Official Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Parsaclisib in Participants With Primary Warm Autoimmune Hemolytic Anemia (PATHWAY)

NCT Number: NCT05073458

Document Date: Clinical Study Protocol Amendment Version 2: 10 MAY 2023

Clinical Study Protocol

INCB 50465-309

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Parsaclisib in Participants With Primary Warm Autoimmune Hemolytic Anemia (PATHWAY)

Product:	**INCB050465 (Parsaclisib)**
IND Number:	**147,208**
EudraCT Number:	**2021-002844-66**
Phase of Study:	**3**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, Delaware, USA 19803**
Original Protocol:	**27 MAY 2021**
Amendment 1:	**18 AUG 2022**
Amendment 2:	**10 MAY 2023**

INVESTIGATOR'S AGREEMENT

I have read the INCB 50465-309 Protocol Amendment 2 (dated 10 MAY 2023) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

(Printed Name of Investigator)

(Signature of Investigator) (Date)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
6MWT	6-minute walk test
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AIHA	autoimmune hemolytic anemia
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
ANSM	National Agency for the Safety of Medicines and Health Products (France)
anti-HCV	hepatitis C virus antibody
AST	aspartate transaminase
BfArM	The Federal Institute for Drugs and Medical Devices (Germany)
CAD	cold agglutinin disease
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation
[redacted]	[redacted]
CMH	Cochran-Mantel-Haenszel
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DAT	direct antiglobulin test
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECI	Events of Clinical Interest
eCRF	electronic case report form
EDC	electronic data capture
eDSMB	external Data Safety Monitoring Board
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of treatment
EQ-VAS	EuroQol Visual Analogue Scale
FACIT	Functional Assessment of Chronic Illness Therapy

Abbreviations and Special Terms	Definition
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
Fc	fragment crystallizable
FDA	Food and Drug Administration (US)
FSH	follicle-stimulating hormone
FUP	follow-up period
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HBV	hepatitis B virus
HCV	hepatitis C virus
Hemoglobin response	A hemoglobin level ≥ 10 g/dL with a 2 g/dL increase from baseline (Day 1)
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRT	hormonal replacement therapy
IB	Investigator's Brochure
IC_{50}	concentration that results in 50% inhibition
IC_{90}	concentration that results in 90% inhibition
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IFN-γ	interferon γ
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
IQRMP	Integrated Quality Risk Management Plan
IRB	institutional review board
IRT	interactive response technology
ITT	intent to treat
IVIG	intravenous immunoglobulin
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines & Healthcare products Regulatory Agency
NCCN	National Comprehensive Cancer Network
PBMC	peripheral blood mononuclear cell
[redacted]	[redacted]
[redacted]	[redacted]
PHL	potential Hy's law

Abbreviations and Special Terms	Definition
PI3K	phosphoinositide 3-kinase
PJP	*Pneumocystis jirovecii* pneumonia
[redacted]	[redacted]
PMDA	Pharmaceuticals and Medical Devices Agency
PP	per protocol
PRO	patient-reported outcome
QD	once daily
RBC	red blood cell
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SoA	schedule of activities
SOP	standard operating procedure
Study drug	Parsaclisib or matching placebo
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
[redacted]	[redacted]
wAIHA	warm autoimmune hemolytic anemia
WBC	white blood cell
WOCBP	woman of childbearing potential
[redacted]	[redacted]

1. PROTOCOL SUMMARY

Protocol Title:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Parsaclisib in Participants With Primary Warm Autoimmune Hemolytic Anemia (PATHWAY)

Protocol Number: INCB 50465-309

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 the efficacy of parsaclisib in the treatment of participants with wAIHA.	• Proportion of participants attaining a durable hemoglobin response, defined as hemoglobin ≥ 10 g/dL with an increase from baseline of ≥ 2 g/dL not attributed to rescue therapy at ≥ 3 of the 4 available visits at Week 12 and/or later during the 24-week double-blind treatment period.
Key Secondary	
To further evaluate the efficacy of parsaclisib in the treatment of participants with wAIHA.	• Proportion of participants with a ≥ 3-point increase from baseline in FACIT-F score at Week 24.

Overall Design:

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

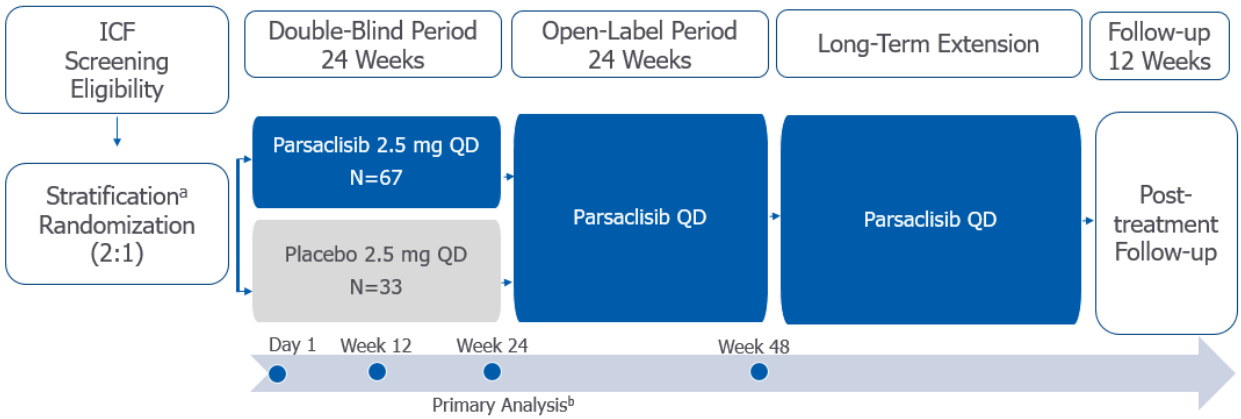
Table 2: Key Study Design Elements

Study Phase	Phase 3
Clinical Indication	Primary wAIHA
Population	Men and women, aged 18 years or older with primary wAIHA, a hemoglobin level ≥ 6.5 to < 10 g/dL with symptomatic anemia at screening, a FACIT-F score ≤ 43 at screening without an underlying lymphoproliferative malignancy or AIHA secondary to an autoimmune-related condition who have failed at least 1 prior standard therapy that is known to confer clinical benefit or who are intolerant to treatment or for whom treatment is contraindicated.
Number of Participants	Approximately 100 participants will be randomized 2:1 (approximately 67:33) to receive either parsaclisib or matched placebo. Participants will be stratified by hemoglobin at screening as determined by local laboratory (hemoglobin < 9 g/dL or ≥ 9 g/dL), and corticosteroid (prednisone or equivalent) dose at screening (≤ 20 mg/day vs > 20 mg/day). *Note*: Japan must meet a minimum enrollment regulatory requirement; therefore, enrollment in Japan may continue after enrollment in other countries ends. *Note:* Upon implementation of Protocol Amendment 2, the study will be closed to further enrollment due to the change in the regulatory landscape for PI3K inhibitors and the challenges and subsequent low numbers in enrollment.
Study Design	Randomized, double-blind, placebo-controlled, multicenter study [redacted]
Estimated Duration of Study Participation	Screening period: Up to 32 days. Double-blind treatment period: 24 weeks. Open-label treatment period: 24 weeks. Long-term extension: approximately 2 years Post-treatment follow-up visits: 12 weeks. It is estimated that an individual will participate for approximately 3 years. *Note:* Upon implementation of Protocol Amendment 2, protocol-required procedures and visits will be reduced or eliminated for ongoing participants.
DSMB	Yes (external)
Coordinating Principal Investigators	Prof. [redacted], Austria Dr. [redacted], Italy

Treatment Groups and Duration:

The study design is shown in Figure 1. The SoA for the double-blind treatment period, open-label treatment period, and long-term extension are detailed in Table 3, Table 4, and Table 5, respectively. The specific laboratory analytes are described in Table 11.

Figure 1: Study Design Schema



[a] Hemoglobin at screening as determined by local laboratory (< 9 g/dL or ≥ 9 g/dL) and corticosteroid (prednisone or equivalent) dose at screening (≤ 20 mg/day vs > 20 mg/day)
[b] The primary analysis will be conducted when the last randomized participant has completed the 24-week, double-blind treatment period.

Participants will receive parsaclisib 2.5 mg QD or matching placebo QD for 24 weeks during the double-blind treatment period. All participants who complete the double-blind treatment period, are tolerating study treatment, and in the investigator's opinion may benefit from treatment may continue into an open-label treatment period for an additional 24 weeks of parsaclisib QD. All participants who complete the open-label treatment period, are tolerating study treatment, and in the investigator's opinion may benefit from continued treatment may enter into the long-term extension. During the long-term extension, participants may take a drug holiday 1 time with the option for re-treatment if they experience worsening of wAIHA after the drug holiday.

Note: Upon implementation of Protocol Amendment 2:

- Participants randomized to placebo during the 24-week double-blind treatment period may receive parsaclisib before reaching Week 24.
- Once treatment with parsaclisib is started, participants will enter the open-label treatment period (see Table 4) regardless of visits completed during the double-blind treatment period.

Participants who permanently discontinue study treatment will enter the 12-week post-treatment follow-up period, which includes 3 visits (1 every 4 weeks) to assess safety and persistence of effect.

Note: Upon implementation of Protocol Amendment 2:

- Participants receiving parsaclisib who permanently discontinue study drug will enter the post-treatment follow-up period for 1 visit (FUP1/EOS) approximately 4 weeks after the last dose of study drug.
- Participants receiving placebo who permanently discontinue study drug will no longer be required to enter the post-treatment follow-up period and will perform EOT/EOS upon discontinuation of treatment.

Throughout the study, dose reductions from 2.5 mg to 1 mg are allowed due to intolerable AEs or hemoglobin levels in the high end of normal range that in the investigator's opinion requires a dose reduction. During the study, the investigator may treat a participant with low hemoglobin or symptomatic anemia requiring treatment according to the rescue treatment plan (Section 6.7.4).

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Note: Upon implementation of Protocol Amendment 2, protocol-required procedures and visits will be reduced or eliminated for ongoing participants (see Table 3, Table 4, and respective sections for details).

Table 3: Schedule of Activities (Double-Blind)

Visit Day (Range)	Screening	Double-Blind Treatment Period										Notes and Protocol Section
	Day −32 to −1	Day 1	W2 ± 3 d	W4 ± 3 d	W6 ± 3 d	W8 ± 3 d	W10 ± 3 d	W12 ± 3 d	W16 ± 3 d	W20 ± 3 d	EOT1[a]/EOS[b] W24 ± 3 d	
In-office visit	X	X	X	X		X		X	X	X	X	
Remote visit					X		X					May be performed in office at the discretion of the investigator. Note: Where local laws and/or regulations do not permit remote visits, these assessments will be performed in office.
Administrative procedures												
Informed consent	X											Section 8.1.1
[redacted]												
Contact IRT	X	X	X	X		X		X	X	X	X	Section 8.1.3
Inclusion/exclusion criteria	X	X										Section 5.1 and Section 5.2
Demography, wAIHA disease history and medical history and AIHA symptoms	X											Demography will be collected as permitted per local regulations. Section 8.1.5
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	Section 6.7
Randomize to treatment arm		X										Section 6.3 and Section 8.1.3
Distribute reminder cards		X	X	X		X		X	X	X	X	Section 8.1.4
Dispense study drug		X	X	X		X		X	X	X	X*	*Participants continuing into open-label treatment period. Section 6.1 and Section 8.1.3
Study drug return, accountability and compliance assessment			X	X		X		X	X	X	X	Section 6.4
Prophylactic treatment for PJP		As prescribed by the investigator throughout study										Section 6.7.1.1
Healthcare resource utilization*		X	X	X		X		X	X	X	X	Section 8.3.8 *No longer required upon implementation of Protocol Amendment 2.
Safety assessments												
Comprehensive physical examination	X										X	Height and weight at screening only. Section 8.4.2
Targeted physical examination		X		X		X		X	X	X		Section 8.4.2

Table 3: Schedule of Activities (Double-Blind) (Continued)

Visit Day (Range)	Screening	Double-Blind Treatment Period										Notes and Protocol Section
	Day −32 to −1	Day 1	W2 ± 3 d	W4 ± 3 d	W6 ± 3 d	W8 ± 3 d	W10 ± 3 d	W12 ± 3 d	W16 ± 3 d	W20 ± 3 d	EOT1[a]/EOS[b] W24 ± 3 d	
Safety assessments (continued)												
Vital signs	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.3
12-lead ECG	X							X			X	Section 8.4.4
AE assessment	X	X	X	X	X	X	X	X	X	X	X	Section 9
Laboratory assessments[c]												
Serum FSH	X											Confirmation of lack of childbearing potential.
Serology	X						X*					Hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. *CMV testing only and monitor as clinically indicated Section 8.4.5.2
D-dimer	X			X		X		X		X	X	Section 8.4.5
Vitamin B12/folic acid	X											Section 8.4.5
Serum pregnancy	X										X	WOCBP only. Section 8.4.5.1
Urine pregnancy		X		X		X		X	X	X		WOCBP only. Section 8.4.5.1
Urinalysis	X											Section 8.4.5
Serum chemistry	X	X		X		X		X	X	X	X	Section 8.4.5
Efficacy assessments												
Hematology	X	X	X*	X	X*	X	X*	X	X	X	X	Section 8.2.1 and Section 8.4.5 *No longer required upon implementation of Protocol Amendment 2.
[redacted]												
DAT	X										X	Section 8.2.1 and Section 8.4.5

Table 3: Schedule of Activities (Double-Blind) (Continued)

Visit Day (Range)	Screening Day −32 to −1	Double-Blind Treatment Period Day 1	W2 ± 3 d	W4 ± 3 d	W6 ± 3 d	W8 ± 3 d	W10 ± 3 d	W12 ± 3 d	W16 ± 3 d	W20 ± 3 d	EOT1[a]/EOS[b] W24 ± 3 d	Notes and Protocol Section
PRO and clinical outcome assessments (Note: Upon implementation of Protocol Amendment 2, the PROs noted herein will no longer be required)												
FACIT-F scale	X	X				X		X	X	X	X	Should be completed before any other assessments. Must be completed before all other PRO assessments. Section 8.3.1
6MWT		X									X	Vital signs should be conducted pre- and post-test. 6MWT must be performed after all other PRO assessments are completed. Section 8.3.2
[redacted]												

Table 3: Schedule of Activities (Double-Blind) (Continued)

Visit Day (Range)	Screening Day −32 to −1	Double-Blind Treatment Period Day 1	W2 ± 3 d	W4 ± 3 d	W6 ± 3 d	W8 ± 3 d	W10 ± 3 d	W12 ± 3 d	W16 ± 3 d	W20 ± 3 d	EOT1[a]/EOS[b] W24 ± 3 d	Notes and Protocol Section
[redacted]												

[a] Participants receiving parsaclisib who permanently discontinue study drug will enter the post-treatment follow-up period (see Table 4 and Section 8.10).
[b] Participants receiving placebo who permanently discontinue study drug will no longer be required to enter the post-treatment follow-up period and will perform EOT1/EOS upon discontinuation of treatment.
[c] Fasting is not required for central laboratory assessments.

Table 4: Schedule of Activities (Open-Label)

Visit Day (Range)	Open-Label Treatment								Post-Treatment Follow-Up			Notes and Protocol Section
	W26 ± 3 d	W28 ± 5 d	W30 ± 5 d	W32 ± 5 d	W36 ± 5 d	W40 ± 5 d	W44 ± 5 d	EOT2 W48 ± 5 d	FUP1[a]/ EOS	FUP2[b]	FUP3[b]	
In-office visit		X		X	X	X	X	X	X		X	
Remote visit	X		X							X		May be performed in-office at the discretion of the investigator. Note: Where local laws and/or regulations do not permit remote visits, these assessments will be performed in office.
Administrative procedures												
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	Section 6.7
Contact IRT		X		X	X	X	X	X	X		X	Section 8.1.3
Distribute reminder cards		X		X	X	X	X	X				Section 8.1.4
Dispense study drug		X		X	X	X	X	X*				*Participants continuing into long-term extension. Section 6.1 and Section 8.1.3
Study drug return, accountability and compliance assessment		X		X	X	X	X	X				Section 6.4
Prophylactic treatment for PJP	As prescribed by the investigator throughout study											Section 6.7.1.1
Healthcare resource utilization*		X		X	X	X	X	X			X	Section 8.3.8 *No longer required upon implementation of Protocol Amendment 2.
Safety assessments												
AE assessments	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.1
Comprehensive physical examination								X	X		X	Section 8.4.2
Targeted physical examination		X		X	X	X	X					Section 8.4.2
Vital signs	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.3
12-lead ECG								X				Section 8.4.4

Table 4: Schedule of Activities (Open-Label) (Continued)

	Open-Label Treatment								Post-Treatment Follow-Up			
Visit Day (Range)	**W26 ± 3 d**	**W28 ± 5 d**	**W30 ± 5 d**	**W32 ± 5 d**	**W36 ± 5 d**	**W40 ± 5 d**	**W44 ± 5 d**	**EOT2 W48 ± 5 d**	**FUP1[a]/ EOS**	**FUP2[b]**	**FUP3[b]**	**Notes and Protocol Section**
Efficacy assessments												
Hematology	X*	X	X*	X	X	X	X	X	X	X	X	Section 8.2.1 and Section 8.4.5 *No longer required upon implementation of Protocol Amendment 2.
[redacted]												
DAT								X				Section 8.2.1 and Section 8.4.5
PRO and clinical outcome assessments (Note: Upon implementation of Protocol Amendment 2, the PROs noted herein will no longer be required)												
FACIT-F scale		X		X		X		X			X	Should be completed before any other assessments. Must be completed before all other PRO assessments. Section 8.3.1
[redacted]												

Table 4: Schedule of Activities (Open-Label) (Continued)

Visit Day (Range)	Open-Label Treatment								Post-Treatment Follow-Up			Notes and Protocol Section
	W26 ± 3 d	W28 ± 5 d	W30 ± 5 d	W32 ± 5 d	W36 ± 5 d	W40 ± 5 d	W44 ± 5 d	EOT2 W48 ± 5 d	FUP1[a]/ EOS	FUP2[b]	FUP3[b]	
PRO and clinical outcome assessments (continued) (Note: Upon implementation of Protocol Amendment 2, the PROs noted herein will no longer be required)												
6MWT								X			X	Vital signs should be conducted pre- and post-test. 6MWT must be performed after all other PRO assessments are completed. Section 8.3.2
[redacted]												
Laboratory assessments[c]												
D-dimer		X		X	X		X	X				Section 8.4.5
Serum pregnancy								X			X	WOCBP only. Section 8.4.5.1
Urine pregnancy		X		X		X			X	X		WOCBP only. Section 8.4.5.1
Serum chemistry		X		X	X	X	X	X	X	X	X	Section 8.4.5
CMV	X*											*Monitor as clinically indicated

[a] Only required for participants receiving parsaclisib; post-treatment follow-up visit to be conducted 4 weeks (± 5 days) after EOT visit (or after the last dose of study drug if the EOT visit was not performed).
[b] No longer required upon implementation of Protocol Amendment 2.
[c] Fasting is not required for central laboratory assessments.

Table 5: Schedule of Activities (Long-Term Extension)

Visit Day (Range)	Long-Term Extension				Notes and Protocol Section
	W56 (± 7 d)	Every 8 Weeks (± 7 d)	Every 16 Weeks (± 7 d)	EOT3[a]	
In-office visit	X	X		X	
Administrative procedures					
Contact IRT	X	X		X	Section 8.1.3
Prior/concomitant medications	X	X		X	Section 6.7
Distribute reminder cards	X	X		X	Section 8.1.4
Dispense study drug	X	X			Section 6.1 and Section 8.1.3
Study drug return, accountability and compliance assessment	X	X		X	Section 6.4
Prophylactic treatment for PJP	As prescribed by the investigator throughout study				Section 6.7.1.1
Healthcare resource utilization	X		X	X	Section 8.3.8
Safety assessments					
Comprehensive physical examination				X	Section 8.4.2
Targeted physical examination	X	X			Section 8.4.2
Vital signs	X	X		X	Section 8.4.3
AE assessment	X	X		X	Section 8.4.1
Laboratory assessments[b]					
CMV	X*				*Monitor as clinically indicated
D-dimer	X*				*Perform as clinically indicated Section 8.4.5
Serum pregnancy				X	WOCBP only. Section 8.4.5.1
Urine pregnancy	X	X			WOCBP only. Section 8.4.5.1
Serum chemistry	X	X		X	Section 8.4.5
Efficacy assessments					
Hematology	X	X		X	Section 8.2.1 and Section 8.4.5
[redacted]					
DAT				X	Section 8.2.1 and Section 8.4.5

Table 5: Schedule of Activities (Long-Term Extension) (Continued)

Visit Day (Range)	Long-Term Extension				Notes and Protocol Section
	W56 (± 7 d)	Every 8 Weeks (± 7 d)	Every 16 Weeks (± 7 d)	EOT3[a]	
PRO and clinical outcome assessments Note: Upon implementation of Protocol Amendment 2, the PROs noted herein will no longer be required					
FACIT-F scale	X		X	X	Should be completed before any other assessments. Must be completed before all other PRO assessments. Section 8.3.1
[redacted]					

[a] Participants receiving parsaclisib who permanently discontinue study drug will enter the post-treatment follow-up period (see Table 4 and Section 8.10).
[b] Fasting is not required for central laboratory assessments.

2. INTRODUCTION

Parsaclisib is a potent inhibitor of PI3Kδ (IC_{50} value = 1.1 ± 0.5 nM), with approximately 20,000-fold selectivity for the other PI3K family members (refer to the IB). B-cell proliferation triggered by anti–IgM-mediated cross-linking of the B-cell receptor is known to be PI3Kδ dependent. Parsaclisib potently inhibits antibody-induced proliferation of human CD19+ B cells with an IC_{50} value of 0.21 nM. In addition, parsaclisib also inhibited B-cell proliferation in response to multiple inflammatory stimuli (IL-4, lipopolysaccharides, CD40L, anti-CD40, IL-6, and B-cell activation factor). These effects were not due to parsaclisib-mediated general cytotoxicity.

Parsaclisib inhibited the production of IL-17, IFN-γ, and IL-13 by naive T cells cultured under Th17, Th1, and Th2 differentiation conditions, respectively. These data suggest that in addition to the effects of PI3Kδ inhibition on B cells, it may also potentially impact some aspects of T-cell function.

Clinical experiences of parsaclisib are based on a Phase 2 study (INCB 50465-206) in participants with wAIHA, CAD, or mixed-type AIHA, and oncology studies in patients with cancer who received higher doses for longer periods of time (refer to the IB).

2.1. Background

2.1.1. Warm Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia is a rare acquired disorder in which autoantibodies directed against RBC membrane antigens lead to accelerated destruction of RBCs. The estimated incidence of AIHA in adults is 0.8 to 3 per 100,000 per year, with a mortality rate of 11% (Zanella and Barcellini 2014). The disease can be distinguished on the basis of the autoantibody Ig class and thermal characteristics in wAIHA (IgG-mediated) and CAD (IgM-mediated). Mixed-type AIHA (7%-8% of all AIHA) is the coexistence of warm autoantibodies and high-titer cold agglutinins.

Autoimmune hemolytic anemia is also classified as primary (idiopathic), in which hemolysis dominates the clinical picture in the absence of any other coexisting disorder, and secondary forms, which accompany and are complications of an underlying disease (eg, lymphoproliferative disease, infections, immunodeficiency, and tumors). Warm AIHA accounts for 70% to 80% of all cases in adults, and at least half of the wAIHA cases are associated with an underlying disease. Primary CAD accounts for approximately 15% of AIHA and is defined as an AIHA mediated by cold agglutinins without any underlying disease such as aggressive lymphoma, other overt malignancies, or specific infections (Berentsen 2016).

There are several immunologic mechanisms involved in the pathogenesis of wAIHA that include ADCC, phagocytosis, and direct complement-mediated lysis (Barcellini 2015). The most frequent autoantibodies against RBCs are IgG, which mainly determine extravascular hemolysis through the ADCC. Cytotoxic CD8+T cells and natural killer cells that carry membrane receptors for the Fc portion of IgG directly lyse RBCs in the reticuloendothelial system (spleen and liver). Phagocytosis by macrophages is another way RBCs are destroyed. The macrophage surface expresses receptors for the Fc region of IgG, which enables trapping and ingestion of

opsonized RBCs that are coated with IgG, primary in the spleen. Moreover, for RBCs heavily coated with IgG, the amount of antigen-antibody complex can be sufficient for binding complement protein complex C1 and thus activate the classical complement pathway. Upon complement activation in wAIHA, phagocytosis of C3b-opsonized erythrocytes by Kupffer cells in the liver is responsible for most of the RBC destruction.

Currently there is no approved therapy for wAIHA. For wAIHA, corticosteroids remain the first-line therapy; however, high initial doses are required, responses are often achieved slowly, and only a minority of patients (< 20%) achieve a lasting response (Barcellini et al 2014). Because most RBC destruction occurs in the spleen in wAIHA, it is not surprising that splenectomy is a reasonably efficient second-line treatment with a sustained response rate of 60% to 70%. However, there is increasing concern not only with susceptibility to infection following splenectomy, but also increasing recognition of thrombosis risk from splenectomy, resulting in some reluctance to use this in the treatment algorithm.

Rituximab is a chimeric monoclonal antibody that targets CD20 antigen on B lymphocytes. By binding to CD20, it induces apoptosis of CD20-positive B cells. Rituximab is licensed in rheumatoid arthritis and is also widely used off-label in various autoantibody mediated autoimmune diseases, such as immune thrombocytopenic purpura and systemic lupus erythematosus. Rituximab has been considered as second-line therapy for wAIHA. Second-line treatment of wAIHA with rituximab leads to response rates similar to splenectomy (~70%), but rituximab-induced responses seem less sustained, and relapses are frequent. Major concerns regarding the adverse effects from rituximab are related to long-lasting B-cell suppression and include increased risk of infection including hepatitis B reactivation (Artz et al 2010) and possibly progressive multifocal leukoencephalopathy (Carson et al 2009).

In the third-line situation, immunosuppressive drugs such as danazol, azathioprine, cyclophosphamide, or cyclosporine are used, although response rates are poorly documented, and most publications are case reports or small retrospective studies.

2.2. Study Rationale

Note: The regulatory landscape for the development and approval of PI3K inhibitors in hematologic diseases has recently changed. Furthermore, enrollment into this study has been challenging and only 12 participants have been randomized since the start of the study in MAR 2022. Therefore, upon implementation of Protocol Amendment 2, the study will be closed to further enrollment considering these aspects.

Currently, there is no approved therapy for primary wAIHA and there are limited placebo-controlled studies that document the course of the disease. Despite current treatment algorithms, there is a significant morbidity and mortality rate, and disease relapse remains an ongoing challenge for a significant number of patients with wAIHA. Therefore, there remains an unmet need for new treatments for wAIHA. In addition to showing efficacy in a number of B-cell–related cancers, treatment with parsaclisib has shown significant improvement in animal models of AIHA and lupus nephritis, as well as other antibody-mediated diseases. Parsaclisib may represent an alternative treatment for participants who have failed at least 1 prior treatment. While many patients with wAIHA respond to prednisone, many patients either do not tolerate higher doses of prednisone or are unable to withdraw from prednisone without flare of wAIHA; parsaclisib may provide an option to patients who are intolerant to or unable to withdraw from

steroids or when corticosteroid treatment is contraindicated. In addition, parsaclisib may be a more flexible intervention, as current therapy with rituximab results in profound and sustained depletion of circulating B cells.

In the ongoing Phase 2 study, efficacy was shown by an increase in hemoglobin at Week 12 and an improvement in FACIT-F scores. In addition, parsaclisib was generally well-tolerated in participants treated up to 585 days (mean: 240.57; range: 7-585 days). The dose and design of this Phase 3 study is supported by the preliminary results from Study INCB 50465-206. The rationale for the study design appears in Section 2.2.1.

2.2.1. Scientific Rationale for Study Design

This Phase 3, double-blind, randomized, multicenter, placebo-controlled study is designed to evaluate the efficacy and safety of parsaclisib in participants with primary wAIHA. The clinical manifestations of wAIHA are driven through production of autoantibodies via aberrant B-cell activity.

Eligible participants in this study must have failed at least 1 prior therapy, have been intolerant to prior therapy, or other therapy must be contraindicated for them. Approximately 100 participants will be eligible for enrollment. A significant percentage of wAIHA patients fail or relapse following first-line therapies, including withdrawal from corticosteroids, and are a population who may benefit from novel treatments.

A placebo comparator was selected in order to evaluate the hemoglobin response and safety of parsaclisib. Placebo control is appropriate when 1) there is no proven effective treatment for the condition under study, 2) withholding treatment poses negligible risks to participants, 3) there are compelling methodological reasons for using placebo, and 4) the research is intended to develop interventions that can be implemented in the population from which study participants are drawn and the study does not require participants to forgo treatment they would otherwise receive (Millum and Grady 2013).

As corticosteroid treatment plays an important role in the management of AIHA, participants who are eligible for the study and are receiving ≤ 40 mg/day of prednisone at randomization will continue on corticosteroids (equivalent to ≤ 40 mg/day of prednisone) during the double-blind treatment period. Taper or withdrawal of steroids will be permitted during the study at the investigator's discretion when a stable hemoglobin response has been achieved (see Table 10).

Due to onset of action of parsaclisib in modulating B-cell function and reducing circulating autoantibodies, the effect of parsaclisib on hemoglobin may not be observed until Week 6. Given the natural history of wAIHA, participants may require supportive care for hemoglobin over the initial 6 weeks. Participants who experience worsening of wAIHA may receive rescue treatment during the study (see Section 6.7.4). Participants who receive rescue therapy after Week 6 will be considered nonresponders in the primary efficacy analysis but may continue in the study at the discretion of the investigator.

At Week 24, all participants who complete the double-blind treatment period, are tolerating study treatment, and in the investigator's opinion may benefit from treatment with parsaclisib may continue into an open-label treatment period. These participants will receive 24 weeks of parsaclisib QD, which will provide placebo participants access to active treatment and will evaluate the long-term efficacy and safety of parsaclisib in participants that originally received

parsaclisib. Access to parsaclisib with further evaluation of long-term efficacy and safety will then continue in the long-term extension period of this study.

The primary endpoint will be the proportion of participants attaining a durable hemoglobin response (defined as hemoglobin ≥ 10 g/dL with an increase from baseline of ≥ 2 g/dL not attributed to rescue therapy) at ≥ 3 of the 4 available visits at Week 12 and/or later during the 24-week double-blind treatment period. Hemoglobin is the most direct indicator of clinical severity in hemolytic diseases (Barcellini and Fattizzo 2015). Because wAIHA is a chronic condition, a durable hemoglobin response during the double-blind period may represent a more stable and beneficial effect over time for wAIHA patients than a single visit value. This is supported by the data from the Phase 2 study in which most patients who achieved a hemoglobin response did so by Week 12.

The FACIT-F scale was developed to assess anemia related fatigue (Yellen et al 1997). A clinically meaningful change in the FACIT-F score will be defined as ≥ 3-point increase from baseline. In patients with fatigue symptoms associated with anemia, a difference of 3 in the FACIT-F score was reported as the minimum clinically important difference (Cella et al 2002).

2.2.2. Justification for Dose

Parsaclisib 2.5 mg QD or matching placebo will be self-administered for 24 weeks, followed by continued treatment with parsaclisib QD in the open-label period for up to 24 weeks and in the long-term extension.

In study INCB 50465-206, exploration of parsaclisib dose in AIHA participants resulted in a determination of 2.5 mg QD as the recommended dose.

In Cohort 1 (N = 10), all participants were initially treated with parsaclisib 1.0 mg QD. Based on insufficient hemoglobin response by Week 6, 8 of the 10 enrolled participants had their dose increased to 2.5 mg QD at Week 6 (1 participant remained on 1.0 mg and 1 participant discontinued before Week 6).

In Cohort 2 (N = 15), all participants were treated with parsaclisib 2.5 mg QD for 12 weeks.

During the course of the study, 7 out of 21 (33.3%) participants (N = 2 Cohort 1, N = 5 for Cohort 2) achieved a complete response (hemoglobin ≥ 12 g/dL) at any visit from Week 6 to Week 12. Fourteen of 21 (66.7%) participants (N = 6 Cohort 1, N = 8 Cohort 2) achieved a partial response (defined as a hemoglobin of ≥ 10 g/dL or a ≥ 2 g/dL increase from baseline). Mean increases in hemoglobin were seen at Week 2 and continued to increase through Week 12 with Cohort 2 achieving a higher mean increase of 2.4 g/dL compared with 1.3 g/dL in Cohort 1 at Week 12. Overall, the dose of parsaclisib 2.5 mg QD is generally well–tolerated (refer to parsaclisib IB). The dose of 2.5 mg is proposed to provide sufficient exposure (estimated to be approximately 1 × IC_{90} at trough) to maintain PI3K pathway inhibition while minimizing the frequency of late-onset AEs that may lead to study treatment withdrawal. Higher doses of parsaclisib have been explored in the oncology program (up to 45 mg QD). In oncology patients, higher rates of AEs were observed at doses above 5 mg per day.

If there are any intolerable AEs or hemoglobin in the high end of normal range in individual participants who receive 2.5 mg QD of study treatment, the dose should be decreased to 1 mg QD (see Section 6.5).

2.3. Benefit/Risk Assessment

Parsaclisib monotherapy provided a durable improvement in hemoglobin in participants with AIHA (see Section 2.2.2). The safety profile for parsaclisib is described in the parsaclisib IB. Briefly, AEs were observed in participants administered parsaclisib monotherapy in inflammatory and autoimmune indications (N = 35), with the most common (in ≥ 10% of participants) being diarrhea and pyrexia (22.9% each); headache and rash (14.3% each); and AIHA, nausea, and peripheral edema (11.4% each). Parsaclisib has effects on the immune system and serious infection events have occurred in patients treated with parsaclisib, including PJP, CMV, and COVID-19. Due to the severity, these events may impact the benefit-risk balance of parsaclisib if not managed appropriately. Furthermore, a pharmacological effect of concurrent corticosteroid use or recent rituximab therapy can contribute to further immunosuppression and such effects pose an additional risk of infections. In an effort to manage this risk, guidelines for managing serious infections have been implemented in this study, and include careful monitoring and supportive care measures. If supportive care interventions are unsuccessful and causes other than parsaclisib-related infections have been ruled out, then either parsaclisib dose modification or permanent discontinuation is recommended. Participants are required to receive a standard PJP prophylaxis regimen while receiving parsaclisib as described in Section 6.7.1.1. Information regarding the additional risks of diarrhea or colitis, neutropenia, and severe cutaneous reactions is outlined in the Warnings and Precautions of the parsaclisib IB. Dose modification guidance and supportive care guidelines for these AEs have been implemented in this study, and participants will be closely monitored for evidence of toxicities, including long-term toxicities.

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

3. OBJECTIVES AND ENDPOINTS

Table 6 presents the objectives and endpoints.

Table 6: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of parsaclisib in the treatment of participants with wAIHA.	Proportion of participants attaining a durable hemoglobin response, defined as hemoglobin ≥ 10 g/dL with an increase from baseline of ≥ 2 g/dL not attributed to rescue therapy at ≥ 3 of the 4 available visits at Week 12 and/or later during the 24-week double-blind treatment period.
Key Secondary	
To further evaluate the efficacy of parsaclisib in the treatment of participants with wAIHA.	• Proportion of participants with a ≥ 3-point increase from baseline in FACIT-F score at Week 24.
Other Secondary	
To further evaluate the efficacy of parsaclisib in the treatment of participants with wAIHA.	• Proportion of participants with a 50 m increase from baseline to Week 24 in a 6MWT. • Change and percent change from baseline in FACIT-F score at each postbaseline visit. • Change and percentage change from baseline in hemoglobin at each postbaseline visit. • Proportion of participants who received transfusions from Week 6 to Week 24 and from Week 24 to Week 48. • Change and percentage change from baseline in daily corticosteroid dose at Week 24. • Proportion of participants who required rescue therapy at any visit from Week 6 through Week 24, and from Week 24 to Week 48.
To evaluate the safety and tolerability of parsaclisib in participants with wAIHA.	• Frequency and severity of AEs, including the evaluation of clinical laboratory results, vital signs, ECGs, and the results of physical examinations.

Table 6: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

Table 6: Objectives and Endpoints (Continued)

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of parsaclisib 2.5 mg QD compared with placebo over a 24-week double-blind treatment period followed by a 24-week open-label treatment period of parsaclisib. Participants may then continue to receive parsaclisib in a long-term extension period.

The study will enroll approximately 100 men and women ≥ 18 years with primary wAIHA. Participants will be stratified by hemoglobin at screening as determined by local laboratory (< 9 g/dL or ≥ 9 g/dL) and corticosteroid (prednisone or equivalent) doses at screening (≤ 20 mg/day vs > 20 mg/day).

Note: Japan must meet a minimum enrollment regulatory requirement; therefore, enrollment in Japan may continue after enrollment in other countries ends.

Figure 1 presents the study design schema, and Table 3, Table 4, and Table 5 present the SoA for the double-blind, placebo-controlled and open-label treatment periods and the long-term extension, respectively.

Note: Upon implementation of Protocol Amendment 2, the study will be closed to further enrollment due to the change in the regulatory landscape for PI3K inhibitors and the challenges and subsequent low numbers in enrollment.

Participants will be screened for up to 32 days before the first dose of study drug (parsaclisib or placebo). Key entry criteria for participants are those with a diagnosis of wAIHA, who were inadequately controlled with, were intolerant to, or have a contraindication to other therapies, and have a baseline FACIT-F of ≤ 43. Participants who meet all the study entry inclusion criteria and none of the exclusion criteria will return to the study site on Day 1 of dosing and be randomized in a 2:1 ratio to parsaclisib 2.5 mg QD or matching placebo QD. Concomitant treatment with corticosteroids (equivalent to ≤ 40 mg/day of prednisone) is allowed throughout the study.

Participants who experience worsening of wAIHA may receive rescue therapy during the study as outlined in Section 6.7.4. Participants who continue to use rescue therapy after Week 6 will be considered nonresponders in the primary efficacy analysis but will be allowed to continue in the study at the discretion of the investigator.

All participants who complete the 24-week double-blind treatment period, are tolerating study treatment, and in the investigator's opinion may benefit from treatment may enter the 24-week open-label treatment period and will receive parsaclisib administered at the same dose and schedule as in the double-blind treatment period.

Note: Upon implementation of Protocol Amendment 2:

- Participants randomized to placebo during the 24-week double-blind treatment period may receive parsaclisib before reaching Week 24.
- Once treatment with parsaclisib is started, participants will enter the open-label treatment period (see Table 4) regardless of visits completed during the double-blind treatment period.

All participants who complete the open-label treatment period, are tolerating study treatment, and in the investigator's opinion may benefit from continued treatment, may enter into the long-term extension. Parsaclisib will be administered at the same dose and schedule as in the open-label treatment period. During the long-term extension, participants may take a drug holiday 1 time with the option for re-treatment if they experience worsening of wAIHA after interrupting parsaclisib (see Section 6.6 for re-treatment criteria).

Participants will receive study treatment until any of the criteria for permanent discontinuation of study drug are met (see Section 7.1.1). Participants who permanently discontinue study treatment will enter the 12-week post-treatment follow-up period with visits scheduled every 4 weeks for 12 weeks after the last dose of study drug.

Note: Upon implementation of Protocol Amendment 2:

- Participants receiving parsaclisib who permanently discontinue study drug will enter the post-treatment follow-up period for 1 visit (FUP1/EOS) approximately 4 weeks after the last dose of study drug.
- Participants receiving placebo who permanently discontinue study drug will no longer be required to enter the post-treatment follow-up period and will perform EOT1/EOS upon discontinuation of treatment.

An external DSMB will review safety data periodically throughout the study as defined in the DSMB charter and may provide recommendations regarding changes in the study conduct (see Section 5.6).

Participants will be assessed for efficacy by monitoring hemoglobin level [redacted] and completing the FACIT-F to assess self-reported fatigue and its impact upon daily activities and function. [redacted] The primary analysis will be conducted when the last randomized participant has completed the double-blind treatment period.

Participants will be assessed for safety and tolerability by monitoring the frequency and severity of AEs and performing physical examinations, ECGs, vital sign measurements, and clinical laboratory assessments during the study per the SoA.

[redacted]

Note: Upon implementation of Protocol Amendment 2, protocol-required procedures have been reduced or eliminated for ongoing participants.

The COVID-19 global pandemic may present challenges to the normal conduct of this study and require the outline of potential mitigation strategies described in Appendix B.

4.2. Overall Study Duration

The study begins when the first participant signs the study ICF. The end of the study is defined as the date of the last visit of the last participant in the study or the last scheduled procedure shown in the SoAs (see Table 3, Table 4, and Table 5).

An individual's participation is estimated to be approximately 3 years including up to 32 days for screening, continuous treatment in the double-blind treatment period (24 weeks); the open-label treatment period (24 weeks); and the long-term extension (≈2 years), followed by a 12-week post-treatment follow-up.

A participant is considered to have completed the study if they have completed the double-blind, open-label, long-term extension, and post-treatment follow-up periods. The study is considered completed when the last participant visit has occurred.

In EU/EEA, the results of the study will be based on the date of the last visit of the last participant in the study globally.

4.3. Study Termination

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

The sponsor may terminate the study electively, if, for example, required by regulatory decision or upon advice of the DSMB. If the study is terminated prematurely, the sponsor will notify the investigators/head of the study site (Japan), the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study. The DSMB will recommend termination of the study if warranted, as described in Section 5.6. For Japan, the decision from the sponsor will be via the head of the study site(s) who will notify the investigators and the IRBs of the decision and reason for termination of the study.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. Ability to comprehend and willingness to sign a written ICF for the study.
2. Men or women, age ≥ 18 years at the time of signing the ICF.
3. Diagnosis of primary wAIHA based on the presence of hemolytic anemia and serological evidence of anti-erythrocyte antibodies, detectable by a DAT positive for IgG only or IgG plus C3d.

   Note: A DAT performed at screening is preferred; however, prior documentation of DAT results within 3 months of randomization is permitted.
4. Participants who were inadequately controlled with, were intolerant to, or have a contraindication to other therapies. There is no limit to the number of prior treatment regimens.
5. Hemoglobin ≥ 6.5 to < 10 g/dL with symptoms of anemia as assessed by the investigator at screening (hemoglobin as determined by local laboratory).
6. FACIT-F score ≤ 43 at screening.
7. Willingness to avoid pregnancy or fathering children based on the criteria below.
   a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children (with 99% certainty) from screening through 90 days after the last dose of study drug and must refrain from donating sperm during this period. Permitted methods in that are at least 99% effective preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   b. Female participants who are WOCBP must have a negative serum pregnancy test at screening and a negative urine pregnancy test before randomization and must agree to take appropriate precautions to avoid pregnancy (with 99% certainty) from screening through 90 days after the last dose of study drug and must refrain from donating oocytes during this period. Permitted methods that are at least 99% effective preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   c. A female participant not considered to be of childbearing potential as defined in Appendix A is eligible.
      Note: This criterion does not apply to women of nonchildbearing potential (i.e., surgically sterile with a hysterectomy and/or bilateral oophorectomy OR

postmenopausal, defined as amenorrhea at least 12 months before screening, confirmed by FSH levels at screening).

8. Willingness to receive PJP prophylaxis during the study period from Day 1 through at least 2 to 6 months after the last dose of study drug.
9. For participants in France only: COVID-19 vaccination at least 2 weeks prior to randomization.
10. For participants in France only: Participant is up-to-date with mandatory vaccinations according to the national vaccination program as assessed by the investigator.

5.2. Exclusion Criteria

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

1. Women currently pregnant or breastfeeding or participants expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 90 days from the date of last dose of study drug.
2. A diagnosis of other types of AIHA; CAD, cold agglutinin syndrome, mixed-type AIHA or paroxysmal cold hemoglobinuria.
3. Warm AIHA suspected to be secondary to a lymphoproliferative malignancy or secondary to an autoimmune disease (eg, systemic lupus erythematosus, Castleman's disease, Sjögren's syndrome, or other autoimmune diseases) or diagnosis of Evans syndrome.
4. A splenectomy less than 3 months before randomization.
5. Concurrent conditions or history of other diseases:
   a. History or clinical manifestations of significant unstable metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, urological, neurological, or psychiatric disorders.
   b. Current or previous malignancy within 5 years of study entry, except basal or squamous cell skin cancer with removal considered to be curative, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy without sponsor approval.
   c. Clinically significant cardiac disease, including unstable angina, acute myocardial infarction, and/or cardiac conduction issues within 6 months of randomization.
   d. Current New York Heart Association Class II to IV congestive heart failure or uncontrolled arrhythmia.
6. Known diagnosis of anti-phospholipid syndrome or history of persistent anti-phospholipid antibodies.

   Note: Participants at risk for thrombosis who are on adequate prophylaxis or those with thrombosis on stable treatment for 3 months prior to randomization are eligible.
7. Hepatitis B (HBV) or hepatitis C (HCV) infection: Participants who are positive for the hepatitis B surface antibody or hepatitis B core antibody will be eligible if they are negative for HBV-DNA; these participants should be considered for prophylactic

antiviral therapy. Participants who are positive for the anti-HCV antibody will be eligible if they are negative for HCV-RNA.

8. Known HIV infection or positivity on immunoassay.

   Note: HIV screening test is optional for participants enrolled in the United States, but participants with known HIV infection enrolled in the United States will be excluded.

9. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Participants with screening QTc interval > 470 milliseconds for males and > 480 milliseconds for females (corrected by Fridericia) are excluded. In the event that a single QTcF is > 470 milliseconds for males or > 480 milliseconds for females, the participant may enroll if the average QTcF for triplicate ECGs is < 470 milliseconds for males or < 480 milliseconds for females.

10. Use of the following medications:

    a. Treatment with rituximab within 6 weeks of randomization.
    b. Use of immunosuppressive therapy within 28 days of the randomization. Immunosuppressive therapy includes, but is not limited to, cyclosporine A, azathioprine, mycophenolate mofetil, or cyclophosphamide.
       Note: Participants receiving corticosteroids must be at a stable dose level (no change in daily dose) ≤ 40 mg/day (prednisone or equivalent corticosteroid dose) for at least 14 days prior to randomization.
    c. Use of IVIG or erythropoietin within 2 weeks of randomization.
    d. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment or exposure to a live vaccine within 30 days of randomization.
    e. Use or expected use during the study of any prohibited medications (see Section 6.7.3), including potent CYP3A4 inhibitors or moderate or potent CYP3A4 inducers, within 14 days or 5 half-lives (whichever is longer) before randomization (see Appendix E).

11. Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before randomization with another investigational medication, or current enrollment in another investigational drug and/or device protocol.

12. Known hypersensitivity or severe reaction to parsaclisib or its excipients (IB).

13. Unable to swallow oral medication, malabsorption syndrome, disease significantly affecting gastrointestinal function, total resection of the stomach or small bowel, ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.

14. Current alcohol or drug use that, in the opinion of the investigator, will interfere with the participant's ability to comply with the dose regimen and study evaluations.

15. Participants who, in the opinion of the investigator, are unable or unlikely to comply with the dose regimen and study evaluations.

16. 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.

17. Prior treatment with parsaclisib or another PI3Kδ, or a pan-PI3K inhibitor for any indication.
18. Participants with laboratory values at screening defined in Table 7.

Table 7: Exclusionary Laboratory Values

Laboratory Parameter[a]		Exclusion Criterion
Hematology		
a	Platelets	≤ 100 × 10^9/L
b	ANC	≤ 1.5 × 10^9/L
c	WBCs	≤ 1.5 × 10^9/L
Hepatic		
d	ALT	≥ 2 × ULN
e	AST	≥ 2 × ULN unless clearly related to active hemolysis
Renal		
f	eGFR using 2021 CKD-EPI (Inker et al 2021)	≤ 45 mL/minute/1.73m^2

[a] If the central laboratory is unable to perform the test due to hemolysis related to wAIHA or the analytical method, then local laboratory test results may be used to determine participant eligibility.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Parsaclisib/placebo will be taken orally with water without regard to food except on mornings of [redacted] clinic visits. See Section 8.5 for details on further requirements before and after the start of [redacted].

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.

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

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

5.5. Replacement of Participants

No participants will be replaced at any time during this study. However, the COVID-19 global pandemic may present challenges to the normal conduct of this study and may require the outline of potential mitigation strategies described in Appendix B.

5.6. Data Safety Monitoring Board

This study will use an eDSMB to monitor safety as detailed in the DSMB charter.

The voting members of the committee are external to the sponsor. The members of the eDSMB will not be involved with the study in any other way (eg, they cannot be study investigators) and will have no competing interests that could affect their roles with respect to the study.

The eDSMB will make recommendations to the sponsor regarding steps to ensure both participant safety and the continued ethical integrity of the study. Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the sponsor, IEC, and protocol team; and requirements for and proper documentation of eDSMB reports, minutes, and recommendations will be described in the eDSMB charter that is reviewed and approved by all eDSMB members.

6. STUDY TREATMENT

6.1. Study Treatments Administered

Information regarding study drug and study drug administration is provided in Table 8. Further information regarding study drug administration is provided in Appendix C. The COVID-19 global pandemic may present challenges to the normal conduct of this study, requiring the outline of potential mitigation strategies described in Appendix B.

Table 8: Study Treatment Information

Study treatment name:	**Parsaclisib**	**Matching Placebo**
Mechanism of action:	PI3Kδ inhibitor	Not applicable
Dosage formulation:	Tablet	Matching Tablet
Unit dose strength(s)/dosage level(s):	2.5 mg 1 mg	2.5 mg 1 mg
Administration instructions:	1 tablet orally QD. Parsaclisib or matching placebo will be taken orally with water without regard to food except on mornings of [redacted] clinic visits. Participants should not take their dose at home when they have a [redacted] visit. Parsaclisib should be taken at approximately the same time each day.	
Packaging and labeling:	Parsaclisib and matching placebo will be packaged in high-density polyethylene bottles. No preparation is required. All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country.	
Storage:	Bottles of parsaclisib and matching placebo should be stored at ambient conditions (15°C-30°C or 59°F-86°F).	
Status of treatment in participating countries:	Investigational	Not applicable

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 the following:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Participant use of the study drug, including tablet 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 (see Section 6). The investigator will also maintain records adequately documenting that the participants were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

Completed accountability records will be archived by the site. The investigator, 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 treatments are provided in the Study Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to study treatment using an IRT (see Section 8.1.3). Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the IRT will be provided to each site. Full details will be provided in the IRT Study Reference Manual.

Study drug will be dispensed at the study visits summarized in the SoA (see Table 3 and Table 4). Returned study drug should not be redispensed to the participants.

Participants, investigators, and the sponsor will remain blinded to each participant's treatment assignment throughout the double-blind portion of 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 9.7 and refer to the IRT Study Reference Manual).

6.4. Study Treatment Compliance

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

Compliance with study drug administration will be calculated by the sponsor based on study drug accountability records documented by the site staff and monitored by the sponsor/designee.

Participant compliance must be within 80% to 120%, assessed at each study visit. If compliance is outside of this range, it will be considered a protocol deviation. Participants consistently noncompliant with the study drug may be withdrawn from the study. The decision to withdraw a participant will be made by the investigator after consultation with the sponsor, and relevant correspondence will be archived in the site study file.

6.5. Dose Modifications

Dose modifications will be allowed during the study as defined in Section 6.5.1. In some circumstances, it may be necessary to temporarily interrupt treatment with study drug as a result of AEs or laboratory abnormalities that have an unclear relationship to the study drug.

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

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

Dose modifications are allowed in the study. Dose reductions from 2.5 mg QD to 1 mg QD are allowed after consultation with the medical monitor, if the participant is experiencing an AE assessed as related or of unknown relationship to study drug or for hemoglobin levels in the high end of normal range. Because participants may enter the study with extensive pretreatment and/or hemolysis associated with the primary disease, these dose reduction rules are provided as guidelines (see Table 9). Dose re-escalation is permitted provided the investigator consult with the sponsor medical monitor and the sponsor approves before dose re-escalation.

In some circumstances, it may be necessary to temporarily interrupt treatment with parsaclisib as a result of AEs or laboratory abnormalities that have an unclear relationship to the study drug (see Table 9). Except in cases of emergency, it is recommended that any laboratory findings be confirmed and that the investigator consult with the sponsor medical monitor (or other representative of the sponsor) before temporarily interrupting study drug. Participants who experienced a recurrence of the AEs or laboratory abnormalities upon restarting the study drug may have the study drug permanently discontinued (see Section 7.1.2).

During the study, study treatment may be delayed up to 21 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 7 days before restarting study treatment. See Appendix D for action required for potential Hy's law cases.

Table 9: Guidelines for Interruption and Restarting of Study Drug

ADVERSE EVENT	ACTION TAKEN
Chemistry	
Grade 2 AST and/or ALT is > 3.0 - 5.0 × ULN	**Step 1:** Interrupt study drug up to 21 days and repeat ALT/AST assessments weekly for up to 3 weeks (local blood collection may be used) or until ALT and/or AST results are < 3.0 × ULN. **Step 2:** Restart study drug at the same dose and monitor as clinically indicated. • If ALT and/or AST result(s) do not decrease to < 3.0 × ULN after 3 weeks of drug interruption, discontinue study drug administration, and the participant will enter the post-treatment follow-up period. • If AST or ALT elevation > 3.0-5.0 × ULN reoccurs following restarting study medication administration, repeat Step 1 and then restart study drug at 1 mg QD dose. • If AST and ALT > 3.0-5.0 × ULN reoccurs on lower dose, discontinue study drug administration, and the participant will enter the post-treatment follow-up period.
≥ Grade 3 AST and/or ALT is > 5.0 × ULN	**Step 1:** Interrupt study drug up to 21 days and repeat ALT/AST assessments weekly for up to 3 weeks (local blood collection may be used) or until the toxicity has resolved to <3.0 x ULN (≤ Grade 1). **Step 2:** Restart study drug at a 1 mg dose and monitor as clinically indicated. If reoccurs, discontinue study drug and monitor as clinically indicated and the participant will enter the post-treatment follow-up period.
Hematology	
• Grade 3 ANC (≤ 1.0 × 10^9/L), unless due to underlying disease • Grade 2 platelet count (50 × 10^9/L to < 75 × 10^9/L)	**Step 1:** Interrupt study drug up to 21 days until the toxicity has resolved to ≤ Grade 1 or baseline. For Grade 3 ANC, monitor at least weekly. **Step 2:** Restart study drug at same dose and monitor as clinically indicated. If reoccurs, repeat Step 1 and then restart at the 1 mg QD dose. **Step 3:** If reoccurs at 1 mg dose, discontinue study drug administration and the participant will enter the post-treatment follow-up period.

Table 9: Guidelines for Interruption and Restarting of Study Drug (Continued)

ADVERSE EVENT	ACTION TAKEN
Hematology (continued)	
• Grade 4 ANC (< 0.5×10^9/L) • ≥ Grade 3 ANC with an oral temperature of at least 38.5°C OR with ≥ Grade 3 infection • ≥ Grade 3 platelet count (< 50×10^9/L)	**Step 1:** Interrupt study drug up to 21 days until the toxicity has resolved to ≤ Grade 1 or baseline. For ≥ Grade 3 ANC, monitor at least weekly. **Step 2:** Restart study drug at same dose and monitor as clinically indicated. If reoccurs, repeat Step 1 and then restart at the 1 mg QD dose. If event persists, discontinue study drug administration and the participant will enter the post-treatment follow-up period.
Other toxicities	
Diarrhea/colitis (Grade 1)	**Step 1:** Treat with antimotility agents (eg, loperamide) and initiate supportive care (see Section 6.5.2). If not improved after 48 hours, treat per guidance for ≥ Grade 2.
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 6.5.2). Monitor clinical progress closely. **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 1 mg QD 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 and the participant will enter the post-treatment follow-up period.

Table 9: Guidelines for Interruption and Restarting of Study Drug (Continued)

ADVERSE EVENT	ACTION TAKEN
Other toxicities (continued)	
• Diarrhea (≥ Grade 3) • Noninfectious colitis (any grade; confirmed or suspected)	**Step 1:** Interrupt parsaclisib or matching placebo. Perform workup for infection (including CMV, *C. difficile*, etc) immediately. Initiate or continue supportive care (see Section 6.5.2). Consider colonoscopy with biopsy for diarrhea ≥ Grade 3 and/or if symptoms suggestive of colitis. Monitor clinical progress closely 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 or matching placebo 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 or matching placebo at 1 mg QD with approval of the medical monitor. Continue to monitor. If reoccurs, discontinue study drug and the participant will enter the post-treatment follow-up period.
Pneumonitis (Grade 1)	**Step 1:** Interrupt parsaclisib or matching placebo until the toxicity has resolved. **Step 2:** Restart parsaclisib or matching placebo at the 1 mg QD dose. Monitor as clinically indicated.
Pneumonitis (≥ Grade 2)	Permanently discontinue parsaclisib or matching placebo and the participant will enter the post-treatment follow-up period.
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 1 mg QD dose.
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 1 mg QD dose. Monitor as clinically indicated.
Exfoliative dermatitis (≥ Grade 2)	**Step 1:** Interrupt parsaclisib or matching placebo until the toxicity has resolved. **Step 2:** Restart parsaclisib or matching placebo.

Table 9: Guidelines for Interruption and Restarting of Study Drug (Continued)

ADVERSE EVENT	ACTION TAKEN
Other toxicities (continued)	
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 reduce to 1 mg QD dose 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	Continue study drug administration and treat the toxicity; monitor as clinically indicated.
Any Grade 3 toxicity, if clinically significant and not manageable by supportive care	**Step 1:** Interrupt study drug up to 2 weeks (14 days), until toxicity resolves to ≤ Grade 1. **Step 2:** Restart study drug at same dose. If assessed as related to study drug, restart study drug at 1 mg QD dose if receiving 2.5 mg and monitor as clinically indicated.
Any recurrent Grade 3 toxicity after dose reduction	Discontinue study drug administration and the participant will enter the post-treatment follow-up period. (Exceptions require approval of sponsor.)
Any other Grade 4 toxicity	Discontinue study drug administration and the participant will enter the post-treatment follow-up period.

6.5.2. 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 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 as 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, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

6.5.3. Follow-Up for Immune-Related Adverse Events

An AE with a potential immunologic etiology, or an immune-related AE, 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 immune-related AEs. Suspected immune-related AEs 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 9. For each AE, attempts should be made to rule out other causes, including but not limited to bacterial or viral infection, which might require specific supportive care.

6.5.4. 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. Pi3K-delta 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 participating in trials of parsaclisib, alone or in combinations, need to be aware of these potential risks and consider the local standards of care and available therapies for disease prevention, vaccination (see Section 6.7.1.3), and infection management of COVID-19.

6.5.5. Criteria for Permanent Discontinuation of Study Drug

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

- The occurrence of an AE that is related to study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest
- Adverse events that reoccur and/or persist after reduction to 1 mg QD.
- Persistent AE requiring a delay of therapy for more than 21 days unless a greater delay has been approved by the sponsor.
- Specific AEs requiring permanent discontinuation as described in Table 9.

See Section 7.1.2 for discontinuation procedures.

6.6. Treatment With Parsaclisib During Long-Term Extension

Participants may take a drug holiday one time during the long-term extension. Participants who take a drug holiday may be eligible to resume parsaclisib if they have worsening of wAIHA after the drug holiday. *Note*: Resuming treatment with parsaclisib is not an option for participants who permanently discontinue study treatment for criteria described in Section 7.1.1.

Participants may take a drug holiday during the long-term extension if they meet the following condition:

- Were clinically stable for at least 8 weeks and tolerating treatment before taking a drug holiday.
  - Clinically stable defined as hemoglobin ≥ 10 g/dL with an increase from baseline of ≥ 2 g/dL not attributed to rescue therapy and no worsening or new symptoms of wAIHA

Re-treatment with parsaclisib is available if the study remains open and the participant meets all of the following conditions:

- Experienced worsening of wAIHA defined as a continuing decline in absolute hemoglobin level, a > 1 g/dL decrease in hemoglobin from the prior assessment, or the participant develops new or worsening symptoms of wAIHA after the drug holiday.

  AND

- In the opinion of the investigator, resuming treatment with parsaclisib would not pose a significant safety risk to the participant.

Participants will resume parsaclisib at the same dose level and frequency as when they last received parsaclisib. Re-treatment after a drug holiday is permitted one time. Participants will continue study treatment until any of the criteria for permanent discontinuation of study drug are met (see Section 7.1.1). Participants who permanently discontinue study treatment will enter the 12-week post-treatment follow-up visits scheduled every 4 weeks for 12 weeks after the last dose of study drug.

Note: Upon implementation of Protocol Amendment 2, participants receiving parsaclisib who permanently discontinue study drug will enter the post-treatment follow-up period for 1 visit (FUP1/EOS) approximately 4 weeks after the last dose of study drug.

6.7. 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 12 weeks before the first dose of study drug and 12 weeks after the last dose of study drug, will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the

eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.7.1. Permitted Medications and Procedures

6.7.1.1. *Pneumocystis jirovecii* Pneumonia Prophylaxis

All participants will receive a PJP prophylaxis regimen determined by the investigator, which will be locally sourced and reimbursed by the sponsor. The investigator must actively determine if a participant has a known sulfa allergy.

Examples of standard PJP prophylaxis therapies include sulfamethoxazole and trimethoprim, atovaquone, dapsone (diaphenylsulfone) with or without pyrimethamine, and pentamidine (NCCN 2020). (In Japan, diaphenylsulfone and pentamidine are not approved for PJP prophylaxis and thus will not be used.) Due to reports of cross-sensitivity between sulfonamides and dapsone, all participants who have a known or suspected allergy to sulfonamides must receive either inhaled pentamidine or atovaquone for PJP prophylaxis. If inhaled pentamidine or atovaquone are not available, the participants should not be enrolled.

Prophylaxis must be given while participants are receiving study drug and must continue for at least 2 to 6 months after the last dose of study drug.

Further details are available in the Pharmacy Manual.

6.7.1.2. Folic Acid, Vitamin B12, or Iron Deficiencies

Participants who are noted to be deficient in folic acid, vitamin B12, or iron should have replacement determined by the investigator as per current standard of care.

6.7.1.3. Vaccinations

Participants who elect to receive the COVID-19 vaccine during the study should stop study drug 5 days before and for 10 days after administration of the vaccine. For other non-live vaccines, investigators should consult with the sponsor medical monitor before administration.

6.7.1.4. Corticosteroids

Continued use of systemic corticosteroid (prednisone or equivalent) doses ≤ 40 mg/day is permitted through the EOT visit as long as the dose has been stable for at least 14 days prior to randomization.

Prednisone (or equivalent) may be tapered if the investigator considers it appropriate based on the participant's clinical response. The recommended taper schedule is detailed in Table 10.

Table 10: Tapering Guidelines for Corticosteroids

Current Dose of Prednisone	Taper Schedule
> 20 mg QD	Taper by 10 mg every 7 days until a 20 mg daily dose is achieved in participants with a hemoglobin > 10 g/dL with at least a 2 g/dL increase from Day 1.
20 mg QD	Taper by 5 mg every 14 days from 20 mg to 10 mg QD in participants with a hemoglobin > 10 g/dL with at least a 2 g/dL increase from Day 1.
10 mg QD	Taper by 2.5 mg every 14 days from 10 mg to 5 mg in participants with a hemoglobin > 10 g/dL with at least a 2 g/dL increase from Day 1.
5 mg QD	Stop prednisone after 14 days in participants with a hemoglobin > 10 g/dL with at least a 2 g/dL increase from Day 1. *Note:* Tapering may proceed according to the clinical judgement of the investigator.

See Section 6.7.4 for use of corticosteroids as rescue treatment.

6.7.2. Restricted Medications and Procedures

Restricted medications and procedures include the following:

- Short courses (approximately 2 weeks) of high-dose systemic corticosteroid (doses > 40 mg/day prednisone or equivalent) are permitted (eg, for the treatment of severe or life-threatening AEs or non-wAIHA limited related conditions) but are otherwise discouraged from the screening visit through the EOT visit.
- Use of weak inducers of CYP3A4 or weak or moderate inhibitors of CYP3A4 or use of P-glycoprotein substrates is discouraged, and investigators should seek other options where possible (see Appendix E).

6.7.3. Prohibited Medications and Procedures

Prohibited medications and procedures include the following:

- Use of moderate or potent inducers of CYP3A4 and potent inhibitors of CYP3A4 is prohibited, with the exception of topical ketoconazole because of its low bioavailability.
- Apart from the study treatments, the use of any medications as described in the exclusion criteria (see Section 5.2) through the post-treatment follow-up is prohibited.
  - If rituximab is required, the participant must discontinue from study treatment.
- Exposure to a live vaccine within 30 days of randomization through 3 months after the last dose of study drug is prohibited.

6.7.4. Rescue Treatment

Given the natural history of wAIHA, participants may require supportive care for hemoglobin during the study. Rescue medications may be permitted to serve as a bridging strategy to allow time for study drug to affect hemoglobin. Rescue medication will be prescribed by the investigator and obtained locally. Rescue medication should be considered if the absolute hemoglobin level continues to decline, there is a > 1 g/dL decrease in hemoglobin from the prior assessment, or the participant develops new or worsening symptoms of wAIHA. The following protocol-permitted rescue medications may be used during the study:

- New or increased dose of corticosteroids (prednisone or equivalent) from Day 1 dose
- Transfusions
- IVIG
- Erythropoietin

The date of rescue medication administration as well as the name and dose regimen of the rescue medication must be recorded in the eCRF.

Participants who continue to receive rescue treatment after Week 6 will be considered nonresponders in the primary efficacy analysis, but may continue in the study at the discretion of the investigator.

6.8. Treatment After the End of the Study

Participants who have completed at least 2 months of active study treatment (starting from first dose of parsaclisib) and are receiving benefit will have the option to continue to receive parsaclisib provided within a rollover study or through commercially available supply where applicable.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- The participant becomes pregnant.
- Informed consent is withdrawn.

  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for safety.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity as noted in Section 6.5.5.
- Participant has received a prohibited rescue therapy other than those described in Section 6.7.4.
- Participant meets discontinuation criteria as described in Section 6.5.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

- If a participant is noncompliant with study procedures or study drug administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.
- If the participant experiences worsening of wAIHA, persistent decline in hemoglobin, or the onset of new wAIHA symptoms requiring treatment.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit (EOT1 during the double-blind period, EOT2 during the open-label period, or EOT3 during the long-term extension) should be conducted. The participant will then enter the 12-week post-treatment follow-up period. These visits are described Table 3, Table 4, and Table 5. The last date of the last dose of study drug and the reason for discontinuation of study drug will be recorded in the eCRF.

Note: Upon implementation of Protocol Amendment 2:

- Participants receiving parsaclisib who permanently discontinue study drug will enter the post-treatment follow-up period for 1 visit (FUP1/EOS) approximately 4 weeks after the last dose of study drug.
- Participants receiving placebo who permanently discontinue study drug will no longer be required to enter the post-treatment follow-up period and will perform EOT1/EOS upon discontinuation of treatment.

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 status of the participant should be updated to EOT in the IRT.
- Participants must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to Day 1, or are deemed irreversible, whichever is longest.

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

7.2. Participant Withdrawal From the Study

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

If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. 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. See Table 3, Table 4, 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 they repeatedly fail 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, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

See Appendix B for COVID-19–related guidance.

Note: Upon implementation of Protocol Amendment 2, protocol-required procedures have been reduced for ongoing participants.

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

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

- A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is randomized in the study. Screening may not exceed 32 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process. Central laboratory results will be used to determine eligibility unless otherwise stated (see Section 5.2 and Section 8.4.5). Hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results.

Results from the screening visit evaluations will be reviewed to confirm eligibility before 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 will be used to determine eligibility.

See Sections 5.4 for information regarding screen failures.

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the 2-letter alpha country International Standards Organization code then a 3-digit site number, followed by a 3-digit participant number. Site staff should contact the IRT to obtain the participant ID number during screening. Upon determining that the participant is eligible for randomization, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at the study visits detailed in Table 3, Table 4, and Table 5 to update the study drug supply. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Reminder Cards and Diaries

Participants will be provided with a reminder card at each visit. The reminder card will indicate the date/time of the next visit and will also remind the participant that they should not take their morning dose of study drug before coming to the clinic and they should record the most recent meal or snack in the diary (see Section 8.5).

Participants will be instructed on the use of the diary. The date and time of the last dose of study drug and the time of the most recent snack/ meal [redacted] (see Section 8.5 and Table 12) will be recorded in the diary and captured in the eCRF. Daily study drug administration and any concomitant corticosteroid use will be recorded in the diary and verified by the investigators or designee at study visits as shown in Table 3, Table 4, and Table 5.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected as permitted by local regulations at screening by the investigator or qualified designee and will include year of birth/age, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include

relevant medical or surgical treatment within the last 10 years that are considered to be clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history including date of diagnosis of primary wAIHA, serological test, prior treatment history (all known failed treatments and all treatments within the prior year), number of transfusions within the prior year, number of hospitalizations due to AIHA within the prior year, and symptoms of wAIHA will be collected at screening.

8.2. Efficacy Assessments

Note: Upon implementation of Protocol Amendment 2, the efficacy assessments noted herein will be reduced as detailed in Table 3 and Table 4.

8.2.1. Hemoglobin Level, [redacted] and Direct Antiglobulin Test

Participants will undergo hematology [redacted], and a DAT to evaluate type of AIHA diagnosis and disease status as detailed in Table 3, Table 4, and Table 5. Prior documentation of DAT results are acceptable for study entry (see Section 5.1).

Note: The participants' screening hemoglobin enrollment eligibility will be based on a local laboratory assessment. If hemoglobin and other laboratory values are required for the immediate participant management, it is acceptable to use a local laboratory.

8.3. Patient-Reported Outcomes

Patient reported outcomes will be captured using an electronic PRO device.

Note: Upon implementation of Protocol Amendment 2, the PROs noted herein will no longer be required.

8.3.1. Functional Assessment of Chronic Illness Therapy – Fatigue

The FACIT-F is a 13-item measure that assesses self-reported fatigue and its impact upon daily activities and function over the past 7 days. The questionnaire should be completed by the participant using an electronic platform before any procedures are performed at the visits specified Table 3, Table 4, and Table 5. Additionally, the questionnaire must be completed before all other PRO assessments.

8.3.2. Six-Minute Walk Test

The 6MWT is used to evaluate submaximal exercise capacity (ATS 2002). It is a self-paced measurement of the distance that a participant can quickly walk on a flat, hard surface in a period of 6 minutes. The test should be performed after all other PRO assessments have been completed as detailed in the Study Manual and at the visits specified in Table 3 and Table 4. Approximately 10 minutes before and within 5 minutes after the 6MWT is performed, vital signs (blood pressure, pulse, and respiration) should be assessed.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.4. Safety Assessments

8.4.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 12 weeks after the last dose of study drug. Adverse events for enrolled participants that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study drug. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

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

All SAEs will be reported to the sponsor or designee within 24 hours (immediately in Germany). The investigator will submit any updated SAE data to the sponsor within 24 hours (immediately in Germany) of it being available.

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

At remote visits, adverse events will also be assessed via a phone call conducted by the study site, except for countries where remote visits are not permitted by local laws and/or regulations (see Table 3, Table 4, and Table 5).

8.4.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits at the visits detailed in Table 3, Table 4, and Table 5. 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 drug. Investigators should pay special attention to clinical signs related to previous serious illnesses.

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

A targeted physical examination should be conducted as indicated by symptoms reported by the participant, AEs, or other findings. Abnormalities that are considered clinically significant in the judgment of the investigator (or designee) are to be reported as AEs.

During the study, participants will be assessed by the investigator or medically qualified designee per institutional standard of care. These assessments should be an evaluation as indicated by participant symptoms, AEs, or other findings and documented on the AE eCRF.

8.4.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests), include blood pressure, pulse, respiratory rate, and body temperature. If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest.

Abnormal vital sign results identified after the first dose of study drug constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug.

8.4.4. Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the SoA (see Table 3 and Table 4) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF 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 discontinue study treatment based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor as appropriate. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs. In the event that a single QTc is > 470 milliseconds at screening, the participant may enroll if the average QTc for triplicate ECGs conducted over a brief period is ≤ 470 milliseconds or with approval from the medical monitor. For participants with an intraventricular conduction delay (QRS interval > 120 milliseconds) at screening, the JTc interval may be used in place of the QTc with medical monitor approval. In addition, the JTc interval should be used for all subsequent assessments.

8.4.5. Laboratory Assessments

See Table 11 for the list of clinical laboratory tests to be performed and Table 3, Table 4, and Table 5 for the timing and frequency. A central laboratory will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function, and urinalysis). Additional testing may be required by the sponsor based on emerging safety data. All Protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and Table 3, Table 4, and Table 5.

Note: The participants' screening hemoglobin enrollment eligibility will be based on a local laboratory assessment. Additionally, if the central laboratory is unable to perform any other required screening tests due to hemolysis related to wAIHA or the analytical method, then local laboratory test results may be used to determine participant eligibility.

At-home blood collection will be conducted during remote visits, except for countries where remote visits are not permitted by local laws and/or regulations (see Table 3 and Table 4). At-home sampling for additional laboratory assessments may also be conducted, except for countries where remote visits are not permitted by local laws and/or regulations; see Appendix B for COVID-19–related guidance. Information regarding collection, processing, and shipping of samples for laboratory assessment 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 drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If screening laboratory assessments are performed more than 32 days before Day 1, then the tests must be repeated and eligibility confirmed before study drug administration on Day 1.

Laboratory sample collection on Day 1 must be performed before study drug administration.

See Section 9.1 for information regarding laboratory abnormalities that should be recorded as an AE in the eCRF.

Table 11: Required Laboratory Analytes

Chemistry[a]	Hematology[a,b]	Urinalysis With Microscopic Examination	Serology	Coagulation
Albumin Alkaline phosphatase ALT AST Bicarbonate[c] Blood urea nitrogen Calcium Chloride Creatinine Ferritin (screening visit and repeat at Week 6 if participant has ongoing transfusion requirements) Folic acid (screening visit only) Glucose [redacted] Iron (screening visit and repeat at Week 6 if participant has ongoing transfusion requirements) [redacted] Phosphate Potassium Sodium [redacted] Total protein Total iron-binding capacity (screening visit and repeat at Week 6 if participant has ongoing transfusion requirements) Uric acid	Complete blood count, including: Hemoglobin Hematocrit Platelet count Red blood cell count White blood cell count Differential count, including: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Absolute values must be provided for: WBC differential laboratory results	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen	CMV Hepatitis B surface antigen Hepatitis B surface antigen antibody Hepatitis B core antibody HBV-DNA HCV antibody HCV-RNA HIV[e]	D-dimer
		[redacted]		**Pregnancy Testing**
		[redacted] **DAT** DAT for IgG and C3d **Other Assessments** Vitamin B12 (screening visit only) [redacted] FSH		Female participants of childbearing potential only require a serum test at screening and EOT and a urine pregnancy test before the first dose on Day 1 and monthly during the study. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

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

[a] Chemistry and hematology parameters may be managed in real-time by local laboratory assessments.

[b] Hematology panels [redacted] need to be performed in accordance with the standard of care at each investigational site for the participant's condition and monitoring at the investigator's discretion.

[c] Bicarbonate not applicable in Japan.

[redacted]

[e] HIV screening test is optional for participants enrolled in the US.

8.4.5.1. Pregnancy Testing

A serum pregnancy test will be required for all WOCBP during screening (before the first dose of study drug) and at the visits indicated in Table 3, Table 4 , and Table 5. Urine pregnancy tests will be performed locally as outlined in Table 3, Table 4, and Table 5 as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement (note that country required- urine pregnancy testing will be outlined and communicated to investigational sites under separate cover). If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

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

If a pregnancy is confirmed by a serum pregnancy test, the participant should be instructed to immediately discontinue study drug (see Section 9.8 for procedures and reporting requirements).

8.4.5.2. Serology

Hepatitis screening assessments will be performed at the screening visit to rule out hepatitis infection; required analytes are shown in Table 11. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

[redacted]

[redacted]

8.7. Unscheduled Visits

Unscheduled visits may be held at any time at the investigator's discretion, and appropriate clinical and laboratory measurements performed based on AEs or other findings.

8.8. Long-Term Extension

To allow continued treatment with parsaclisib after completion of Week 48, a long-term extension is available for all participants who are tolerating study treatment and in the investigator's opinion may benefit from continued treatment with parsaclisib. Parsaclisib will be administered at the same dose level and frequency as in the open-label treatment period. During the long-term extension, participants may take a drug holiday one time with the option for re-treatment as described in Section 6.6. Participants who enter the long-term extension will be monitored for safety and persistence of effect. The SoA is detailed in Table 5.

8.9. End of Treatment

When the participant permanently discontinues study drug, then the EOT visit (EOT1 for double-blind period, EOT2 for open-label period, and EOT3 for long-term extension) should be

conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The participant should enter the post-treatment follow-up visits.

8.10. Post-Treatment Follow-Up

The post-treatment follow-up period, comprised of 3 visits (one every 4 weeks; FUP1, FUP2, and FUP3), is the interval between the EOT visit and the scheduled follow-up visits, which should occur at a minimum of 30 days to 84 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). The FUP1 and FUP2 visits will be conducted remotely, except for countries where remote visits are not permitted by local laws and/or regulations. Adverse events and SAEs must be reported up until 1) at least 84 days after the last dose of study drug or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the FUP3 visit and report any AEs that may occur during this period. In exceptional cases when the participant cannot return to the site for the FUP3 visit, the participant should be contacted by telephone for assessment of AEs and SAEs and the site should properly document the contact.

Note: Upon implementation of Protocol Amendment 2:

- Participants receiving parsaclisib who permanently discontinue study drug will enter the post-treatment follow-up period for 1 visit approximately 4 weeks after the last dose of study drug.
- Participants receiving placebo who permanently discontinue study drug will no longer be required to enter the post-treatment follow-up period and will perform EOT/EOS upon discontinuation of treatment.

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 drug.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to worsening of underlying disease) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in 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 drug administration are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from dosing errors of a study drug (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy," "disease worsening," 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 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, or suspected transmission of an infectious agent via a medicinal product. Secondary malignancies should always be considered SAEs.
- For Japan, 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. AEs/SAEs should be reported for enrolled participants, but only SAEs need to be reported for screen failure participants. For enrolled participants, conditions that were present at the time informed consent was given should be recorded on the Medical History eCRF. For detailed information refer to the eCRF guidelines.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator (or 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 Reference Manual or as per SAE completing guidelines.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

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

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study drug: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study drug 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 drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the RSI in the IB or Product Information for study drug, or marketed products, respectively, in making their assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and have provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change their opinion of causality in light of follow-up information and submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- Once an AE is detected, it should be followed in the AE eCRFs until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology.
- Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance 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 (immediately in Germany) of receipt of the information.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug, or study procedures), all SAEs occurring after the participant has signed the ICF through the last safety visit or at least 30 to 35 days after the last dose of study drug must be reported to the sponsor (or designee) immediately, without undue delay but not later than within **24 hours** (immediately in Germany) of obtaining knowledge of its occurrence unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) immediately, without undue delay but not later than within 24 hours (immediately in Germany) 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 drug. If the investigator learns of any SAE, including death, at any time during this period, and they consider the event to be reasonably related to the study drug or study participation, then the investigator must notify the sponsor (or designee) within 24 hours (immediately in Germany) of becoming aware of the event.

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

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

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

suspected expected deaths and life-threatening events to the PMDA as per local regulatory requirements.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug 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 (immediately in Germany) of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available. The contact information for Incyte Pharmacovigilance by email/fax is listed in the Study Reference Manual. • 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 (immediately in Germany), refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form. Once the EDC system is functional, the SAE report should be retrospectively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form or Study Reference Manual for details and for the email address or fax number). • Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

9.5. Potential Drug-Induced Liver Injury

For information on management of potential Hy's Law cases, see Appendix D.

9.6. Events of Clinical Interest

An ECI is an AE (serious or nonserious) that Incyte wishes to document in an organized manner for monitoring or understanding. An ECI does not require rapid communication by an investigator to Incyte unless it meets criteria for rapid communication as an SAE (see Section 9.2). The ECIs include laboratory abnormalities and clinical AEs as follows:

- ALT ≥ 5 × ULN
- AST ≥ 5 × ULN
- Colitis
- Diarrhea ≥ Grade 2
- Intestinal perforation
- Rash ≥ Grade 2
- Exfoliative dermatitis
- Pneumonitis
- PJP
- CMV infection
- Herpes simplex
- Varicella zoster virus infection

9.6.1. Adverse Events of Special Interest

Not applicable.

9.7. Emergency Unblinding of Treatment Assignment

In case of a medical emergency, for a participant's safety management, the procedure for emergency unblinding is provided to the investigator in the IRT Manual. The investigator has the primary right to break the blind to treat a participant in emergency circumstances.

If a participant's treatment assignment is unblinded, the sponsor or its designee should be notified immediately by telephone for awareness.

If an investigator, the site personnel performing assessments, or a participant is unblinded, then the participant must discontinue study drug 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.

9.8. Pregnancy

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

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

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

Any SAE occurring during pregnancy of a study participant must be recorded and reported as described in Section 9.4.

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

9.9. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study as necessary. If new significant risks are identified, they will be added to the ICF.

9.10. Product Complaints

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

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

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

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

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

9.11. Treatment of Overdose

Overdose is not an SAE unless it meets the criteria of an SAE (see Section 9.2).

For this study, any daily dose of study drug greater than 2.5 mg during the study within a 24-hour time period (± 4 hours) will be considered an overdose and recorded in the eCRF.

Incyte does not recommend specific treatment for an overdose. Overdose with concomitant medication treatment will not be recorded in the eCRFs unless it resulted in an AE.

In the event of an overdose, the investigator should do the following:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study drug can no longer be detected systemically (at least 3 days).
- [redacted]
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant. Treatment of overdose should consist of general supportive measures.

10. STATISTICS

Note: Upon implementation of Protocol Amendment 2, enrollment has been closed and protocol-required procedures have been reduced for ongoing participants. With limited participants enrolled in each treatment group and the option for early cross-over to parsaclisib, most of the statistical analyses defined by the protocol are not applicable. Therefore, the final analyses to accommodate those changes will be specified in the Statistical Analysis Plan.

10.1. Sample Size Determination

Approximately 100 participants will be randomized 2:1 (approximately 67:33) to parsaclisib 2.5 mg QD or matching placebo using a fixed block size within each stratum. For the statistical comparison on the binary primary efficacy endpoint, the sample size calculation is based on a Chi-square test.

Based on the results of the Phase 2 study (INCB 50465-206), the response rate for the primary endpoint is assumed to be 70% for parsaclisib 2.5 mg. With limited data, such response rates in the placebo group are not reported in historical studies. The response rate for placebo group can only be assumed to around 25% from the literature review (Barcellini et al 2014, Birgens et al 2013, Lechner and Jäger 2010). Based on these assumptions, the sample size of 100 will provide enough power (over 90%) to detect such a difference with a 2-sided alpha of 0.05.

10.2. Populations for Analysis

The populations for analysis are provided in Table 13.

Table 13: Populations for Analysis

Population	Description
ITT	The ITT population includes all randomized participants. Treatment groups for this population will be defined according to the treatment assignment at randomization.
PP	The PP population includes randomized participants who are considered to be sufficiently compliant with the Protocol.
Safety	The safety population includes all participants who received at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the participant received on Day 1.
[redacted]	[redacted]

10.3. Statistical Analyses

10.3.1. Primary Analysis

The primary analysis will occur after the primary database lock, when the last randomized participant has completed the double-blind treatment period. The primary endpoint is defined as

the proportion of participants attaining durable hemoglobin response, defined as hemoglobin ≥ 10 g/dL with an increase from baseline of ≥ 2 g/dL not attributable to rescue therapy at ≥ 3 of the 4 available visits at Week 12 and/or later during the 24-week double-blind treatment period. The primary analysis will be based on the intent-to-treat population. The primary alternative hypothesis (superiority of parsaclisib 2.5 mg compared with placebo) will be tested using CMH test stratified by stratification factors. The p-value for between-treatment group testing will be compared with 0.05. Odds ratio and corresponding 95% confidence interval will be provided for comparing active and placebo groups. All nonresponders in the double-blind treatment period, as well as all participants who have missing values on the durable response, will be defined as nonresponders for the nonresponder imputation analysis. Participant missing 2 or more values on hemoglobin among the 4 visits will be defined as nonresponders for the primary endpoint. Participants who continue to receive rescue treatment after Week 6 will be considered nonresponders. Summary of the response rates will be reported for the 2 treatment groups. The response rates difference (parsaclisib 2.5 mg − placebo) will be reported along with the 95% confidence interval, which is derived from normal approximation.

Similar analysis will also be performed in the PP population for the primary endpoint. The following deviations are considered major:

- Missing 2 or more hemoglobin values among the 4 visits for the primary endpoint;
- Compliance less than 60%;
- Using prohibited medications or procedures as specified in Section 6.7.3.

Participants with 1 or more such deviations will be excluded from the PP population. In addition, protocol deviations related to inclusion/exclusion criteria, discontinuation criteria, and use of excluded concomitant medications will be evaluated and decided whether they should be excluded. Any exclusion from the PP population will be decided before breaking the blind.

In addition, the following sensitivity analyses may be performed.

- Exact logistic regression: The primary alternative hypothesis will also be tested using exact logistic regression (Mehta and Patel 1995). This model will include the treatment group (parsaclisib 2.5 mg QD and placebo) and stratification factors.
- Multiple imputation: A fully conditional specification method (van Buuren et al 2007) that assumes the existence of a joint distribution for all variables will be used to impute hemoglobin values. A regression model including treatment group, stratification factors, and baseline and postbaseline hemoglobin up to Week 24 will be specified for the fully conditional specification method. After the missing values are imputed, the binary variables will be derived based on the definition. The CMH tests will be applied to each imputed dataset, and then the results will be combined for the inference.
- Tipping point analysis: A tipping point analysis will be conducted to examine the potential effects of missing data. The missing binary response on primary endpoint in each treatment group will be replaced by a range of values from the most conservative case to the most aggressive case. The most conservative case is that all the missing participants in active treatment groups are nonresponders and all the missing participants in the placebo group are responders, while the most aggressive

case is the other way around. For each scenario, between-treatment comparisons will be performed using a chi-square test.

Subgroup analysis by baseline character, for example, age and region, will be performed.

10.3.2. Secondary Analysis

Key secondary efficacy analyses will be conducted in sequence for the ITT population. The gatekeeping testing strategy for the primary and key secondary analyses will be implemented to control the overall Type I error rate, 2-sided $\alpha = 0.05$. The key secondary endpoint, proportion of participants with a $\geq$ 3-point increase from baseline in FACIT-F score at Week 24, will be tested in a fixed sequence at 2-sided $\alpha = 0.05$ level only if the null hypothesis of the primary endpoint is rejected.

All other secondary [redacted] efficacy endpoints will be summarized using descriptive statistics. For categorical measurements, summary statistics will include sample size, frequency, and percentages. Similar models as specified in the primary analysis may be used. For continuous measurements, summary statistics, including sample size, mean, median, SD, standard error of the mean, minimum, and maximum, will be provided the actual measurement, change from baseline, and percentage change from baseline.

10.3.3. Safety Analyses

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

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE 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 14). Participants exhibiting clinically notable ECG abnormalities will be listed.

Table 14: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 460 ms	< 295 ms
PR	> 220 ms	< 75 ms
QRS	> 120 ms	< 50 ms
QT	> 500 ms	< 300 ms
RR	> 1330 ms	< 600 ms

QTcF = Fridericia correction.

Measures of exposure of parsaclisib will be summarized by means of summary statistics.

10.4. Interim Analysis

No formal interim analysis is planned in this study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol Amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator 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 this site until the regulatory approval of the study drug 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 his or her responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

11.2. Data Management

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

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the Protocol, such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and as designated by the sponsor, will have their own data flow management plans, study charters, [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, or sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed 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.

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Quality Assurance

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

Quality tolerance limits will be predefined in the IQRMP 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 (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

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

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

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

11.7. Study and Site Closure

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

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.

12. REFERENCES

Artz AS, Somerfield MR, Feld JJ, et al. American Society of Clinical Oncology provisional clinical opinion: chronic hepatitis B virus infection screening in patients receiving cytotoxic chemotherapy for treatment of malignant diseases. J Clin Oncol 2010;28:3199-3202.

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-117.

Barcellini W. New insights in the pathogenesis of autoimmune hemolytic anemia. Transfus Med Hemother 2015;42:287-293.

Barcellini W, Fattizzo B, Zaninoni A, et al. Clinical heterogeneity and predictors of outcome in primary autoimmune hemolytic anemia: a GIMEMA study of 308 patients. Blood 2014;124:2930-2936.

Barcellini W, Fattizzo B. Clinical applications of hemolytic markers in the differential diagnosis and Management of Hemolytic Anemia. Dis Markers 2015;2015:63567.

Berentsen S. Cold agglutinin disease. Hematology Am Soc Hematol Educ Program 2016;2016:226-231.

Birgens H, Frederiksen H, Hasselbalch HC, et al. A phase III randomized trial comparing glucocorticoid monotherapy versus glucocorticoid and rituximab in patients with autoimmune haemolytic anaemia. Br J Haematol. 2013;163:393-399.

Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009;113:4834-4840.

Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. J Pain Symptom Manage 2002;24:547-561.

Cheson BD. Death and clinical trials in the plague years. Accessed July 21, 2022. https://ascopost.com/issues/july-10-2022/death-and-clinical-trials-in-the-plague-years.

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

Coutré SE, Barrientos JC, Brown JR, et al. Management of adverse events associated with idelalisib treatment: expert panel opinion. Leuk Lymphoma 2015;56:2779-2786.

[redacted]

Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med 2021;385:1737-1749.

Jee J, Foote MB, Lumish M, et al. Chemotherapy and COVID-19 outcomes in patients with cancer. J Clin Oncol 2022;38:3538-3546.

Lechner K, Jäger U. How I treat autoimmune hemolytic anemias in adults. Blood 2010;116:1831-1838.

Lee CY, Shah MK, Hoyos D, et al. Prolonged SARS-CoV-2 infection in patients with lymphoid malignancies. Cancer Discov 2022;12:62-73.

Lyudovyk O, Kim JY, Qualls D, et al. Impaired humoral immunity is associated with prolonged COVID-19 despite robust CD8 T cell responses. Cancer Cell 2022;40:738-753.

Mehta CR, Patel NR. Exact logistic regression: theory and examples. Stat Med 1995;14:2143-2160.

Millum J, Grady C. The ethics of placebo-controlled trials: methodological justifications. Contemp Clin Trials 2013;36:510-514.

National Comprehensive Cancer Network. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: B-Cell Lymphomas Version 1.2020.

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

[redacted]

Shree T, Shankar V, Lohmeyer JJK, et al. CD20-targeted therapy ablates de novo antibody response to vaccination but spares preestablished immunity. Blood Cancer Discov 2022;3:95-102.

van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 2007;16:219-242.

Yellen SB, Cella D, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage 1997;13:63-74.

Zanella A, Barcellini W. Treatment of autoimmune hemolytic anemias. Haematologica 2014;99:1547-1554.

APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

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

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal with 1 of the following:[a]
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For male participants of reproductive potential[b]

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

- Use of a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
- Vasectomy with medical assessment of the surgical success (verified by site personnel's review of the participant's medical records)
- Sexual abstinence[c]
  - Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent (sexual abstinence is not approved in Japan).

The following are **not** acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, post ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method.
- Male condom with cap, diaphragm, or sponge with spermicide.
- Male and female condom used together.

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration (sexual abstinence is not approved in Japan).

For female participants who are WOCBP
The following methods during the Protocol-defined timeframe in Section 5.1 that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods: • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation.[d] – oral – intravaginal (administration route is not approved in Japan) – transdermal (administration route is not approved in Japan) • Progestogen-only hormonal contraception associated with inhibition of ovulation[d] (progesterone-only hormonal contraception is not approved in Japan, so this bullet and its sub-bullets will not apply for Japan) – oral – injectable – implantable[e] • Intrauterine device[e] • Intrauterine hormone-releasing system[e] • Bilateral tubal occlusion[e] • Vasectomized partner[e,f] • Sexual abstinence[c] (sexual abstinence is not approved in Japan).

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
[b] If the male participant has a partner with child-bearing potential the partner should also use contraceptives.
[c] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.
[d] It is unknown if hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method. Therefore, 2 methods of contraception should be used.
[e] Contraception methods that in the context of this guidance are considered to have low user dependency.
[f] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.
Source: Clinical Trials Facilitation and Coordination Group (2020).

APPENDIX B. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

The COVID-19 global pandemic is an evolving situation and presents numerous challenges to the ongoing conduct of clinical studies. The sponsor has issued the following Protocol considerations to ensure participant safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain.

Recognizing the flexibility required to manage the impact of the pandemic on this clinical study, additional details will be added as needed to respective study manuals and project plan documents and communicated to the investigative sites as needed.

Number of Study Participants

The evolving situation of the pandemic may result in a substantial number of participants' early dropout from the study, which could affect the data integrity of the study. Because of this risk and in order to mitigate it, the sponsor may decide to recruit additional participants in the study, beyond the expected number.

Study Visits

Remote Site Visit Guidelines:

In addition to the remote visits already specified in the Protocol, the evolving situation of the pandemic may require further travel restrictions and isolation requirements, or the investigator's benefit/risk assessment may determine it to be unsafe for participants to attend study visits at the investigational site. **Note:** Remote visits are not applicable in locations where remote visits are not permitted by local laws and/or regulations. In such cases, the site staff may elect to pursue the following:

- In order to minimize participant risk, study visits may be conducted via telemedicine modalities (phone or video calls). At a minimum, a review of AEs, concomitant medications, and study drug compliance must be completed. Periodic on-site visits should be conducted whenever feasible, in addition to the mandatory on-site visits outlined below.
- No efficacy assessments can be performed via telemedicine (video call, phone call, or via photography).
- Laboratory sampling: in order to support investigator oversight of participant safety and disease management, off-site laboratory sampling (in accordance with the SoA, see Table 3 and Table 4) may be allowed in 1 of 2 ways:
  - Use of home nursing services (unless not applicable by local laws and/or regulations).
  - Instruct the participant to undergo some laboratory tests at a local (nearby) hospital laboratory or facility closer to the participant's residence rather than at the investigational site. In this case, the study physician will provide the participant with the list of parameters to be checked. These tests should be performed at certified laboratories and copies of results provided to the site.

Mandatory On-Site Visits:

The visits outlined below **must be performed in person** in order to capture the investigator's efficacy assessments and the patient-reported outcomes, even if the date that the participant eventually comes into the clinic deviates from the visit window.

No efficacy assessments can be performed via telemedicine (video call, phone call, or photography).

The visit window deviation must be documented, and the sponsor's representative must be informed of when it is believed that the participant can come into the clinic. Further instructions will be provided if needed.

During the placebo-controlled period, the following visits must be performed in person:

- Screening
- Day 1 (Baseline)
- Week 12 visit
- Week 24 visit
- During the extension period, the following visits must be performed in person:
- Week 36 visit
- Week 48 visit

Investigational Medicinal Product Dispensation and Distribution

In order to ensure the continuity of providing their participants' clinical supplies within the constraints imparted by the pandemic, the site staff can decide to supply study drug via shipment to participants.

If the participant cannot attend a visit at the study site, adequate supplies of study drug determined by the investigator can be shipped to the participant by the investigator or appropriately delegated staff (eg, the study pharmacy staff) using a third-party service if duly authorized by the participant.

The study site may use their own preferred courier, provided the courier adheres to certain standards (eg, use of personal protection equipment, maintenance of temperature-controlled transit environment), or one centrally contracted by the sponsor.

Clinical Study Monitoring

Study monitoring visits may be postponed due to documented COVID-19–related reasons; however, the site monitor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, e-mails, video visits) with the sites to get information on study progress, subject status, and information on issue resolution. The study monitor may remotely review data entered into the EDC for accuracy and completeness. If allowed by local regulations, remote source data verification may be implemented with agreement of the principal investigator and institution, as applicable.

If the study site monitor cannot be on-site to perform the final drug accountability for reconciliation purposes and the operation cannot be postponed, it may be performed by a

pharmacist from the hospital pharmacy or by the study coordinator/data manager with suitable training. The study drug can be returned to the sponsor by the hospital pharmacy directly or destroyed in accordance with local practices, if applicable, and with sponsor approval.

Other Considerations

In case of need, participants may refer to the local health care provider. Participants will be requested to obtain certified copies of the source data at the local health facility with the outcome of the contact and provide those to the investigator for appropriate oversight. The investigator/delegate will be requested to enter any relevant information into the EDC.

Should COVID-19–related restrictions be localized and have an effect on a limited number of sites, the affected sites may use direct contracting of third parties to support continuous study conduct (eg, home nursing services, couriers, etc).

Reimbursement of Extraordinary Expenses

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

APPENDIX C. INSTRUCTIONS TO PARTICIPANTS FOR HANDLING STUDY DRUG

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

- Store study drug at room temperature (15°C-30°C/59°F-86°F).
- Keep study drug in a safe place and out of reach of children.
- Only remove the number of tablets needed at the time of administration.
- Do not remove doses in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed doses/lost tablets.
- Take study drug, preferably in the morning, with a full glass of water, without regard to food. Withhold drug self-administration for visits at Week 2, Week 8, Week 12, and Week 24, when the dose will be taken at the study site. The Day 1 dose will also be administered at the study site.
- If vomiting occurs after taking study drug, do not take another dose. The next scheduled dose should be taken at the usual time. If vomiting is persistent, contact the study site.
- Bring all used and unused study drug kits to the study site at each visit.
- If a dose is missed within the morning period, it is acceptable to take the dose within the same day (afternoon or evening). The next scheduled dose should occur at the usual time in the morning, unless required otherwise.

APPENDIX D. MANAGEMENT OF POTENTIAL HY'S LAW CASES

INTRODUCTION

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

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

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

DEFINITIONS

For the purpose of this process, definitions are as follows:

Potential Hy's Law

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

Hy's Law

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

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

Identification and Determination of Potential Hy's Law

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

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

Potential Hy's Law Criteria Not Met

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

- Perform follow-up on subsequent laboratory results according to the guidance provided in Section 6.5.

Potential Hy's Law Criteria Met

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

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

REVIEW AND ASSESSMENT

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

Evaluation of Alternative Causes

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

- Active viral hepatitis
- Alcoholic and autoimmune hepatitis

- Hepatobiliary disorders
  - Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if alkaline phosphatase is increased. Malignant interruption of the biliary tract also should be considered.
- Concomitant treatment
- Other causes such as systemic infections (eg, bacterial, fungal, viral), nonalcoholic steatohepatitis, and cardiovascular diseases

Actions After Review and Assessment

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

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

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

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

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

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

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

If the alternative cause for the previous occurrence of PHL was not due to the disease under study, please follow the process for PHL review and assessment as described in this appendix.

If the alternative cause for the previous occurrence of PHL was due to the disease under study:

- Determine whether there has been a significant change* in the participant's condition.
  - If there is no significant change, no action is required.
  - If there is a significant change, follow the process described for PHL review and assessment as described in this appendix.

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

APPENDIX E. CYP3A INHIBITORS AND INDUCERS

CYP3A inhibitors or inducers may alter parsaclisib concentration. These include, but are not limited, to the drugs listed below.

CYP3A Inhibitors

Inhibitor	Therapeutic Class
Potent CYP3A Inhibitors	
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
Moderate CYP3A Inhibitors	
erythromycin	Antibiotics

Inhibitor	Therapeutic Class
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
Weak CYP3A Inhibitors	
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

Inhibitor	Therapeutic Class
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
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

Inhibitor	Therapeutic Class
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

CYP3A Inducers

Inducers	Therapeutic Class
Potent Inducers	
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 Inducers	
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
Weak Inducers	
eslicarbazepine	Anticonvulsants
telaprevir	Antivirals
daclatasvir and asunaprevir and beclabuvir	Antivirals

Inducers	Therapeutic Class
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
Stribild	Treatments of AIDS
pioglitazone	Thiazolidinediones
VIEKIRA PAK	Antivirals

Inducers	Therapeutic Class
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

AIDS = acquired immunodeficiency syndrome; CETP = cholesteryl ester transfer protein; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; MAO-B = monoamine oxidase B; NNRTI = non-nucleoside reverse transcriptase inhibitor; RIT = ritonavir.

APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	18 AUG 2022
Amendment 2	10 MAY 2023

Amendment 2 (10 MAY 2023)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to reduce or eliminate protocol-required procedures and visits due to closure of study enrollment.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 2.2, Study Rationale; Section 4.1, Overall Design**

   Description of change: Added text regarding decision to close the study to further enrollment.

   Rationale for change: Due to the change in the regulatory landscape for PI3K inhibitors and the challenges in enrollment, a decision was made to close further enrollment into the study.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Table 3: Schedule of Activities (Double-Blind); Table 4: Schedule of Activities (Open-Label); Table 5: Schedule of Activities (Long-Term Extension); Section 4.1, Overall Design; Section 8, Study Assessments and Procedures; Section 8.2, Efficacy Assessments; Section 8.3, Patient-Reported Outcomes;** [redacted]

   Description of change: Added text regarding reduction or elimination of procedures pertaining to efficacy assessments, PROs, and collection of samples for [redacted].

   Rationale for change: To reduce study participation burden for ongoing participants.

3. **Section 1, Protocol Summary; Section 4.1, Overall Design**

   Description of change: Added text to allow participants randomized to placebo to receive parsaclisib before completing the 24-week double-blind treatment period.

   Rationale for change: To allow earlier access to active study treatment.

4. **Section 1, Protocol Summary; Table 4: Schedule of Activities (Open-Label); Section 4.1, Overall Design; Section 6.6, Treatment With Parsaclisib During Long-Term Extension; 7.1.2, Discontinuation Procedures; Section 8.10, Post-Treatment Follow-Up**

   Description of change: Revised post-treatment follow-up period to remove FUP2 and FUP3 visits and to clarify that only participants receiving parsaclisib are required to perform FUP1 after permanent discontinuation of study drug.

   Rationale for change: Given low number of participants enrolled, persistence of effect after discontinuation of parsaclisib will no longer be evaluated.

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

   Description of change: Clarified that participants must complete at least 2 months of treatment with parsaclisib before transition to the rollover protocol.

   Rationale for change: Clarification.

6. **Section 10, Statistics**

   Description of change: Added text to clarify that planned statistical analyses will no longer be applicable due to closure in enrollment and access to parsaclisib before completion of Week 24 in participants randomized to placebo.

   Rationale for change: Clarification.

7. **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 (18 AUG 2022)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to incorporate feedback from advisory board members, which includes the addition of a long-term extension for continued access to parscalisib, and to include prior Protocol Administrative Changes. This amendment also includes the changes from local adaptations for Germany (Version 1-DE) and France (Version 1-FR). Additional changes are summarized below.

1. **Title Page**

   Description of change: Added study acronym.

   Rationale for change: For completeness.

2. **Section 1, Protocol Summary, (Table 1: Primary and Secondary Objective Endpoints); Section 3, Objectives and Endpoints (Table 6: Objectives and Endpoints)**

   Description of change: Clarified that the key secondary object is to further evaluate the efficacy of parsaclisib.

   Rationale for change: For clarification.

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

   Description of change: Added the names of the coordinating principal investigators.

   Rationale for change: To update the coordinating principal investigator field in the table.

4. **Section 1, Protocol Summary, (Figure 1: Study Design Schema); Section 4.1, Overall Design**

   Description of change: Updated to explain when primary analysis would be conducted.

   Rationale for change: To be consistent with Section 10.3.1.

5. **Section 1, Protocol Summary, (Table 2: Key Study Design Elements; Figure 1: Study Design Schema; Table 4: Schedule of Activities [Open-Label]; Table 5: Schedule of Activities [Long-Term Extension]); Section 2.2.1, Scientific Rationale for Study Design; Section 2.2.2, Justification for Dose; Section 4.1, Overall Design; Section 4.2, Overall Study Duration; Section 6.6, Treatment With Parsaclisib During Long-Term Extension; Section 7.1.2, Discontinuation Procedures; Section 8.8, Long-Term Extension; Section 8.9, End of Treatment**

   Description of change: Added language describing a long-term extension phase of the study.

   Rationale for change: To provide continued access to parsaclisib following the 24-week open-label treatment period.

6. **Section 1, Protocol Summary, (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 4.1, Overall Design; Section 5.1, Inclusion Criteria (Criterion 2)**

   Description of change: Removed age requirement, ≥ 20 years, specified for study population enrolled in Japan.

   Rationale for change: Effective 01 APR 2022, the age of an adult participant in Japan changed from ≥ 20 years to ≥ 18 years; therefore, all adult participants will be ≥ 18 years of age.

7. **Section 1, Protocol Summary, (Table 2: Key Study Design Elements); Section 5.1, Inclusion Criteria (Criterion 5)**

   Description of change: Decreased the required hemoglobin value prior to randomization from ≥ 7.0 g/dL to ≥ 6.5 g/dL.

   Rationale for change: To identify participants who may require more frequent rescue therapy and; therefore, be in need of new treatment options.

8. **Section 1, Protocol Summary, (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 4.1, Overall Design; Section 10.1, Sample Size Determination**

   Description of change: Changed randomization to study treatment (parsaclisib or matching placebo) from a 1:1 ratio to a 2:1 ratio.

   Rationale for change: To increase the number of participants who will receive treatment with parsaclisib (approximately 67 vs 50 participants).

9. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 4.1, Overall Design**

   Description of change: Deleted region (North America vs non-North America) and added daily dose of corticosteroids at screening (≤ 20 mg/day vs >20 mg/day) as a stratification factor.

   Rationale for change: The randomization of participants from North American is expected to be low; therefore, stratifying by region was deemed unnecessary. Corticosteroid treatment plays an important role in the management of AIHA. Therefore, to prevent imbalance between treatment groups, the daily dose of corticosteroids at screening was added as a stratification factor.

10. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 4.1, Overall Design**

    Description of change: Added language noting Japan will require a minimum enrollment of participants as a regulatory requirement.

    Rationale for change: To ensure Japan meets the regulatory requirement of minimum enrollment even if enrollment in other countries may have ended.

[redacted]

12. **Section 1, Protocol Summary [Table 3: Schedule of Activities (Double-Blind)]; Section 8.1.5.1, Demographics and General Medical History**

    Description of change: A statement was added to indicate that demographic data will be collected as permitted by local regulations.

    Rationale for change: To clarify that collection of certain demographic data may not be permitted in some countries.

13. **Section 1, Protocol Summary (Table 3: Schedule of Activities [Double-Blind]; Table 4: Schedule of Activities [Open-Label]); Section 8.4.5, Laboratory Assessments (Table 11: Required Laboratory Analytes)**

    Description of change: Added test to monitor CMV.

    Rationale for change: In participants receiving parsaclisib, regular clinical and laboratory monitoring of CMV infections is recommended in participants with history of CMV infections or having positive CMV serology without associated signs of clinical CMV.

14. **Section 1, Protocol Summary (Table 3: Schedule of Activities [Double-Blind]);** [redacted]

    Description of change: [redacted]

15. **Section 1, Protocol Summary [Table 3: Schedule of Activities (Double-Blind); Table 4: Schedule of Activities (Open-Label)]; Section 8.4.1, Adverse Events; Section 8.4.5, Laboratory Assessments; Section 8.10, Post-Treatment Follow-Up; Appendix B, COVID-19 Pandemic Mitigation Strategies and Instructions**

    Description of change: Revised language to note that an in-office visit(s) would be required if the scheduled remote visit(s) is not permitted per local laws and/or regulations.

    Rationale for change: To acknowledge that remote visits may not be permitted in some countries.

16. **Section 1, Protocol Summary (Table 3: Schedule of Activities [Double-Blind];); Section 4.1, Overall Design; Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 9: Guidelines for Interruption and Restarting of Study Drug); Section 7.1.2, Discontinuation Procedures**

    Description of change: Added and revised language to clarify that all participants who permanently discontinue study drug will enter the post-treatment follow-up period.

    Rationale for change: For clarification.

17. **Section 1, Protocol Summary (Table 4: Schedule of Activities [Open-Label])**

    Description of change: Added D-dimer testing.

    Rationale for change: To continue monitoring participants for blood clotting conditions during the open-label treatment period.

18. **Section 1, Protocol Summary (Table 4: Schedule of Activities [Open-Label]); Section 8.10, Post-Treatment Follow-Up**

    Description of change: Changed designation of post-treatment follow-up visits from Week 52, Week 56, and Week 60 to FUP1, FUP2, and FUP3, respectively.

    Rationale for change: Participants can permanently discontinue study treatment at any time during the study; therefore, noting a particular week (ie, Week 52) for the post-treatment visits is not applicable.

19. **Section 2.2.1, Scientific Rationale for Study Design; Section 4.1, Overall Study Design; Section 5.2, Exclusion Criteria (Criterion 10b); Section 6.7.1.4, Corticosteroids; Section 6.7.2, Restricted Medications and Procedures**

    Description of change: Increased the allowed daily dose of corticosteroids prior to randomization and during the study from ≤ 20 mg/day to ≤ 40 mg/day.

    Rationale for change: To identify participants who require higher-dose steroids and; therefore, may benefit from a new treatment option, which may allow tapering and/or weaning off steroids.

20. **Section 2.2.1, Scientific Rationale for Study Design; Section 4.1, Overall Study Design; Section 7.1.1, Reasons for Discontinuation**

    Description of change: Deleted repetition of differing definitions of worsening wAIHA.

    Rationale for change: For clarification.

21. **Section 2.2.2, Justification for Dose**

    Description of change: Revised language regarding data, which support the selection of parsaclisib dose used in this study.

    Rationale for change: For clarification.

22. **Section 2.3, Benefit/Risk Assessment**

    Description of change: Modified section to delete preclinical and clinical data that are presented and will be annually updated in the parsaclisib IB. Added language regarding the effects of parsaclisib on the immune system and risks of serious infection events along with the pharmacological effect of concurrent corticosteroid use or recent rituximab therapy, which can contribute to further immunosuppression.

    Rationale for change: To avoid redundancy with information in parsaclisib IB and to provide informational language on the risks of immunosuppression given the changes in eligibility criteria, which increased the allowed corticosteroid daily dose and decreased the washout interval of previous treatment with rituximab.

23. **Section 3, Objectives and Endpoints (Table 6: Objectives and Endpoints)**

    Description of change: 1) Added language to a secondary objective endpoint to evaluate percent change from baseline in FACIT-F score at each postbaseline visit; [redacted]

    Rationale for change: 1) To allow for analysis of both change and percent change from baseline in FACIT-F score; 2) To allow for analysis of duration of hemoglobin response in all participants with a response; 3) [redacted]; therefore, analysis at Week 48 was deleted; and 4) To evaluate the persistence of effect after stopping treatment with parsaclisib.

24. **Section 4.1, Overall Study Design**

    Description of change: Added language to describe key eligibility criteria and efficacy assessments to be performed during the study.

    Rationale for change: For completeness of the study design.

25. **Section 5.1, Inclusion Criteria (Criterion 3)**

    Description of change: Added language to specify that results from DAT at screening is preferred and specified a timeframe for when previous DAT results would be acceptable.

    Rationale for change: Direct antiglobulin test results are necessary for confirmation of wAIHA diagnosis; therefore, a test through central laboratory is preferred for eligibility. However, due to hemolysis related to wAIHA or the analytical method, central laboratory results may not be available; therefore, a prior DAT result within 3 months of randomization was deemed acceptable since results would be reflective of current clinical picture.

26. **Section 5.1, Inclusion Criteria (Criterion 7b); Section 5.2, Exclusion Criteria (Criteria 5c, 10b, 10c, 10d, 10e, and 11); Section 6.7.1.4, Corticosteroids**

    Description of change: Updated references to Day 1 visits to randomization.

    Rationale for change: Randomization is expected to occur on Day 1; however, due to the location of the drug supply (eg, satellite pharmacy), the participant may not dosed until the next day.

27. **Section 5.1, Inclusion Criteria (Criteria 9 and 10)**

    Description of change: Added inclusion criteria specific to participants in France to indicate: COVID-19 vaccination is required at least 2 weeks prior to randomization (criterion 9) and requirements for up-to-date mandatory vaccinations according to the national vaccination program as assessed by the investigator (criterion 10).

    Rationale for change: Requested by France's Health Authority, ANSM.

28. **Section 5.2, Exclusion Criteria (Criterion 3)**

    Description of change: Added language to exclude participants with Evans syndrome.

    Rationale for change: To exclude participants that have accompanying thrombocytopenia.

29. **Section 5.2, Exclusion Criteria (Criterion 6); Section 8.4.5, Laboratory Assessments (Table 11: Required Laboratory Analytes)**

    Description of change: 1) Removed elevated anti-streptolysin antibodies as exclusionary and 2) Revised to exclude participants with known diagnosis of antiphospholipid syndrome or history of persistent anti-phospholipid antibodies and added language to allow randomization of participants at risk for thrombosis if receiving adequate prophylaxis and those with thrombosis if on stable treatment for 3 months prior to randomization

    Rationale for change: 1) The risk of elevated anti-streptolysin antibodies as a cause of AIHA is very rare; and 2) To allow participants deemed at low risk for either developing or worsening thrombosis to be randomized.

30. **Section 5.2, Exclusion Criteria (Criterion 10a)**

    Description of change: Changed the washout period for prior rituximab treatment from within 3 months to within 6 weeks of randomization.

    Rationale for change: Rituximab as treatment for wAIHA may show benefit within 6 weeks; therefore, the washout period was changed to allow participants not deriving benefit to be randomized.

31. **Section 5.2, Exclusion Criteria (Criterion 10e); Section 6.7.2, Restricted Medications and Procedures; Section 6.7.3, Prohibited Medications and Procedures**

    Description of change: Revised to ensure that moderate or potent inducers of CYP3A4 and potent inhibitors are included as prohibited medications.

    Rationale for change: Requested by the UK MHRA.

32. **Section 5.2, Exclusion Criteria (Criterion 18)**

    Description of change: 1) Added language to clarify that an AST result of ≥ 2 × ULN is exclusionary unless clearly related to active hemolysis; 2) Added language to specify eGFR will be estimated using 2021 CKD-EPI calculation; and 3) Corrected result parameter for WBCs.

    Rationale for change: 1) To allow participants whose AST elevations are associated with hemolysis and not due to hepatic etiology to be randomized; 2) To clarify the method used to calculate eGFR; and 3) Typographical error.

33. **Section 5.2, Exclusion Criteria (Criterion 18); Section 8.1.2, Screening Procedures; Section 8.4.5, Laboratory Assessments**

    Description of change: Added language to clarify that local laboratory test results may be used to confirm participant eligibility if the central laboratory is unable to perform the test due to hemolysis related to wAIHA or the analytical method.

    Rationale for change: To address the impact of hemolysis related to wAIHA on the laboratory test analysis.

34. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug**

    Description of change: Added language to clarify that the criteria for dose modifications are provided as guidelines and dose re-escalation is permitted after consultation with and approval by the sponsor medical monitor. Added a reference in the text to Appendix D for Hy's law case.

    Rationale for change: For clarification.

35. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 9: Guidelines for Interruption and Restarting of Study Drug)**

    Description of change: Clarified the grading of chemistry and hematology toxicity, and simplified actions to be taken in the event of AST and/or ALT elevations. In addition, removed language pertaining to action required for potential Hy's law cases.

    Rationale for change: For clarification.

36. **Section 6.5.2, Supportive Care for Diarrhea/Colitis**

    Description of change: Added language describing suggested clinical work-up in participants with diarrhea and/or colitis.

    Rationale for change: For consistency with parsaclisib IB.

37. **Section 6.5.3, Follow-Up for Immune-Related Adverse Events**

    Description of change: Revised language defining immune-related AEs.

    Rationale for change: For completeness of information consistent with the clinical development program of parsaclisib.

38. **Section 6.5.4, COVID-19**

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

    Rationale for change: Provided for informational purposes.

39. **Section 6.5.5, Criteria for Permanent Discontinuation of Study Drug**

    Description of change: Added language to further characterize unacceptable toxicity, which would meet criteria to permanently discontinue study drug.

    Rationale for change: For completeness of defining unacceptable toxicity consistent with Incyte's standard language for protocol template.

40. **Section 6.7.1.1, *Pneumocystis jirovecii* Pneumonia Prophylaxis**

    Description of change: Added text that requires investigators to actively determine if a participant has a known sulfa allergy.

    Rationale for change: Requested by the UK MHRA to ensure proper selection of PJP prophylaxis given reports of cross-sensitivity between sulfonamides and dapsone.

41. **Section 6.7.1.3, Vaccinations; Section 6.7.1.4, Corticosteroids; Section 6.7.2, Restricted Medications and Procedures**

    Description of change: Removed language regarding COVID-19 vaccinations from Section 6.7.2 and added Section 6.7.1.3, which is specific to vaccinations. In addition, language was provided to consult sponsor before administration of non-live vaccinations.

    Rationale for change: To clarify that COVID-19 vaccinations are permitted and when consultation with the sponsor is recommended.

42. **Section 6.7.1.4, Corticosteroids (Table 10: Tapering Guidelines for Corticosteroids); Section 6.7.2, Restricted Medications and Procedures**

    Description of change: Removed language regarding permitted corticosteroids from Section 6.7.2 and added Section 6.7.1.4, specific to corticosteroids. For Table 10, language was added to allow further tapering according to clinical judgement.

    Rationale for change: To clarify that corticosteroids are permitted and can be tapered at investigator discretion.

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

    Description of change: Deleted language regarding transfusions.

    Rationale for change: To clarify that transfusions are permitted as rescue treatment.

44. **Section 6.7.3, Prohibited Medications and Procedures; Section 6.7.4, Rescue Treatment**

    Description of change: Language regarding rituximab was removed from Section 6.7.4, revised, and added to Section 6.7.3.

    Rationale for change: To clarify that rituximab is a prohibited treatment.

45. **Section 6.7.4, Rescue Treatment**

    Description of change: A correction was made to indicate that rescue medication should be considered if there is a > 1 g/dL decrease in hemoglobin from the prior assessment. The documentation of time will not have to be recorded for administration of rescue medication.

    Rationale for change: To correct a typographical error and to specify a less prescriptive decrease in hemoglobin to allow for the clinical judgment of the investigator. Documentation of the date of rescue therapy administration is sufficient.

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

    Description of change: Revised language regarding access to continued treatment with parsaclisib after the completion of the study.

    Rationale for change: To clarify that parsaclisib will be provided either in a rollover study or through commercially available supplies, where applicable.

47. **Section 8.4.1, Adverse Events; Section 9.3, Recording and Follow-Up of Adverse Events and/or Serious Adverse Events; Section 9.4, Reporting of Serious Adverse Events**

    Description of change: Revised to note that SAE reporting must happen immediately in Germany.

    Rationale for change: Requested by Germany's Health Authority, BfArM.

48. [redacted]

    Description of change: [redacted]

    Rationale for change: For clarification.

49. **Section 9.5, Events of Clinical Interest**

    Description of change: Added language regarding ECI consistent with the clinical development program of parsaclisib.

    Rationale for change: To ensure organized documentation of ECIs for the sponsor’s monitoring and understanding.

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

    Description of change: Added language regarding emergency unblinding if an AE requires the investigator to be made aware of the participant's treatment assignment.

    Rationale for change: Requested by the UK MHRA.

51. **Section 9.10, Treatment of Overdose**

    Description of change: Added language regarding treatment of overdose.

    Rationale for change: For consistency with Incyte's standard language for clinical protocols.

52. **Section 10.1, Sample Size Determination**

    Description of change: Added language describing type of randomization.

    Rationale for change: Requested by France's Ethics Committee.

53. **Section 10.2, Populations for Analysis (Table 13: Population for Analysis)**

    Description of change: Corrected 'applied 'to 'received' with regard to study treatment.

    Rationale for change: Typographical error

54. **Section 10.3.1, Primary Analysis**

    Description of change: Corrected language describing study treatment and updated the major deviations defining the PP population. In addition, 'disease type' was deleted as a factor for subgroups analyses.

    Rationale for change: To correct a typographical error which listed the incorrect concentration and frequency. For the PP population, to clarify the missing endpoint and include the use of prohibited medications or procedures. Only participants with wAIHA will be randomized; therefore, 'disease type' should not be included.

55. **Section 10.3.1, Primary Analysis; Section 10.4, Interim Analysis**

    Description of change: Removed language regarding primary analysis from Section 10.4 and added to Section 10.3.1. In addition, language regarding unblinding was removed from Section 10.4.

    Rationale for change: For clarification.

56. **Section 11.3, Data Quality Assurance; Section 11.4, Data Privacy and Confidentiality of Study Records**

    Description of change: Revised and added language regarding data management, data quality, and data privacy and protection.

    Rationale for change: To be consistent with Incyte's standard language for clinical protocols.

57. **Appendix A, Information Regarding Effectiveness Of Contraceptive Methods And Definitions**

    Description of change: Revised footnote "d" to clarify that it is unknown if hormonal contraception interacts with the investigational medicinal product and as a result may reduce the efficacy of the contraception method; therefore, 2 methods of contraception should be used.

    Rationale for change: Requested by the UK MHRA.

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

    Description of change: The Week 52 visit was replaced with a Week 48 visit as a mandatory visit.

    Rationale for change: Week 48 is the end of the open-label treatment period and therefore, is a mandatory visit.

59. **Appendix C, Instructions to Participants for Handling Study Drug**

    Description of change: Corrected the visits at which participants will withhold self-administration of study drug [redacted].

    Rationale for change: To correct typographical error and maintain consistency with the [redacted] section(s) of the Protocol.

60. **Appendix E, CYP3A4 Inhibitors and Inducers**

    Description of change: Added medications known to be inhibitors and inducers of CYP3A4.

    Rationale for change: Provided for informational purposes.

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

Signature Page for VV-CLIN-014098 v5.0

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

Signature Page for VV-CLIN-014098 v5.0