-sulfamethoxazole, atovaquone, diaminodiphenylsulfone (Dapsone) with or without pyrimethamine, and pentamidine (National Comprehensive Cancer Network 2017). *Note*: In Japan, diaminodiphenylsulfone and pentamidine are not approved for PJP prophylaxis, thus these will not be used. Participants with sulfonamide allergy should be treated with either inhaled

pentamidine or atovaquone for PJP prophylaxis; diaminodiphenylsulfone should not be used in such participants. Prophylaxis should be given while participants are receiving parsaclisib and continue for 2 to 6 months after the last dose of study treatment. Prophylaxis may be started as soon as the baseline visit but no later than Day 1 of the study.

6.8.3. Use of Growth Factors Such as Erythropoietin

Hematopoietic growth factor receptor agonists (eg, erythropoietin, granulocyte-colony stimulating factor, romiplostim, eltrombopag) are strongly discouraged. Ruxolitinib may interfere with efficacy of growth factors, and they may cause an increase in spleen size.

6.8.4. Restricted Medications and Procedures

- Aspirin in doses exceeding 125 mg/day is not permitted. Low-dose aspirin (≤ 125 mg/day) is permitted.
- Caution should be used when administering ibuprofen or other nonsteroidal anti-inflammatory drugs. Systemic corticosteroid doses less than or equal to the equivalent of 10 mg prednisolone per day are permitted, and higher dosages are not allowed. Participants should be monitored closely for toxicity, especially for myelosuppression and renal and gastrointestinal toxicity.
- Inducers of CYP3A4 may be used with caution, and investigators should seek other options if available (see Appendix G).
- Moderate CYP3A4 inhibitors may be used with caution. Differences in individual sensitivity and variation in potency of inhibition of various CYP enzymes may result in the need for a reduced dose of ruxolitinib during a period of concomitant medication use. If required for safety, the dose of ruxolitinib may be reduced from BID to QD in these circumstances; this should be clearly documented in the treating physician's notes. The sponsor's medical monitor may be consulted for advice when using these agents.

If concomitant administration of an anticoagulant/antiplatelet medication is indicated, then caution and enhanced monitoring is required. History of thrombocytopenia and any concurrent ruxolitinib-related thrombocytopenia should be a factor in the choice of anticoagulant and dose.

6.8.5. Prohibited Medications and Procedures

The following medications are prohibited during the treatment and maintenance portions of the study (see also Jakafi 2021 and Jakavi 2022):

- Any concurrent MF therapy other than that specified in the Protocol.
- Use of experimental drug therapy for MF or any other standard drug used for MF (whether for treatment of MF or another indication), with the exception of ruxolitinib, within 3 months of starting study drug (ie, Day 1).
- Any investigational medication (for a non-MF indication) within 28 days or 5 half-lives, whichever is longer, before the first dose of study drug and at any time before complete withdrawal from the study.

- Use of potent inhibitors of CYP3A4 (eg, ketoconazole, clarithromycin, itraconazole, nefazodone or telithromycin, voriconazole or posaconazole); ketoconazole may be used with caution if other options are not available. Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole in the study.
- Any live vaccine beginning 30 days before the first dose of study drug through the safety follow-up visit.

6.8.6. Treatment After Week 24

After 24 weeks, participants will enter the extension period of the study. Treatment will continue as long as the regimen is tolerated and the participant does not meet discontinuation criteria. Participants randomized to placebo will have the opportunity to crossover to receive parsaclisib (together with continued ruxolitinib) once they have reached Week 24 and all relevant data are entered and cleaned. These crossover participants may also continue as long as the regimen is tolerated and they do not meet discontinuation criteria. It is anticipated that individual participants will continue in the study for approximately 2 years. Extension studies may be implemented for continued access to study treatment.

7. DISCONTINUATION OF STUDY TREATMENTS AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

Participants **must** be discontinued from study treatments (parsaclisib/matching placebo and ruxolitinib) for the following reasons:

- The participant becomes pregnant.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that he/she does not want to be followed any longer; in this case, no further data, except data in the public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study 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.
- Unacceptable toxicity such as noted in Section 6.7.2.
- 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 drug and reference treatment as follows:

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

7.1.2. Discontinuation Procedures

The decision to discontinue study treatment and reference treatment will not constitute study withdrawal or study completion. In the event that the decision is made to discontinue study treatment and reference treatment, the treatment portion will be considered complete and the follow-up part of the study will begin.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the eCRF.
- The EOT visit should be performed and date recorded.
- The last date of the last dose of study drug/reference treatment will be recorded in the eCRF.
- The status of the participant should be updated to EOT in the IXRS.
- Participants must be followed for safety until the time of the follow-up visit or until study drug/reference treatment–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.
- Participants will be followed for subsequent MF treatment regimens and survival via periodic telephone contact. Results of these contacts will be recorded in the eCRF.

If the participant discontinues study treatment/reference treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, participants will have the option of withdrawing consent for study treatment/reference treatment and further assessments but allowing survival follow-up.

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

7.3. Lost to Follow-Up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

All assessments mandated throughout the study must be performed on a calendar schedule; delays in treatment administration will not delay performance of study visits, laboratory-only visits, or assessments [redacted] see Section 8.4.1).

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 country(ies) in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF during their participation in the study.

- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the beginning of the 7-day baseline period (ie, Day –35 to Day –7). 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. Assessments to be performed are indicated in Table 3.

Participants should arrive for the screening visit after an overnight fast (no food or liquid except water) of at least 8 hours or since midnight. A participant who has not fasted should be scheduled for the screening blood draws on a morning when he/she can arrive after an overnight fast of at least 8 hours. For participants who are randomized into the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be used for screening provided that the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, up to 35 days before Day 1).

Bone marrow biopsy and aspirate collection for confirmation of MF diagnosis and degree of fibrosis must be performed at the screening or baseline visit intervals. *Note:* Participants may use a historical biopsy obtained within 2 months before screening as long as a written report showing the diagnosis is available along with biopsy/aspirate samples. Participants without a prior biopsy report and biopsy/aspirate as indicated in the preceding text must have a biopsy at screening/baseline in order to participate in the study. The prior data or the newly obtained data must be entered into the eCRF.

Results from the screening visit evaluations will be reviewed to confirm eligibility before enrollment/randomization or the administration of study drug and reference treatment. 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 randomization/treatment assignment will be used to determine eligibility. Treatment should start as soon as possible but within 3 days after the date of enrollment/randomization.

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

8.1.3. Baseline

Participants who have signed the ICF and meet all of the inclusion criteria (see Section 5.1) and none of the exclusion criteria (see Section 5.2) may be enrolled in the study and will be contacted by clinical site staff to schedule the baseline visit. The baseline interval corresponds to the 7 days before initiating treatment with parsaclisib/matching placebo plus ruxolitinib and during which the baseline MRI (or CT scan in applicable participants) and symptom diary will be initiated.

- The MFSAF v4.0 diary should be distributed. Participants will be issued a handheld device and will complete the diary questions each night beginning on Day –7 up to the Week 24 visit.
- The MRI (or CT scan in applicable participants) should be conducted on the first or second day of the baseline interval to allow ample time for the laboratory to verify scan quality.
- To ensure per-Protocol imaging completions, all MRI (or CT) scans for the study should be scheduled if possible to avoid missing scans at later timepoints in the study.
- Baseline laboratory samples for serum chemistry and hematology should be obtained as close as possible to Day 1 but may be drawn up to 3 days before first dose. Only 1 sample for baseline/Day 1 is required. Baseline platelet count values will be used for stratification/randomization. Note that platelet count at baseline for a participant with a screening value of $\geq 50 \times 10^9$/L may have decreased below 50×10^9/L. For such participants, the screening value for platelet count will be used for stratification/randomization.

8.1.4. Interactive Response Technology Procedure

The IXRS will be accessed to obtain a participant ID number when a participant enters the screening portion of the study. After determining that the participant is eligible for study entry, and the participant has entered the baseline interval and is completing the daily diary for symptoms, using the platelet value determined at baseline, the IXRS will be contacted to obtain treatment group assignment and study drug assignment. The IXRS will be contacted at each regular study visit, except for the end of Week 2 visit, to update the study drug supply and at EOT (see Table 3 and Table 4). Full details will be provided in the IXRS Manual.

8.1.5. Distribution of Reminder Cards

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 study drug or reference treatment (ruxolitinib) on the day of the study visit. The reminder card will also indicate to arrive after an overnight fast (no food or liquid except water) of at least 8 hours for the visits at screening, Week 12, Week 24, the extension visits every 12 weeks thereafter, and the EOT visit, since blood samples for lipid profile will be drawn at these visits. Laboratory-only visits do not require overnight fasting or holding of morning doses of parsaclisib/matching placebo or ruxolitinib. Space will be provided on the reminder card for the Week 2 and Week 4 visits to record the time of the prior evening dose of ruxolitinib.

8.1.6. Prior and Concomitant Medications

Prior and concomitant medications and procedures will be reviewed to determine participant eligibility. All concomitant medications and measures must be recorded in the CRF, and any medication received or procedure performed within 30 days before the first dose of parsaclisib/matching placebo plus ruxolitinib and up to the end of study will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include

any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF.

8.1.7. Demography and Medical History

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

8.1.7.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's history of MF and other MPNs, including date of diagnosis, as well as relevant disease characteristics and prior treatments, including systemic treatments, radiation, and surgical procedures, will be recorded.

8.1.7.3. Transfusion History Status

All transfusions of RBC products or platelets from at least 12 weeks before the screening visit up to the first dose of study drug will be recorded on the transfusion history page. After the first dose of study drug, all transfusions of RBC products or platelets will be recorded on the transfusion page located within the logs area of the eCRF. Information collected in the eCRF includes product delivered, data of transfusion, and units delivered.

8.1.7.4. Dosing Diary

A diary will be provided to the participant to record doses of parsaclisib and ruxolitinib taken each day. Participant will bring the diary with them to each study visit.

8.1.7.5. Screening Symptom Form

In order to satisfy Inclusion Criteria 5, active symptoms of MF at the screening visit as demonstrated by the presence of a TSS of ≥ 10 using the Screening Symptom Form (see Appendix C) will be recorded in the eCRF.

8.1.8. Study Site Visit Coordination

Participants will follow the study visit schedule shown in Table 3. Unblinding and potential crossover for participants will occur once they have completed Week 24 and the data entered have been verified and cleaned through the Week 24 visit (including imaging). If the planned crossover visit does not coincide with a regularly scheduled study visit, an additional study visit may be scheduled in order to perform visit assessments; the 4-week post-crossover visit will also need to be scheduled (see Table 4 for crossover visit and 4-week post-crossover visit assessments).

For early unblinding/crossover, a regularly scheduled visit may be used once the process defined in Section 4.1.4 has been completed. If the planned crossover visit does not coincide with a

regularly scheduled study visit, an additional study visit may be scheduled in order to perform visit assessments; the 4-week post-crossover visit will also need to be scheduled (see Table 4 for crossover visit and 4-week post-crossover visit assessments).

8.2. Efficacy Assessments

[redacted]

[redacted]

[redacted]

8.2.3. Imaging

The primary measure of spleen volume will be by MRI (or CT scan in applicable participants). An MRI of the upper and lower abdomen and pelvis will be performed at baseline, Week 12, Week 24, and every 12 weeks thereafter through Week 108. An MRI will be performed with a body coil because the objective is to measure organ volume rather than to find very small lesions. MRIs will be read initially by local radiologists who will be instructed to not provide a quantitative measure of spleen volume but may provide a qualitative assessment such as enlarged, smaller, larger, and so on. However, should a quantitative result be provided to the investigator, this will not be considered a protocol violation, and the participant will still be evaluable. The local radiologist should assess the scan for quality and send all scans (MRI or CT) to the central imaging laboratory the same day, if at all possible. The scans from an individual participant will be read by a central reader. The central imaging laboratory radiologist(s) will be blinded to initial treatment assignment. Spleen and liver volume will be obtained by outlining the circumference of the organ and determining the volume using the validated technique of least squares. The MRI will not determine spleen length below the costal margin because there are no validated approaches for determining this measurement.

Procedure-specific training for scanning and image capture will be provided by the vendor and in the Imaging Manual.

An MRI is the preferred method for obtaining spleen volume data. However, CT scans may be performed at the visits where MRI is designated if the participant is not a candidate for MRI (eg, because of the presence of metal clips in the body, because of claustrophobia) or if MRI is not readily available. CT scans will be similarly processed by the same central laboratory as used for MRIs. Procedure-specific training for scanning and image capture will be provided by the vendor. *Note:* The same method (MRI vs CT) must be used for all visits for a given participant unless a new contraindication to the use of MRI occurs (eg, pacemaker insertion).

8.2.4. Symptom Diary

Symptoms of MF will be assessed using a symptom diary (MFSAF v4.0 diary). Participants will be issued a handheld device on which to record answers to queries regarding MF symptoms. Symptoms assessed will include filling up quickly/early satiety, abdominal discomfort, abdominal pain, fatigue, night sweats, itching, and bone/muscle pain. The MFSAF v4.0 diary will be completed by participants each night beginning at Day –7 (first day of baseline) and continuing to the Week 24 visit (25 weeks total). Participants will bring the device to the study site at study visits on Day 1 and Weeks 4, 8, 12, 16, and 20, so that the device charging can be verified and the accumulated data can be downloaded. *Note:* Participants who will have overnight stays associated with their study visit must also bring their docking station so that their device can be fully charged at all times and so that they can complete the evening diary entries. The device will then be returned to the participant at these same visits for continued use each night. The participant will return the device and the docking station for the final time at the Week 24 visit so that the data can be archived. Detailed directions for the administration of the MFSAF v4.0 diary will be provided in a reference manual. Translations of the MFSAF v4.0 diary will be available.

[redacted]

8.2.6. Eastern Cooperative Oncology Group Status

The ECOG performance status score (see Appendix D) will be required at screening to evaluate eligibility and will be assessed at visits noted in the SoA (see Table 3 and Table 4).

[redacted]

8.3. Safety Assessments

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 to 35 days after the last dose of study drug (parsaclisib/placebo). 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 treatment. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. See Section 9 for full reporting requirements for AEs.

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 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 AEs of special interest (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. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, physician assistant, or an advanced registered nurse practitioner, as local law permits. Abnormalities 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 treatment. Investigators should pay special attention to clinical signs related to previous serious illnesses.

At the screening and EOT visits, a complete physical examination should be conducted. The complete physical examination will include height (screening only) 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. The complete examination should also include an assessment of body fluid abnormalities, including ascites and edema.

Targeted physical examinations will be a symptom-directed evaluation and will include assessment of the body systems or organs as indicated by participant symptoms, AEs or other findings as determined by the investigator or designee. The targeted examination will include measurement of body weight and assessment of fluid abnormalities, including ascites and edema.

8.3.3. Vital Signs

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

8.3.4. Electrocardiograms

Twelve-lead ECGs will be obtained as outlined in the SoA (see Table 3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest.

The 12-lead ECGs 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 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.

8.3.5. Laboratory Assessments

See Table 5 for the schedule of laboratory assessments and Table 14 for the laboratory tests that will be performed. All Protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SoA. Information regarding collection, processing, and shipping of laboratory assessments for the central laboratory is provided in the Laboratory Manual.

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

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

Blood samples for hematology and serum chemistry analysis for baseline should be taken as close as possible to Day 1 but may be drawn up to 3 days before the first dose of parsaclisib. This blood sample will serve as the pre-parsaclisib baseline sample; a Day 1 sample is not required as long as the baseline sample is obtained within 3 days of the first dose of parsaclisib.

8.3.5.1. Chemistry

Serum chemistry assessments will be performed by a local laboratory using institutional best practices. Results and normal ranges will be entered in the eCRF.

8.3.5.2. Hematology

Hematology assessments, including complete blood count with differential, and blast percentage will be performed at a local laboratory using institutional best practices. Results and normal reference ranges will be entered in the eCRF.

8.3.5.3. Urinalysis

Urinalysis will be performed by a central laboratory.

8.3.5.4. Serology and Virology

Serology and virology assessments will be performed by the central laboratory. Assessments will include HBV DNA, HIV RNA, CMV DNA, and HCV RNA measurement; hepatitis B surface antigen; anti-hepatitis B surface antigen antibody; and anti–hepatitis B core antibody.

8.3.5.5. Lipid Panel

Lipid panel assessment will be performed by the central laboratory. Overnight fast (no food or liquid except water) is required for these samples. If the participant arrives for the study visit without an overnight fast of at least 8 hours or since midnight, the lipid blood draw must be rescheduled for a date when the participant can arrive in the fasted state.

8.3.5.6. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening and at the safety follow-up visit. This assessment will be performed by the central laboratory. Urine pregnancy tests will be conducted as outlined in Table 5, as medically indicated, or per country-specific requirement. Urine pregnancy tests will be performed locally. If a urine pregnancy test is positive, then the results should be confirmed with a serum pregnancy test to be performed at the local laboratory.

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.

Follicle-stimulating hormone levels will be determined only at screening to verify hormonal menopause in relevant participants.

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

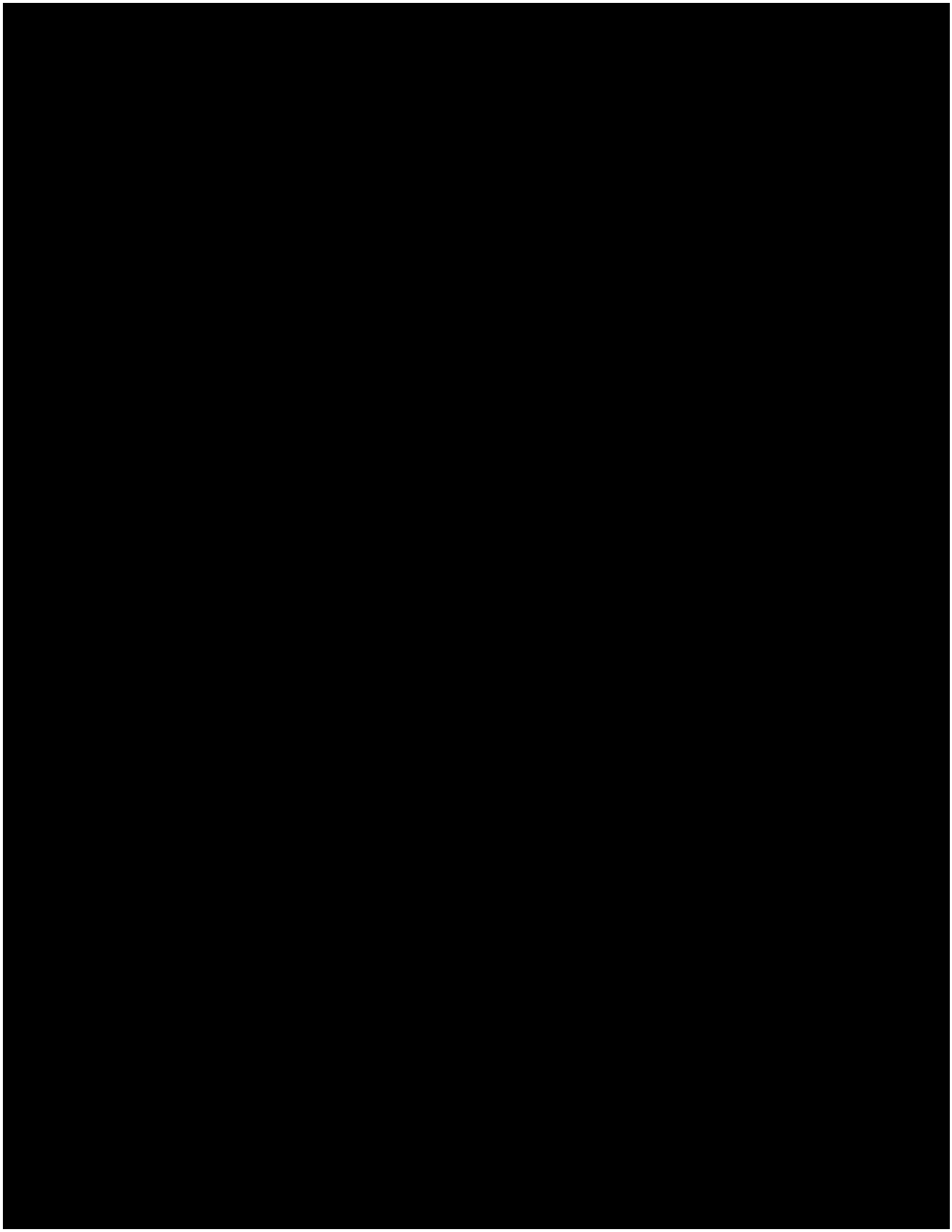
8.3.5.7. Coagulation Panel

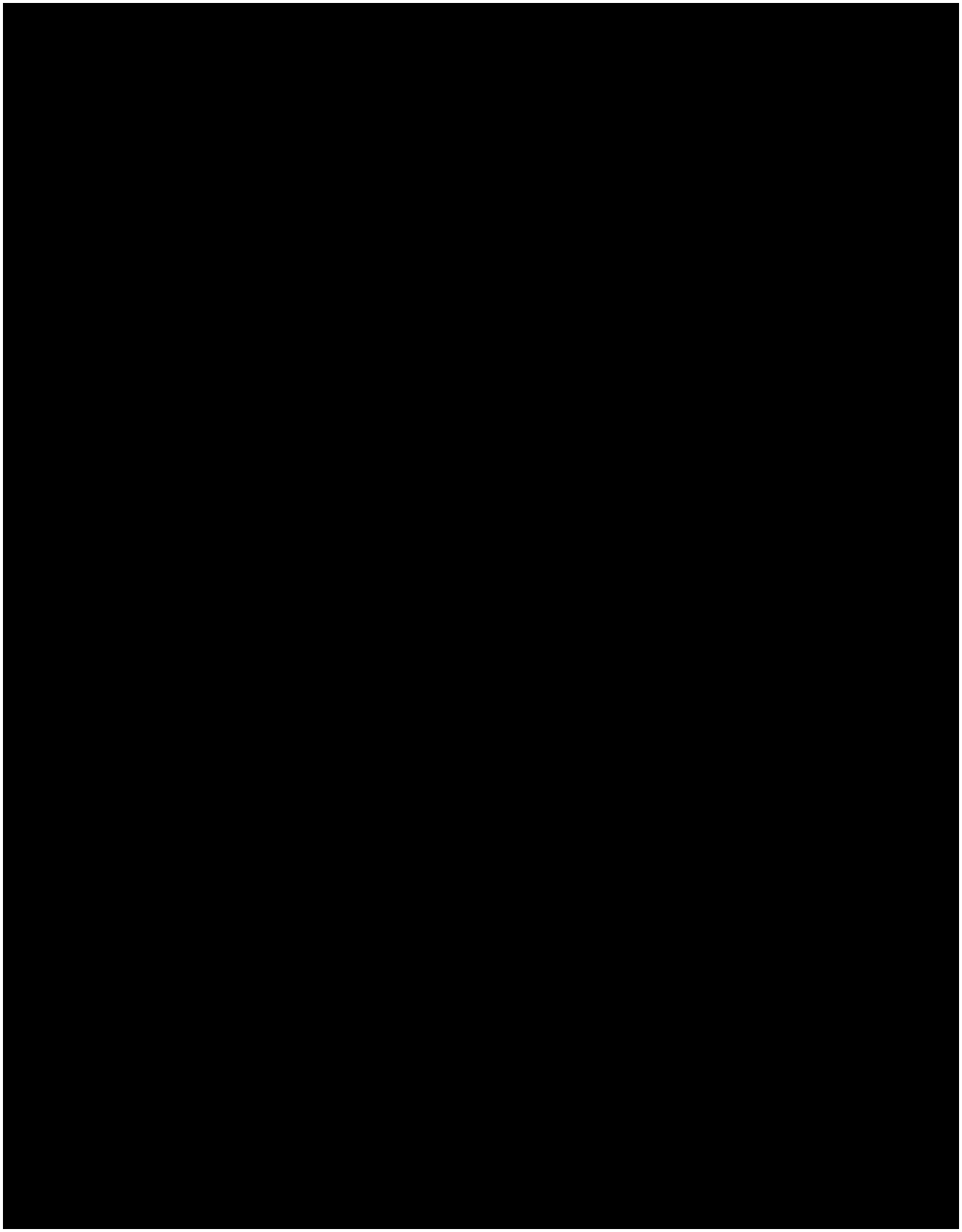
Coagulation parameters (PT, aPTT or PTT, and INR) will be determined at a local laboratory using institutional best practices. Results and normal reference ranges will be entered in the eCRF.

Table 14: Required Laboratory Analytes

Serum Chemistries	Hematology	Urinalysis With Microscopic Examination	Serology	Coagulation
Albumin Alkaline phosphatase ALT AST Amylase Bicarbonate (not applicable in Japan) Blood urea nitrogen Calcium Chloride Creatinine Glucose Lactate dehydrogenase Phosphate Potassium Sodium Total bilirubin Direct bilirubin Total protein Uric acid	Complete blood count, including: Hemoglobin Hematocrit Platelet count RBC count WBC count Blasts Differential count, including: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Blasts Absolute values must be provided for: WBC differential results Platelet count	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein	Hepatitis B surface antigen Hepatitis B surface antigen antibody Hepatitis B core antibody HBV-DNA HCV-RNA CMV DNA HIV RNA	PT PTT or aPTT INR
		Lipid Panel	**MF Specific**[a]	**Pregnancy Testing**
		Total cholesterol Triglycerides LDL HDL	Bone marrow aspirate and biopsy JAK2 mutation status [redacted]	Female participants of childbearing potential only require a serum test at screening and follow-up and a urine pregnancy test before the first dose on Day 1. Pregnancy tests (serum or urine) should be repeated if required by local regulations. FSH only required if hormonal menopause must be verified.

[a] Certain samples will only be collected in designated countries.
Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data or to rule out a diagnosis.
Note: Alternative tests are also allowed as per regional standard of care.





8.6. Unscheduled Visits

Unscheduled visits or laboratory assessments may be conducted at the investigator's discretion. All assessments and laboratory findings will need to be entered in the eCRF using an unscheduled visit page.

8.7. End of Treatment and/or Early Termination

There is no predefined EOT. When the participant permanently discontinues parsaclisib/placebo and ruxolitinib, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, then the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the CRF. 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 30 to 35 days after the EOT visit (or after the last dose of study treatment [parsaclisib/matching placebo and ruxolitinib] if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 30 days after the last dose of study treatment, the date of the follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period. If the participant cannot return to the site for the safety follow-up visit (eg, lives far away), then the participant should be contacted by telephone for assessment of AEs and SAEs. Sites must document this contact in the source.

Participants are required to remain on PJP prophylaxis for at least 2 to 6 months after the last dose of study drug (see Section 6.8.2) and should be reminded of this at the safety follow-up visit. Sites should follow up with participants to confirm that they have been compliant with the prophylactic treatment for the duration of this period.

8.8.2. Survival Follow-Up

Once a participant has received the last dose of study treatment, has confirmed disease progression, or starts a new MF therapy, the participant moves into the survival follow-up period and should be contacted by telephone, e-mail, or visit at least every 12 weeks (± 2 weeks) to assess for subsequent MF treatments and survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

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

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related. • An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to 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 laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after the start of study treatment administration are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from 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. 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 for the participant's condition during study participation.

9.2. Definition of Serious Adverse Event

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization 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 occurs. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

Hospitalization for elective treatment or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE.

Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) are not considered SAEs.

d. Results in persistent or significant disability/incapacity

- The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is an important medical event

An important medical event is an event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers, intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. Secondary malignancies should always be considered SAEs**.**

An event that may lead to disability is also considered an important medical event. It includes a case that is exposed to a risk of dysfunction to an extent that interferes with daily life when the adverse drug reaction occurs. It does not include an adverse drug reaction that, had the reaction been more severe, may have caused disability.

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

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Event Form in the eCRF. 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 diagnostic reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the Adverse Event Form in the eCRF.
- There may be rare instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted by the site staff on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the Study Binder.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

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

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to parsaclisib/matching placebo and ruxolitinib as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity.

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 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 reference therapy is used in combination with an Incyte study drug or if multiple Incyte study drugs are used, then the relationship to each study drug/reference therapy must be assessed (ie for parsaclisib/placebo and for ruxolitinib) If appropriate, the relationship to the combination may be assessed as well.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the RSI in the IB (for parsaclisib or ruxolitinib) or Product Information for ruxolitinib, in making his/her assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study 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 submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • Once an AE is detected, it should be followed in the AE eCRF until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome. • Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance or its designee as directed in the Study Binder 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 drug, reference therapy or study procedure[s]), all SAEs occurring after the participant has signed the ICF through 30 to 35 days after the last dose of study treatment or until the participant starts a new MF therapy, whichever occurs earlier, must be reported to the sponsor (or designee) within 24 hours of learning of its occurrence, unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) within **24 hours** of it being available. For Japan, this information must also be reported immediately to the head of the study site.

Investigators are not obligated to actively seek SAE information after the safety follow-up visit or 30 to 35 days after the last dose of study treatment. If the investigator learns of any SAE, including death, at any time after this period, and he/she considers the event to be reasonably related to the study drug/treatment or study participation, then the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and 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 regarding an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study treatment under clinical investigation are met.

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

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

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

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

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

Serious Adverse Event Reporting
• Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF. • The investigator must report 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 Binder). • 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 in the Study Binder. 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. • Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study treatment because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs. • Contacts for SAE reporting can be found in the Study Binder.

9.5. Adverse Events of Special Interest

The principal toxicity of inhibiting both PI3Kδ and JAK pathways is expected to be reversible effects on immune function. Combined inhibition may adversely affect both B-cell and T-cell immune function, with resultant increased risk of a variety of infections or other immune-related events. Specific AEs or groups of AEs will be followed as part of standard safety monitoring activities. An AE of special interest does not require rapid communication by an investigator to Incyte unless it meets criteria for rapid communication as an SAE (see Section 9.4) and consists of the following based on terms coded per MedDRA v19.0:

- Colitis
- Diarrhoea of Grade 2 or higher
- Rash of Grade 2 or higher
- Pneumonitis
- Dermatitis exfoliative
- Intestinal perforation
- Cytomegalovirus infection
- Herpes simplex infection
- Herpes (varicella) zoster virus infection
- Pneumocystis jirovecii infection
- Alanine aminotransferase increased ≥ 5 × ULN
- Aspartate aminotransferase increased ≥ 5 × ULN

Adverse events of special interest should be captured in the eCRF.

9.6. Emergency Unblinding of Treatment Assignment

In a medical emergency, if knowledge of the treatment assignment is necessary to determine optimal medical management of the participant, the procedure for emergency unblinding is provided in the IXRS/Study Reference Manual. The decision to break the treatment code in an emergency situation resides at the sole discretion of the investigator. This option may be used only if the participant's well-being requires the investigator to be aware of the participant's treatment assignment. If a participant's treatment assignment is unblinded, the sponsor or its designee must be notified immediately by telephone.

If an investigator, site personnel performing assessments, or participant is emergency unblinded, the participant must be withdrawn from the study treatment, unless there are ethical reasons to have the participant remain on the study treatment. In these cases, the investigator must obtain specific approval from the sponsor's (or its designee's) medical monitor for the participant to continue in the study.

9.7. Pregnancy

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

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

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

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 its designee.

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

9.8. Warnings and Precautions

Special warnings or precautions for the study treatment, derived from safety information collected by the sponsor or its designee, are presented in the parsaclisib IB and ruxolitinib 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 e-mail 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

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

Refer to the approved product label of ruxolitinib for advice on overdose.

10. STATISTICS

10.1. Sample Size Determination

The primary endpoint of this study is the proportion of participants with ≥ 25% spleen volume reduction from baseline to Week 24 as measured by MRI (or CT scan in applicable participants). The primary endpoint will be analyzed by CMH test stratified by baseline (or screening, if applicable) platelet count (≥ 100×10^9/L vs 50 to < 100×10^9/L inclusive) and DIPSS risk category (high vs intermediate-2 vs intermediate-1) at randomization (note that if a participant's platelet count is < 50×10^9/L at baseline, the platelet count at screening will be used for stratification/randomization). Assuming a 25% response rate for ruxolitinib + parsaclisib versus 5% for ruxolitinib + placebo, to achieve a 95% power to detect a statistically significant difference with a 2-sided Type I error of 5%, a sample size of 212 participants is required to be randomized equally between treatment groups.

For the key secondary endpoint of MFSAF TSS, assuming a response rate of 35% (25%) in ruxolitinib + parsaclisib for normal (low) platelet participants and a response rate of 15% (10%) in ruxolitinib + placebo for normal (low) platelet participants, a sample size of 212 will provide 81.3% power using CMH test given a 2-sided Type I error of 5%.

A test for OS will be performed when 84 deaths are observed using the log-rank test at a 2-sided Type I error level of 0.05. The log-rank test will provide 80% power to detect a hazard ratio of 0.54. Assuming a median survival time of 3.7 years for ruxolitinib + placebo and enrollment duration of 1 year, the expected total study duration is 4 years.

10.2. Populations for Analysis

The populations for analysis are provided in Table 16.

Table 16: Populations for Analysis

Population	Description
ITT	All randomized participants. The ITT population will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy data. Participants will be analyzed according to the treatment group to which they were randomized regardless of the treatment received during the study.
Per protocol (PP) population	Participants in the ITT population who are considered to be sufficiently compliant with the Protocol.
Safety	All randomized participants who received at least 1 dose of parsaclisib, placebo, or ruxolitinib. Treatment groups for this population will be determined according to the actual treatment the participant received regardless of assigned study drug treatment. All safety analyses will be conducted using the safety population
[redacted]	

10.3. Level of Significance

This study defines a single primary endpoint with a single primary analysis. The study will be claimed to have achieved the primary efficacy objective when the primary endpoint shows a significant result at 2-sided alpha of 0.05 at final analysis. The key secondary efficacy endpoints will be alpha-controlled and will be analyzed only when the study has reached the efficacy objective in the primary endpoint. The key secondary efficacy variables will be tested following a fixed-sequence-testing procedure with each at the 2-sided alpha level of 0.05 in the order below:

1. The proportion of participants who have a ≥ 50% reduction from Baseline to Week 24 in the MFSAF TSS
2. OS

Other secondary [redacted] endpoints will be tested using a 2-sided, 5% significance level but are not considered alpha-controlled hypotheses.

10.4. Statistical Analyses

10.4.1. Primary and Secondary Analyses

The methods and populations for primary and secondary analyses are provided in Table 17.

Table 17: Primary and Secondary Analyses Methods and Populations

Endpoint	Statistical Method	Analysis Population	Primary (P) or Supportive (S)
Primary endpoint			
Proportion of participants achieving ≥ 25% reduction in spleen volume from baseline to Week 24 as measured by MRI (or CT scan in applicable participants).	CMH test stratified by baseline (or screening, if applicable) platelet count (≥ 100 × 10^9/L vs 50 to < 100 × 10^9/L inclusive) and DIPSS (high vs intermediate-2 vs intermediate-1) at randomization	ITT	P
		PP	S
Secondary endpoints			
Proportion of participants who have a ≥ 50% reduction in total symptom score from baseline to Week 24 as measured by the MFSAF v4.0 diary.	CMH test stratified by baseline (or screening, if applicable) platelet count (≥ 100 × 10^9/L vs 50 to < 100 × 10^9/L inclusive) and DIPSS (high vs intermediate-2 vs intermediate-1) at randomization	ITT	P
		PP	S
OS determined from the date of randomization until death due to any cause.	Inference: Log rank test stratified by baseline (or screening, if applicable) platelet count (≥ 100 × 10^9/L versus 50 to < 100 × 10^9/L inclusive) and DIPSS (high vs intermediate-2 vs intermediate-1) at randomization Estimation: Kaplan-Meier	ITT	P
		PP	S
	Inference: Cox regression model including treatment group, baseline (or screening, if applicable) platelet count (≥ 100 × 10^9/L vs 50 to < 100 × 10^9/L inclusive) at randomization, and DIPSS (high vs intermediate-2 vs intermediate-1) at randomization	ITT	S
OS adjusted for crossover using rank preserving structural failure time (RPSFT)	Inference: Cox regression model including treatment group, baseline (or screening, if applicable) platelet count (≥ 100 × 10^9/L vs 50 to < 100 × 10^9/L inclusive) and DIPSS (high vs intermediate-2 vs intermediate-1) at randomization	ITT	S

Table 17: Primary and Secondary Analyses Methods and Populations (Continued)

Endpoint	Statistical Method	Analysis Population	Primary (P) or Supportive (S)
Secondary endpoints (continued)			
Time to the first ≥ 25% reduction in spleen volume	Inference: Log rank test with stratification of baseline (or screening, if applicable) platelet count (≥ 100×10^9/L versus 50 to < 100×10^9/L inclusive) and DIPSS (high vs intermediate-2 vs intermediate-1) at randomization Estimation: Kaplan-Meier	ITT	P
Duration of maintenance of a ≥ 25% reduction in spleen volume	Estimation: Kaplan-Meier	ITT with spleen response	P
Time to the first ≥ 50% reduction in TSS as measured by the MFSAF v4.0 diary	Inference: Log rank test with stratification of baseline (or screening, if applicable) platelet count (≥ 100×10^9/L versus 50 to < 100×10^9/L inclusive) and DIPSS (high vs intermediate-2 vs intermediate-1) at randomization Estimation: Kaplan-Meier	ITT	P

Other secondary endpoints, including change and percentage change in MFSAF TSS from baseline to Week 24 as measured by the MFSAF v4.0 diary, will be summarized descriptively by treatment group.

For the stratifications of platelet and DIPSS, within a platelet category, in the event that a particular DIPSS stratification level has fewer than 30 participants randomized, it will be combined with the nearest adjacent DIPSS level (eg, high vs intermediate-1 vs intermediate-2). For example, if either intermediate-1 or high risk is too small, it will be merged with intermediate-2. If intermediate-2 has too few participants, then it will be merged with the smaller of the 2 adjacent strata.

In the event that 2 DIPSS stratification levels are combined, a sensitivity analysis for the primary endpoint without combining levels will be conducted.

The primary endpoint will also be compared between the treatment groups within each of the following subgroups:

- Baseline platelet count: ≥ 100×10^9/L versus 50 to < 100×10^9/L inclusive (Note that if a participant's platelet count is < 50×10^9/L at baseline, the platelet count at screening will be used instead)
- DIPSS risk category: high vs intermediate-2 vs intermediate-1
- Sex: male and female

- Age group: ≤ 65 years or > 65 years
- MF type: PMF or PPV-MF/PET-MF
- Ruxolitinib average total daily dose during the 8 weeks before randomization: ≥ 20 mg or less than 20 mg
- Presence/absence of V617F mutation at baseline
- Presence/absence of HMR mutations at baseline
- Baseline spleen volume group: ≤ median or > median
- Baseline spleen palpation size group: ≤ 10cm or > 10cm
- Race: white/Caucasian, black/African-American, Asian, American-Indian/Alaska Native, Native Hawaiian/Pacific Islander, or other
- Ethnicity: Hispanic/Latino, not Hispanic/Latino, or other

10.4.2. Safety Analyses

Safety analyses will be conducted for the safety population. Adverse events will be coded by the MedDRA dictionary, and TEAEs (ie, AEs reported for the first time or worsening of a pre-existing event after first dose of study treatment) will be tabulated by preferred term and system organ class for all events, related events, and events of Grade 3 or higher. Quantitative safety variables and their changes from baseline (laboratory, vital signs, etc) will be summarized with descriptive statistics. Clinically notable abnormal values will be flagged and tabulated based on predefined criteria. TEAEs of clinical interest (see Section 9.5) will be summarized descriptively by treatment group.

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

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

Table 18: Criteria for Clinically Notable Electrocardiogram Abnormalities

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

Measures of exposure (eg, days of exposure, duration of treatment, average daily dose, and total daily dose) of parsaclisib, placebo, or ruxolitinib will be summarized by means of summary statistics.

[redacted]

10.5. Interim Analysis

There will be 2 planned, nonbinding, interim analyses conducted for futility for this study, based on the first 30% of participants enrolled in the study. The first interim analysis will be conducted when the first 30% of the planned randomized participants (approximate 32 in each treatment group) reach Week 12 assessments of spleen volume and MFSAF TSS, or discontinue from treatment group. Based on the results of this interim analysis, the DMC may recommend to terminate the study, continue the study with no changes to enrollment, or continue the study with no further enrollment permitted until review of the second interim analysis.

The second interim analysis will be initiated when the first 30% of the planned randomized participants reach their Week 24 assessments of spleen volume and MFSAF TSS, or have discontinued from study. The DMC may recommend to either terminate the study for futility or continue the study, based on the results of this analysis.

At the interim analyses for Week 12 and Week 24 data, MFSAF TSS will be tested for futility only if spleen volume does not cross the futility boundary. An HSD (Hwang et al 1990) with $\gamma = 2$ and HSD with $\gamma = 1$ will be used to determine the nonbinding futility boundary for spleen volume and MFSAF TSS, respectively. The study may be terminated early for futility if either the spleen volume or the MFSAF TSS endpoints cross the futility boundary. Table 19 and Table 20 provide the projected stopping rules if the second interim analysis is conducted at the projected number of participants. The first interim analysis will use the futility boundaries defined in Table 19 and Table 20 for the second interim analysis for a preliminary look at the efficacy of the data on Week 12.

Table 19: Interim Analysis for Spleen Volume With HSD(2)

Number of Participants	**Second Interim Analysis**		**Final Analysis**	
	64		**212**	
Decision outcome	**Stop for Futility**	**Continue to Test MFSAF TSS**	**Do Not Reject Null Hypothesis**	**Reject Null Hypothesis**
Z-statistic	≤ 0.16	> 0.16	≤ 1.96	> 1.96
One-sided p-value	≥ 0.436	< 0.436	≥ 0.025	< 0.025
Parsaclisib + ruxolitinib response rate[a]	≤ 5.9%	> 5.9%	≤ 12.7%	> 12.7%

[a] Assumes spleen volume response rate is 5% in the ruxolitinib + placebo group.

Table 20: Interim Analysis for MFSAF TSS With HSD(1)

Number of Participants	Second Interim Analysis		Final Analysis	
	64		212	
Decision outcome	**Stop for Futility**	**Continue**	**Do Not Reject Null Hypothesis**	**Reject Null Hypothesis**
Z-statistic	≤ 0.22	> 0.22	≤ 1.96	> 1.96
One-sided p-value	≥ 0.413	< 0.413	≥ 0.025	< 0.025
Parsaclisib + ruxolitinib odds ratio (RR for 50× to < 100 × 10^9/L, ≥ 100 × 10^9/L PLT)[a]	≤ 1.08 (11%, 16%)	> 1.08 (11%, 16%)	≤ 2.37 (21%, 29%)	> 2.37 (21%, 29%)

[a] Assumes TSS response rate for 50 × to < 100 × 10^9/L inclusive and ≥ 100 × 10^9/L platelet is 10% and 15% in the ruxolitinib + placebo group.

Preplanned analyses of safety and efficacy will be provided to an independent DMC as specified in the DMC charter. The process by which the DMC will review data and make recommendations and decisions will be documented in the DMC charter.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

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

- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study during the retention period without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.
- For Japan: The record retainer (delegated by the head of the study site) will retain the J-GCP–defined essential documentation at the site until the regulatory approval of the study drug/treatment or at least 3 years after the discontinuation or completion of the study conduct, whichever is later. If the sponsor requires retention of these documents for a longer period of time, the duration and method of retention will be decided upon through discussion between the sponsor and the study site. It is the responsibility of the sponsor to inform the head of the study site as to when the documents no longer need to be retained.

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor before the end of the study. As part of their responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

11.2. Data Management

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

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct

of the Protocol, such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and as designated by the sponsor, will have their own data flow management plans, study charters, [redacted], as applicable.

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

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

The investigator will be responsible for the following:

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

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; participants' files; and e-records/records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.

- Sending participants' data, either as unique samples, or copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
  - As required by privacy and data protection regulations and Incyte's privacy policies, if any photographs of participants are to be taken, the photographs must be limited to the area of the face or the body that is strictly necessary and the photographs should be masked (ie, identifying features such as eyes, mouth, scars, tattoos, or unique markings or features should be either obscured with a black bar or digitally pixelated so as to not permit the reidentification of the participants and preserve their confidentiality) by a specially designated photography vendor prior to sending the photographs to Incyte or any other third-party vendors for analysis or further processing.
  - In accordance with French regulations, sites in France must perform the masking before the photographs are transferred, including to any specially designated photography vendor, Incyte, or any other third-party vendors for analysis or further processing. In addition, the participant's specific consent for photographs shall be collected.
- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.

- Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
- Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Quality Assurance

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

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

11.4. Data Privacy and Confidentiality of Study Records

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

To ensure confidentiality of records and protect personal data, participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study

findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

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

11.5. Financial Disclosure

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

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

11.6. Publication Policy

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

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

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

11.7. Study and Site Closure

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

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

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

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 93 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 93 days after the end of relevant systemic exposure. In addition, male participants must refrain from donating sperm from screening through 93 days after the end of relevant systemic exposure. Males who have had a vasectomy clinically designated as successful 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[b]
  - transdermal[b]
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]
  - oral[b]
  - injectable[b]
  - implantable[b,c]
- Intrauterine device[c]
- Intrauterine hormone-releasing system[c]
- Bilateral tubal occlusion[c]
- Vasectomized partner[c,d]
- Sexual abstinence[e] (not applicable in Japan)

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

[b] Administration route not approved in Japan.

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

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

[e] 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.

Source: Clinical Trials Facilitation and Coordination Group 2014.

APPENDIX B. WORSENING SYMPTOMATIC SPLENOMEGALY FORM

Date of additional MRI _____

Did the imaging vendor report an increase in SV of 25% or more relative to baseline? Yes/No

Ask the patient the following 3 questions and record scores here:

1. During the past 7 days, how severe was your worst abdominal discomfort (feeling pressure or bloating)?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
2. During the past 7 days, how severe was the worst pain under your ribs on your left side?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
3. During the past 7 days, what was the worst feeling of fullness you had after beginning to eat?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

APPENDIX C. SCREENING SYMPTOM FORM

Instructions to participants: Please answer all questions to the best of your ability, based on your memory over the past 7 days (1 week). There is no right or wrong answer.

1. During the past 7 days, how severe was your worst fatigue (weariness, tiredness)?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
2. During the past 7 days, how severe were your worst night sweats (or feeling hot or flushed)?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
3. During the past 7 days, how severe was your worst itching?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
4. During the past 7 days, how severe was your worst abdominal discomfort (feeling pressure or bloating)?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
5. During the past 7 days, how severe was the worst pain under your ribs on your left side?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
6. During the past 7 days, what was the worst feeling of fullness you had after beginning to eat?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
7. During the past 7 days, how severe was your worst bone pain (not joint or arthritis pain)?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Investigators/Site Staff:

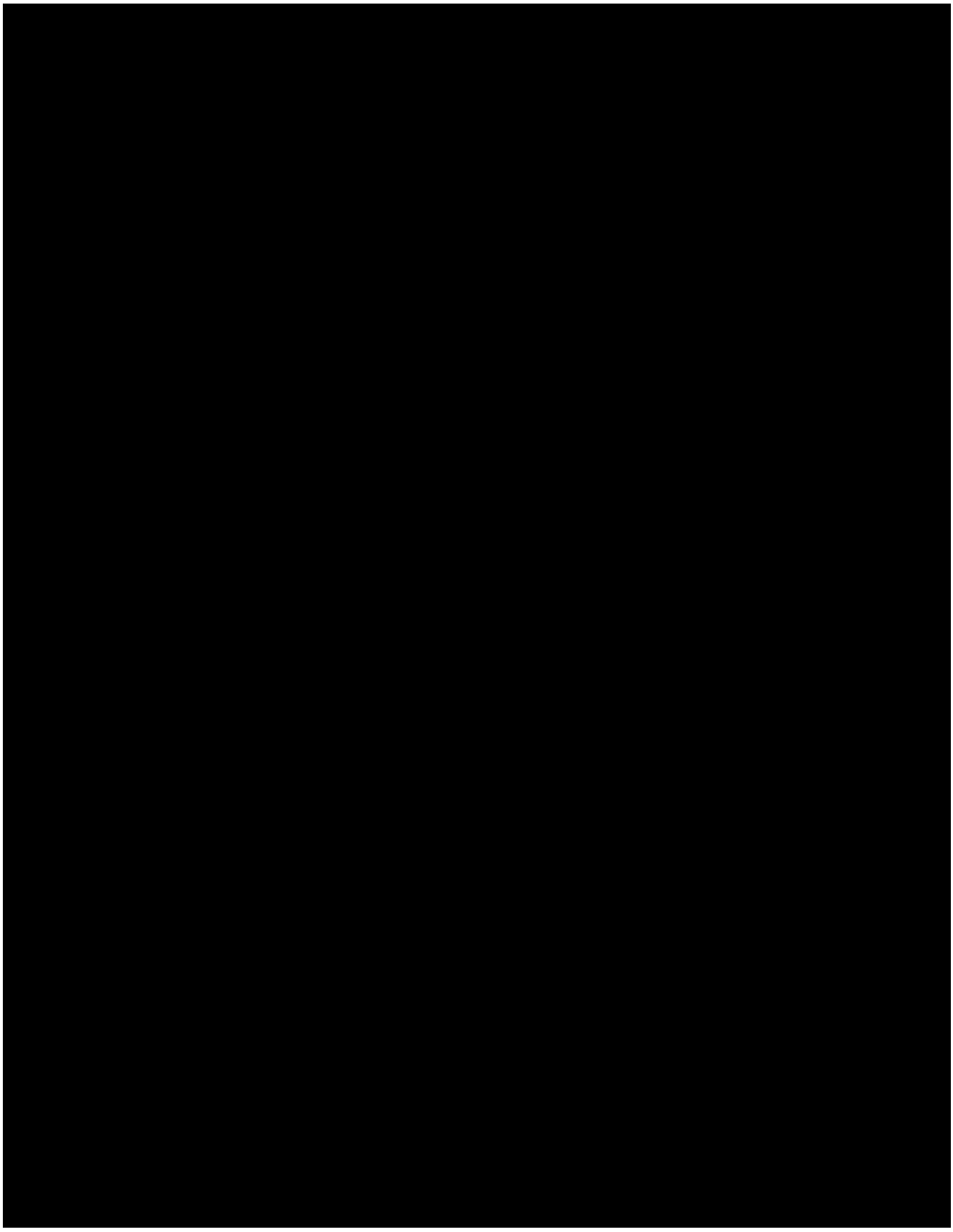
Please complete the table below to confirm the criterion used to confirm the participant's eligibility in the trial based on an assessment of his/her active symptoms of myelofibrosis.

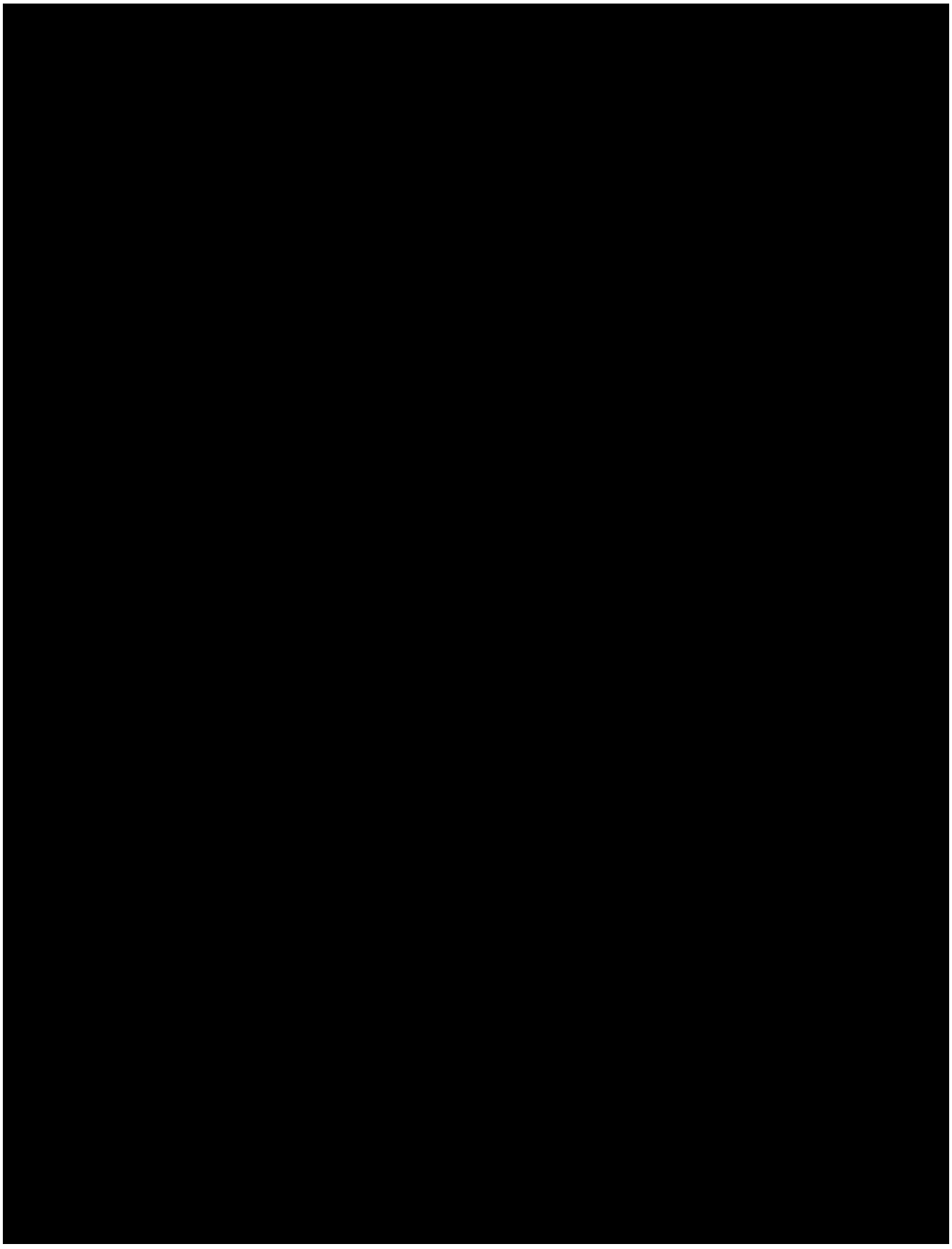
ELIGIBILITY CRITERION	CONFIRMATION
Total Symptom Score of at least 10 (for the 7 items above)	□ Yes □ No

APPENDIX D. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

Source: Oken et al 1982.





APPENDIX G. INHIBITORS AND INDUCERS OF CYTOCHROME P450

CYP 3A4 Inhibitors

Inhibitor	Therapeutic Class
Potent CYP3A	
VIEKIRA PAK	Antivirals
Indinavir/RIT	Protease inhibitors
Tipranavir/RIT	Protease inhibitors
Ritonavir	Protease inhibitors
Cobicistat (GS-9350)	None
Ketoconazole	Antifungals
Indinavir	Protease inhibitors
Troleandomycin	Antibiotics
Telaprevir	Antivirals
Danoprevir/RIT	Antivirals
Elvitegravir/RIT	Treatments of AIDS
Saquinavir/RIT	Protease inhibitors
Lopinavir/RIT	Protease inhibitors
Itraconazole	Antifungals
Voriconazole	Antifungals
Mibefradil	Calcium channel blockers
LCL161	Cancer treatments
Clarithromycin	Antibiotics
Posaconazole	Antifungals
Telithromycin	Antibiotics
Grapefruit juice DS	Food products
Conivaptan	Diuretics
Nefazodone	Antidepressants
Nelfinavir	Protease inhibitors
Saquinavir	Protease inhibitors
Ribociclib	Kinase inhibitors
Idelalisib	Kinase inhibitors
Boceprevir	Antivirals

Inhibitor	Therapeutic Class
Moderate CYP3A	
Erythromycin	Antibiotics
Fluconazole	Antifungals
Atazanavir/RIT	Protease inhibitors
Darunavir	Protease inhibitors
Diltiazem	Calcium channel blockers
Darunavir/RIT	Protease inhibitors
Dronedarone	Antiarrhythmics
Crizotinib	Kinase inhibitors
Atazanavir	Protease inhibitors
Letermovir	Antivirals
GSK2647544	Alzheimer's disease & dementia treatments
Aprepitant	Antiemetics
Casopitant	Antiemetics
Amprenavir	Protease inhibitors
Faldaprevir	Antivirals
Imatinib	Antineoplastic agents
Verapamil	Calcium channel blockers
Netupitant	Antiemetics
Nilotinib	Kinase inhibitors
Grapefruit juice	Food products
Tofisopam	Benzodiazepines
Cyclosporine	Immunosuppressants
ACT-178882	Renin inhibitors
Ciprofloxacin	Antibiotics
Magnolia vine (Schisandra sphenanthera)	Herbal medications
Isavuconazole	Antifungals
Cimetidine	H-2 receptor antagonists
FK1706	Central nervous system agents

Inhibitor	Therapeutic Class
Weak CYP3A	
Tabimorelin	Hormone replacement
Amlodipine	Calcium channel blockers
Ranolazine	Cardiovascular drugs
Breviscapine	Herbal medications
Lomitapide	Other antilipemics
Fosaprepitant (IV)	Antiemetics
Seville orange (Citrus aurantium) juice	Food products
Amiodarone	Antiarrhythmics
Diosmin	Herbal medications
Chlorzoxazone	Muscle relaxants
M100240	Antihypertensive agents
Fluvoxamine	Antidepressants
Ranitidine	H-2 receptor antagonists
Goldenseal	Herbal medications
Clotrimazole	Antifungals
Tacrolimus	Immunosuppressants
Palbociclib	Kinase inhibitors
Cilostazol	Antiplatelets
Ticagrelor	Antiplatelets
Peppermint oil	Food products
Ivacaftor	Cystic fibrosis treatments
GSK2248761	Transcriptase inhibitors
Guan Mai Ning	Herbal medications
Osilodrostat	Adrenal steroidogenesis inhibitors
AZD2327	Depression treatments
Piperine	Food products
Resveratrol	Food products
Roxithromycin	Antibiotics
Suvorexant	Hypnotics - sedatives
Propiverine	Anticholinergics
Isoniazid	Antibiotics
Berberine	Herbal medications
Oral contraceptives	Oral contraceptives
Delavirdine	NNRTIs
Daclatasvir	Antivirals

Inhibitor	Therapeutic Class
Weak CYP3A (continued)	
Simeprevir	Protease inhibitors
Atorvastatin	HMG CoA reductase inhibitors (statins)
Tolvaptan	Vasopressin antagonists
Almorexant	Hypnotics - sedatives
GSK1292263	Other antilipemics
Evacetrapib	CETP inhibitors
Linagliptin	Dipeptidyl peptidase 4 inhibitors
Grazoprevir *(ingredient of Zepatier)*	Antivirals
Lacidipine	Calcium channel blockers
Cranberry juice	Food products
Pazopanib	Kinase inhibitors
Fostamatinib	Other
Everolimus	Immunosuppressants
Blueberry juice	Food products
Flibanserin	Central nervous system agents
Lapatinib	Kinase Inhibitors
Brodalumab	Immunomodulators biologics
AMD070	Fusion inhibitors
Alprazolam	Benzodiazepines
Tong Xin Luo	Herbal medications
Glecaprevir and pibrentasvir	Antivirals
Bicalutamide	Antiandrogens
Sitaxentan	Endothelin receptor antagonists
Azithromycin	Antibiotics
Obeticholic acid	Miscellaneous agents
Ginkgo	Herbal medications
Teriflunomide	Other immunomodulators

CYP 3A4 Inducers

Inducers	Therapeutic Class
Potent CYP3A	
Rifampin	Antibiotics
Mitotane	Other Antineoplastics
Avasimibe	Other Antilipemics
Rifapentine	Antibiotics
Apalutamide	Antiandrogens
Phenytoin	Anticonvulsants
Carbamazepine	Anticonvulsants
Enzalutamide	Antiandrogens
St John's Wort extract	Herbal medications
Lumacaftor	Cystic fibrosis treatments
Rifabutin	Antibiotics
Phenobarbital	Anticonvulsants
Moderate CYP3A	
Ritonavir and St John's wort	None
Semagacestat	Alzheimer's treatments
Efavirenz	NNRTIs
Tipranavir and ritonavir	Protease inhibitors
Dabrafenib	Kinase inhibitors
Lesinurad	Antigout and uricosuric agents
Bosentan	Endothelin receptor antagonists
Genistein	Food products
Thioridazine	Antipsychotics
Nafcillin	Antibiotics
Talviraline	NNRTIs
Lopinavir	Protease inhibitors
Modafinil	Psychostimulants
Pf-06282999	Myeloperoxidase inactivators
Etravirine	NNRTIs
Lersivirine	NNRTIs
Telotristat ethyl	Antidiarrheals

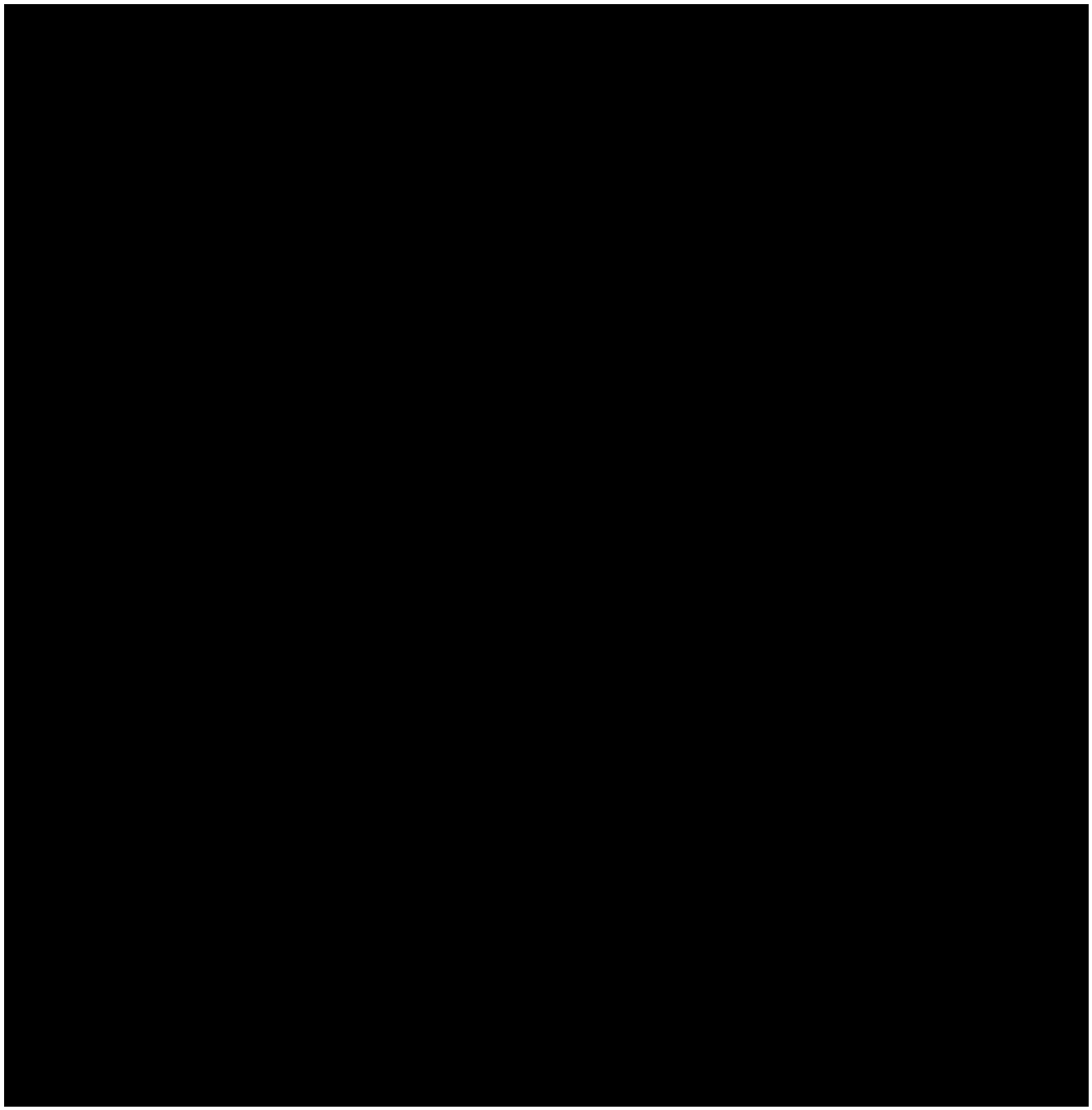
Inducers	Therapeutic Class
Weak CYP3A	
Eslicarbazepine	Anticonvulsants
Telaprevir	Antivirals
Daclatasvir and asunaprevir and beclabuvir	Antivirals
Amenamevir	Antivirals
Garlic	Food products
Bexarotene	Other antineoplastics
Sarilumab	Immunomodulators biologics
Artesunate and mefloquine	Antimalarials
Amprenavir (fosamprenavir)	Protease inhibitors
Raltegravir	HIV-integrase strand transfer inhibitors
Vemurafenib	Kinase inhibitors
Troglitazone	Thiazolidinediones
Dicloxacillin	Antibiotics
Sorafenib	Kinase inhibitors
Rufinamide	Anticonvulsants
Sirukumab	Immunomodulators biologics
Pleconaril	Antivirals
Ginseng	Herbal medications
Boceprevir	Antivirals
Sulfinpyrazone	Antigout and uricosuric agents
Ginkgo	Herbal medications
Vinblastine	Vinca alkaloids
Nevirapine	NNRTIs
Armodafinil (R-modafinil)	Psychostimulants
Ticagrelor	Anticoagulants and antiplatelets
LCL161	Cancer treatments
Vicriviroc and ritonavir	Treatments of AIDS
Ritonavir	Protease inhibitors
Prednisone	Corticosteroids
Oxcarbazepine	Anticonvulsants
Danshen	Herbal medications
Clobazam	Benzodiazepines
Echinacea	Herbal medications
Ticlopidine	Anticoagulants and antiplatelets
Isavuconazole	Antifungals
Brivaracetam	Anticonvulsants

Inducers	Therapeutic Class
Weak CYP3A (continued)	
Stribild	Treatments of AIDS
Pioglitazone	Thiazolidinediones
VIEKIRA PAK	Antivirals
Dexamethasone	Corticosteroids
Terbinafine	Antifungals
Quercetin	Food products
Glycyrrhizin	Herbal medications
Aprepitant	Neurokinin-1 receptor antagonists
Pretomanid (PA-824)	Antibiotics
Safinamide	MAO-B inhibitors
Oritavancin	Antibiotics
AZD 7325	Anxiolytics
Methylprednisolone	Corticosteroids
Topiramate	Anticonvulsants

APPENDIX H. INSTRUCTION TO PARTICIPANTS FOR HANDLING STUDY DRUG (PARSACLISIB OR PLACEBO) AND REFERENCE TREATMENT (RUXOLITINIB)

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

- Store all parsaclisib/matching placebo and ruxolitinib supplies at room temperature.
- Only remove the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed doses or lost tablets.
- If the participant vomits after taking parsaclisib/matching placebo or ruxolitinib, the participant should not take another dose.
- To keep study drug and reference treatment in a safe place and out of reach of children.
- To bring all used and unused study drug bottles/kits to the site at each visit.
- If a dose of parsaclisib/matching placebo or ruxolitinib is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be administered at the usual time.



APPENDIX J. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	07 OCT 2021
Amendment 2	20 OCT 2022

Amendment 2 (20 OCT 2022)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update safety information for parsaclisib, including information regarding COVID-19, and the potential impact of parsaclisib therapy on infection risk, vaccine effectiveness, and severity of disease. Additional clarifications are also provided.

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

   Description of change: Clarified that certain countries have minimum enrollment requirements and added the name of the coordinating principal investigator.

   Rationale for change: To clarify language around enrollment requirements and add the name of the coordinating principal investigator.

2. **Section 2.6.1.2, Potential Risks of Parsaclisib Based on Prior and Ongoing Clinical Studies; Section 2.6.2.2, Potential Risks of Parsaclisib Plus Ruxolitinib**

   Description of change: Updated safety language to reflect the updated Investigator's Brochure (dated MAY 2022) and added a statement to include COVID-19 in potential risks.

   Rationale for change: To provide updated safety information.

3. **Section 4.1.1, Study Schedule/Procedures**

   Description of change: Added language for location options for local laboratory visits.

   Rationale for change: To provide options for participants for local laboratory visits.

4. **Section 4.1.2, Unblinding and Crossover; Section 4.1.4, Early Unblinding/Crossover Process; Section 4.1.5, Participant Unblinding/Crossover Process After Completion of the Week 24 Assessments**

   Description of change: Clarified processes and timing for database cleaning and freezing.

   Rationale for change: To clarify what data/visits will be cleaned and frozen and how approval for unblinding will be communicated.

5. **Section 5, Study Population; Section 5.1, Inclusion Criteria**

   Description of change: Removed requirement for age of 20 years or older for Japan and added language for age requirement of 19 years or older for South Korean participants.

   Rationale for change: Age of 20 years or older is no longer a requirement for Japan. Age of 19 years or older is a requirement for South Korea.

6. **Section 6.1, Study Treatments Administered (Table 10: Study Treatment Information); Section 6.2, Preparation, Handling, and Accountability**

   Description of change: Replaced language regarding storage conditions with reference to the Pharmacy Manual.

   Rationale for change: To improve consistency for storage condition information in the study.

7. **Section 6.7.5, COVID-19**

   Description of change: Added new section describing risks associated with COVID-19 with regard to participants with hematologic disorders and treatment with parsaclisib.

   Rationale for change: Informational purposes.

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

Amendment 1 (07 OCT 2021)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address changes requested by different national regulatory agencies and ethics committees.

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

   Description of change: Included a note regarding the minimum enrollment regulatory requirement in Japan and need for potential continued enrollment after enrollment in other countries ends.

   Rationale for change: To allow minimum enrollment regulatory requirement in Japan.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Table 5: Schedule of Laboratory Assessments for All Participants); Section 4.1, Overall Design; Section 6.3, Measures to Minimize Bias: Randomization and Blinding; Section 8.1.3, Baseline; Section 10.1, Sample Size Determination; Section 10.4.1, Primary and Secondary Analyses (Table 17: Primary and Secondary Analyses Methods and Populations);** [redacted]

   Description of change: Inserted a statement that if a participant's platelet count is $< 50 \times 10^9$/L at baseline, the platelet count at screening will be used for stratification/randomization.

   Rationale for change: To provide guidance for cases in which the platelet count decreases between screening and baseline and to remove discrepancies in the Protocol regarding which value should be used.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Randomized Participants in Group A, Group B, and After Crossover); Section 8.8.2, Survival Follow-Up**

   Description of change: Added a 2-week window for survival follow-up.

   Rationale for change: Administrative error.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Randomized Participants in Group A, Group B, and After Crossover; Table 4: Schedule of Additional Study Visits for Participants Who Cross Over); Section 4.1.1, Study Schedule/Procedures**

   Description of change: Specified end date for PJP prophylaxis as at least 2 to 6 months after the last dose of study treatment, consistent with other sections of the Protocol.

   Rationale for change: Administrative error.

5. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Randomized Participants in Group A, Group B, and After Crossover; Table 5: Schedule of Laboratory Assessments for All Participants); Section 8.1.2, Screening Procedures;** [redacted]

   Description of change: Removed requirement for 0% blasts at screening for an archived biopsy/aspirate to be used for study entry.

   Rationale for change: Requirement for 0% blasts is not reflective of many high-risk patients with MF.

6. **Section 1, Protocol Summary (Table 4: Schedule of Additional Study Visits for Participants Who Cross Over)**

   Description of change: Specified that IXRS needs to be contacted also at the 4 weeks post-crossover visit.

   Rationale for change: Administrative error.

7. **Section 1, Protocol Summary (Table 4: Schedule of Additional Study Visits for Participants Who Cross Over; Table 5: Schedule of Laboratory Assessments for All Participants)**

   Description of change: Inserted statement that collection of plasma correlative samples will be performed approximately 12 and 24 weeks after crossover, coincident with a scheduled or unscheduled visit.

   Rationale for change: To clarify timing of plasma correlative sample collection after crossover.

8. **Section 1, Protocol Summary (Table 5: Schedule of Laboratory Assessments for All Participants)**

   Description of change: Added window values for different laboratory-only visits.

   Rationale for change: Administrative error.

[redacted]

10. **Section 1, Protocol Summary (Table 5: Schedule of Laboratory Assessments for All Participants); [redacted] (Table 14: Required Laboratory Analytes); [redacted]**

    Description of change: [redacted].

    Rationale for change: To meet regulatory and genetic testing requirements of specific countries.

11. **Section 2.6.1.2, Potential Risks of Parsaclisib Based on Prior and Ongoing Clinical Trials**

    Description of change: Updated safety information.

    Rationale for change: To reflect current IB.

12. **Section 2.6.1.4, Potential Benefits of Parsaclisib; Section 2.6.2.2, Potential Risks of Parsaclisib Plus Ruxolitinib**

    Description of change: Updated information to reflect the most recent data analysis.

    Rationale for change: To provide updated information.

[redacted]

14. **Section 4.1.2, Unblinding and Crossover**

    Description of change: Added statement to clarify that if, after the Week 24 assessments, a participant is found to have been randomized to parsaclisib, treatment with both parsaclisib and ruxolitinib will be continued as long as protocol-defined criteria are met.

    Rationale for change: Clarity.

15. **Section 4.1.3, Early Unblinding and Crossover**

    Description of change: Modified text to indicate that when a participant has undergone early unblinding and either is found to have been on parsaclisib or is on placebo but does not choose to cross over, the participant must discontinue treatment with study drugs (parsaclisib and ruxolitinib) and have an EOT visit scheduled.

    Rationale for change: Clarity.

16. **Section 4.1.5, Participant Unblinding and Crossover**

    Description of change: Modified text to describe the unblinding and crossover process for an individual participant rather than for the entire study.

    Rationale for change: Clarity.

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

    Description of change: Clarified that end of study is defined as the date of either the last visit or the last contact of the last participant in the study.

    Rationale for change: Clarity.

18. **Section 4.3, Study Termination; Section 11.6, Study and Site Closure**

    Description of change: Specified responsibility of the head of study site concerning study termination and study completion in Japan.

    Rationale for change: Japan requirement.

19. **Section 5.1, Inclusion Criteria**

    Description of change: Specified Japan-specific requirements for participants under 20 years old.

    Rationale for change: Japan requirement.

20. **Section 5.2, Exclusion Criteria**

    Description of change: Clarified that the definition of inadequate bone marrow reserve is not limited to the parameters listed in the protocol, clarified that platelet count $< 50 \times 10^9$/L and ANC $< 0.5 \times 10^9$/L at screening are also exclusionary, modified the description of inadequate liver function to clarify the statement about direct bilirubin versus total bilirubin, clarified that prophylactic antivirals are allowed, moved the exclusion criterion for participants unwilling to receive RBC transfusions as a separate criterion, and added an exclusion criterion for sensitivity/allergy to study drugs or excipients.

    Rationale for change: To provide flexibility to investigators to characterize what constitutes an inadequate bone marrow reserve, clarify that screening values are also considered in the exclusion/inclusion assessment, remove potentially contradictory language regarding bilirubin criteria, provide clarity regarding use of prophylactic antivirals, separate the transfusion exclusion criterion from the description of inadequate bone marrow reserve for clarity, and fulfill the request of multiple regulatory agencies/ethics committees to explicitly state that sensitivity/allergy to drug/excipients is an exclusion criterion.

21. **Section 5.2, Exclusion Criteria; Section 6.8.5, Prohibited Medications and Procedures**

    Description of change: To clarify that MF drugs used for a non-MF indication must also be washed out within 3 months of starting study drug.

    Rationale for change: To clarify requirements for washout of MF medications before starting study drug.

22. **Section 6.1, Study Treatments Administered (Table 10: Study Treatment Information)**

    Description of change: Inserted details concerning storage conditions for the study treatments.

    Rationale for change: To provide additional information regarding storage conditions.

23. **Section 6.2, Preparation, Handling, and Accountability**

    Description of change: Specified responsibility of the investigational drug storage manager concerning preparation, handling, and accountability in Japan.

    Rationale for change: Japan requirement.

24. **Section 6.7.2, Dose Decreases of Parsaclisib/Placebo for Toxicity**

    Description of change: Specified that individual decisions are in regard to both dose reductions and interruptions.

    Rationale for change: To provide additional clarity to dosing decisions.

25. **Section 6.7.2, Dose Decreases of Parsaclisib/Placebo for Toxicity (Table 11: Guidelines for Interruption and Restarting of Parsaclisib/Matching Placebo)**

    Description of change: Removed the requirement for temperature to be measured orally in the event of a Grade 3 or higher ANC and fever, added a description of symptoms of colitis, and added another step for treatment of Grade 3 or higher diarrhea or noninfectious colitis.

    Rationale for change: To allow body temperature to be measured by any modality for neutropenic fever and administrative errors.

26. **Section 6.7.5, Criteria for Permanent Discontinuation of Parsaclisib/Matching Placebo**

    Description of change: Removed wording regarding exceptions by sponsor for study drug discontinuation because of AEs requiring more than 2 dose reductions.

    Rationale for change: UK MHRA request.

27. **Section 6.7.6, Dose Decreases of Ruxolitinib for Safety**

    Description of change: Clarified that, at the investigator's discretion, ruxolitinib dose interruptions/changes for safety reasons may occur before the end of a 14-day period after the parsaclisib dose was modified or interrupted for safety reasons.

    Rationale for change: UK MHRA request.

28. **Section 6.8.2, *Pneumocystis jirovecii* Pneumonia Prophylaxis**

    Description of change: Specified that diaminodiphenylsulfone and pentamidine will not be used for PJP prophylaxis in Japan.

    Rationale for change: Japan requirement.

29. **Section 6.8.3, Use of Growth Factors Such as Erythropoietin**

    Description of change: Added section advising caution on concomitant use of growth factors.

    Rationale for change: To address multiple questions regarding allowance of growth factors from investigative sites.

30. **Section 6.8.4, Restricted Medications and Procedures**

    Description of change: Modified text regarding use of nonsteroidal anti-inflammatory drugs and added text restricting the dosage of corticosteroids.

    Rationale for change: To recommend caution when administering nonsteroidal anti-inflammatory drugs in general and to provide guidance for steroid therapy, which may be used as supportive care, as use of these corticosteroids at high doses may interfere with readout of study endpoints.

31. **Section 8, Study Assessments and Procedures**

    Description of change: Clarified that delays in treatment administration will not delay mandated visits and assessments, [redacted]

    Rationale for change: Clarity.

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

    Description of change: Deleted wording regarding possible exploratory research with leftover samples.

    Rationale for change: No studies of this nature are planned.

33. **Section 8.1.2, Screening Procedures; Section 8.3.5.5, Lipid Panel**

    Description of change: Clarified that participants may drink water during the overnight fasting period.

    Rationale for change: Drinking water will not affect lipid panel assessments.

34. **Section 8.1.5, Distribution of Reminder Cards**

    Description of change: Clarified the visits where overnight fasting is required for lipid profile sample collection.

    Rationale for change: Clarity.

35. **Section 8.1.7.3, Transfusion History Status**

    Description of change: Clarified the time periods during which RBC and platelet transfusion history will be collected.

    Rationale for change: Clarity.

36. [redacted]

37. **Section 8.3, Safety Assessments (Table 14: Required Laboratory Analytes)**

    Description of change: Specified that bicarbonate is not analyzed in Japan and that direct bilirubin is a required analyte, irrespective of total bilirubin levels, and removed HCV antibodies from the analyte list as this will not be analyzed.

    Rationale for change: Japan requirement, to avoid additional blood draws to determine direct bilirubin, and administrative error concerning HCV antibodies.

38. **Section 8.3.5.6, Pregnancy Testing**

    Description of change: Clarified that, in the case of a positive urine pregnancy test, the confirmatory serum pregnancy test is to be performed at the local laboratory.

    Rationale for change: Clarity.

[redacted]

40. [redacted]

41. **Section 8.7, End of Treatment and/or Early Termination**

    Description of change: Added "or placebo" to the sentence describing when to conduct the EOT visit.

    Rationale for change: Administrative error.

42. **Section 8.8.2, Survival Follow-Up**

    Description of change: Added subsequent MF treatments to the information collected during follow-up.

    Rationale for change: Administrative error.

43. **Section 9.2, Definition of Serious Adverse Event**

    Description of change: Added definition to important medical events (risk of dysfunction) and clarified that an event that may lead to disability is considered an important medical event.

    Rationale for change: Japan requirement and alignment with protocol template.

44. **Section 9.4, Reporting of Serious Adverse Events**

    Description of change: Specified that SAEs must be reported to the head of the study site in Japan and that the sponsor must report suspected expected deaths and life-threatening events to PMDA in Japan.

    Rationale for change: Japan requirement.

45. **Section 9.5, Adverse Events of Special Interest**

    Description of change: Clarified that only AEs of special interest that are also SAEs need to follow SAE reporting timelines and modified the terms for certain infections to include herpes and infection in each term.

    Rationale for change: Clarity.

46. **Section 9.6, Emergency Unblinding of Treatment Assignment**

    Description of change: Clarified that the decision to break the treatment code in an emergency resides at the sole discretion of the investigator.

    Rationale for change: UK MHRA request.

47. **Section 11.1, Investigator Responsibilities**

    Description of change: Added language concerning retention of documents in Japan.

    Rationale for change: Japan requirement.

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

    Description of change: Specified that certain female contraceptive methods are not approved or not applicable in Japan and removed list of birth control methods that have a failure rate of more than 1%.

    Rationale for change: Japan requirement and to remove contraceptive methods that are not at least 99% effective in preventing pregnancy.

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

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Approval Task	[redacted] [redacted] 20-Oct-2022 13:26:43 GMT+0000
Approval Task	[redacted] Approver [redacted] 20-Oct-2022 14:00:38 GMT+0000
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Approval Task	[redacted] Approver [redacted] 20-Oct-2022 16:04:55 GMT+0000

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