Official Title: A Phase 2, Multicenter, Open-Label Study of Parsaclisib, a PI3Kδ Inhibitor, in Japanese Participants With Relapsed or Refractory Follicular Lymphoma (CITADEL-213)

NCT Number: NCT04434937

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Clinical Study Protocol

INCB 50465-213

A Phase 2, Multicenter, Open-Label Study of Parsaclisib, a PI3Kδ Inhibitor, in Japanese Participants With Relapsed or Refractory Follicular Lymphoma

(CITADEL-213)

Product:	**INCB050465**
Phase of Study:	**2**
Sponsor:	**Incyte Biosciences Japan GK 1-1-2 Yurakucho Chiyoda-ku Tokyo 100-0006, Japan**
Original Protocol:	**07 APR 2020**
Amendment 1 (Version 2):	**25 JUN 2020**
Amendment 2 (Version 3):	**19 MAY 2021**
Amendment 3 (Version 4):	**07 OCT 2022**
Amendment 4 (Version 5):	**24 JAN 2023**

INVESTIGATOR'S AGREEMENT

I have read the INCB 50465-213 Protocol Amendment 4 (dated 24 JAN 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)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
CI	confidence interval
[redacted]	[redacted]
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CR	complete response
CRR	complete response rate
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
[redacted]	[redacted]
[redacted]	[redacted]
FAS	full analysis set
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HBs	hepatitis B surface antibody

Abbreviations and Special Terms	Definition
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HPF	high-powered field
[redacted]	[redacted]
HSCT	hematopoietic stem cell transplantation
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 Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
irAE	immune-related adverse events
IRB	institutional review board
IRC	independent review committee
IV	intravenously
IWRS	interactive web response system
J-GCP	Japan Good Clinical Practice
LD	longest dimension
LDi	longest dimension transverse diameter of lesion
LPD	longest perpendicular dimension
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging
MZL	marginal zone B-cell lymphoma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NHL	non-Hodgkin Lymphoma
ORR	objective response rate
OS	overall survival
PD	progressive disease

Abbreviations and Special Terms	Definition
PET	positron emission tomography
PFS	progression-free survival
PI3Kδ	phosphoinositide 3-kinase delta
PJP	*Pneumocystis jiroveci* pneumonia
PK	pharmacokinetic
PMD	progressive metabolic disease
PMDA	Pharmaceuticals and Medical Devices Agency
PP	per Protocol
PPD	cross-product of the longest transverse diameter and perpendicular diameter
PR	partial response
QD	once daily
QW	once weekly
R-chemo	rituximab + chemotherapy
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
RNA	ribonucleic acid
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCT	stem cell transplantation
SD	stable disease
SDi	shortest axis perpendicular to the longest transverse diameter
SoA	schedule of activity
SOP	standard operating procedure
SPD	sum of the product of the perpendicular diameters for multiple lesions
SUSARs	suspected unexpected serious adverse reaction
SUV_{max}	maximum standardized uptake value
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
[redacted]	[redacted]

1. PROTOCOL SUMMARY

Protocol Title: A Phase 2, Multicenter, Open-Label Study of Parsaclisib, a PI3Kδ Inhibitor, in Japanese Participants With Relapsed or Refractory Follicular Lymphoma (CITADEL-213)

Protocol Number: INCB 50465-213

Objectives and Endpoints:

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

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of parsaclisib in terms of ORR in participants with relapsed or refractory FL.	ORR, defined as the percentage of participants with a CR or PR as defined by revised response criteria for lymphomas (Cheson et al 2014), as determined by an IRC.
Key Secondary	
To assess CRR.	CRR, defined as the percentage of participants with a CR as defined by revised response criteria for lymphomas (Cheson et al 2014), as determined by an IRC.
To assess DOR.	DOR, defined as the time from first documented evidence of CR or PR until disease progression or death from any cause among participants who achieve an objective response, as determined by radiographic disease assessment provided by an IRC.
To assess PFS.	PFS, defined as the time from the date of the first dose of study treatment until the earliest date of disease progression, as determined by radiographic disease assessment provided by an IRC, or death from any cause.
To assess OS.	OS, defined as the time from the date of the first dose of study treatment until death from any cause.
To assess best percentage change in target lesion size.	Best percentage change in target lesion size from baseline, where target lesion size is measured by the sum of the product of the diameters of all target lesion sizes.
To characterize the safety and tolerability of parsaclisib.	Safety and tolerability assessed by monitoring the frequency and severity of AEs; includes performing physical examinations and collecting vital signs, 12-lead ECGs, and clinical laboratory data.

Overall Design:

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

Table 2: Key Study Design Elements

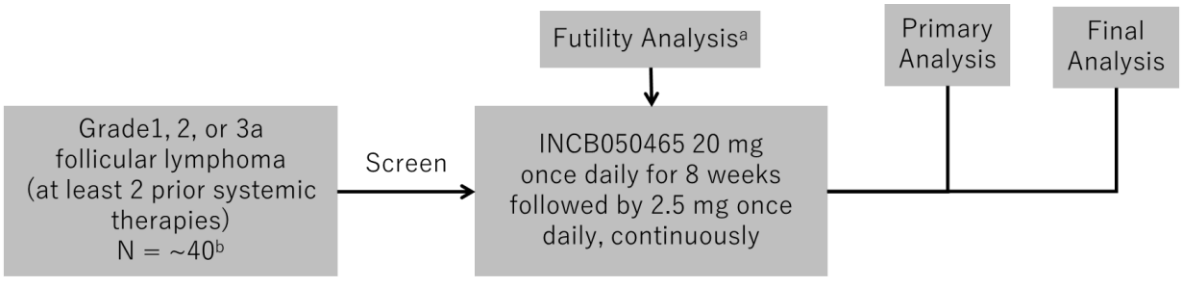
Study Phase	Phase 2
Clinical Indication	Relapsed or refractory FL
Population	Male and female Japanese participants at least 18 years of age who have relapsed or refractory FL (Grade 1, 2 or 3a) with disease progression after 2 or more prior systemic therapies
Number of Participants	Approximately 40 participants with history of 2 or more lines of treatment will be enrolled. Approximately 18 participants should have history of ASCT.
Study Design	Single arm, open-label Participants will receive parsaclisib 20 mg QD for 8 weeks followed by 2.5 mg QD. Participants will be evaluated for ORR by an IRC and followed for CRR, DOR, PFS, OS, and safety. Participants may receive treatment until disease progression, death, unacceptable toxicity, or consent withdrawal. An interim futility analysis is planned when the first 20 participants have been evaluated for response or have been followed for at least 9 weeks or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. Enrollment will continue during the interim futility analysis. The study will be terminated for futility if ≤ 7 of the 20 participants have responded (ie, CR or PR) based on assessments provided by the IRC; otherwise the study will continue. A timely assessment of response will be performed to avoid the risk of overenrollment.
Estimated Duration of Study Participation	Up to 28 days for screening, continuous treatment as long as participants are receiving benefit and have not met any criteria for study treatment withdrawal, 30 to 35 days for safety follow-up, and disease and survival follow-up until the end of the study. It is estimated that an individual will participate for an average of approximately 16 months, which includes each period mentioned above.
IDMC	Yes (external)

Treatment Groups and Duration:

This is a Phase 2, multicenter, open-label study evaluating parsaclisib treatment based on the primary endpoint of ORR. The study treatment will be administered orally. Participants may receive treatment until disease progression, death, HSCT (if become eligible) or unacceptable toxicity, or consent withdrawal.

Figure 1 presents the study design schema.

Figure 1: Study Design Schema



[a]An interim futility analysis is planned when the first 20 participants have been evaluated for response, have been followed for at least 9 weeks, or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death.
[b]Approximately 18 participants with history of ASCT will be involved.

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

Table 3: Schedule of Activities

Procedure	Screening	Treatment			EOT	Follow-Up			Notes and Protocol Section
						Safety	Disease	Survival	
	Day –28 to –1	Day 1*	Every 4 Weeks Through Week 48 (± 3 Days)	Every 12 Weeks From Week 48 (± 1 Week)		EOT +30-35 Days		Every 12 Weeks (± 1 Week) after EOT	*All procedures are to be performed before administration of study treatment.
Informed consent	X								Section 8.1.1.
Contact IWRS	X	X	X	X	X				Section 8.1.3.
Inclusion & exclusion criteria	X	X							Section 5.1, Section 5.2.
Demography and medical history	X								Section 8.1.5.
[redacted]									
Prior/concomitant medications	X	X	X	X	X	X			Section 6.6.
AE assessment	X	X	X	X	X	X			Section 8.3.1.
Comprehensive physical exam	X*				X				*Height required at screening only, Section 8.3.2.
Disease-specific physical exam		X	X	X		X			
Vital signs	X	X	X	X	X	X			Section 8.3.3.
12-lead ECG	X	X	X*	X*	X	X			*Week 4, Week 12, and every 12 weeks thereafter. Section 8.3.4.
ECOG status	X	X	X	X	X	X			Section 8.3.5.

Table 3: Schedule of Activities (Continued)

Procedure	Screening	Treatment			EOT	Follow-Up			Notes and Protocol Section
	Day –28 to –1	Day 1*	Every 4 Weeks Through Week 48 (± 3 Days)	Every 12 Weeks From Week 48 (± 1 Week)		Safety EOT +30-35 Days	Disease	Survival Every 12 Weeks (± 1 Week) after EOT	*All procedures are to be performed before administration of study treatment.
CT/MRI scan	X		Every 8 weeks through Week 24 (± 1 week), then every 12 weeks through Week 96, and then every 24 weeks thereafter until PD.				X*		*Only for participants who discontinue study treatment for reasons other than disease progression. Will continue to be performed per assessment schedule (every 8, 12, 24 weeks as appropriate) until disease progression, start of new anti-lymphoma therapy, withdrawal of consent, end of the study, or death, whichever occurs first. Section 8.2.1.
Bone marrow exam	X		X*	X*			X*		Required at baseline except if participant had a bone marrow exam per standard of care within ~60 days of first dose or had a previous exam after the last therapy. *If disease is present in bone marrow at baseline, a bone marrow biopsy is required to confirm CR. Section 8.2.2.
FDG-PET	X								Only for participants who submit earlier archived lymph nodes or tissue biopsies instead of newly obtained samples after the previous therapy. If FDG-PET assessment was performed as standard of care before signing of the ICF, but within 28 days of Day 1, then the results from that assessment can be used.
PJP prophylaxis		X							PJP prophylaxis will continue for 2 to 6 months after the last dose of study treatment. Section 6.6.1.

Table 3: Schedule of Activities (Continued)

Procedure	Screening	Treatment			EOT	Follow-Up			Notes and Protocol Section
	Day –28 to –1	Day 1*	Every 4 Weeks Through Week 48 (± 3 Days)	Every 12 Weeks From Week 48 (± 1 Week)		Safety EOT +30-35 Days	Disease	Survival Every 12 Weeks (± 1 Week) after EOT	*All procedures are to be performed before administration of study treatment.
Study drug dispensing		X	X	X					Section 8.1.3.
Study drug compliance		X	X	X	X				Section 6.4.
Study drug administration at site		X	X						[redacted] Day 1, Week 4, and Week 12. Section 8.4.
Disease follow-up							X		Only for participants who discontinue study treatment for reasons other than disease progression. Section 8.8.2.
Survival follow-up								X	May be conducted by phone or email. Section 8.8.3.

Table 4: Schedule of Laboratory Assessments

Laboratory Tests	Screening	Treatment				EOT	Safety Follow-Up	Notes and Protocol Section
	Day –28 to –1	Day 1	Week 2 and Week 6 (± 3 Days)	Every 4 Weeks Through Week 48 (± 3 Days), (Week 4 included)	Every 12 Weeks From Week 48 (± 1 Week)		EOT + 30-35 Days	
Serum chemistries	X	X*		X	X	X	X	*Day 1 assessments may be omitted if the screening tests occurred in the preceding 7 days. If needed, Day 1 blood draws should be performed before administration of study treatment. Section 8.3.6.1.
Hematology	X	X*	X	X	X	X	X	
Serology	X			X*	X*	X*		*Samples for CMV DNA analysis only. Section 8.3.6.3.
Serum pregnancy	X					X	X	Only for females of childbearing potential; negative pregnancy test must be obtained within 14 days before administration of study treatment. Section 8.3.6.2.
Urine pregnancy				X	X			
HIV testing	X							Section 8.3.6.
[redacted]								

Table 4: Schedule of Laboratory Assessments (Continued)

Laboratory Tests	Screening	Treatment				EOT	Safety Follow-Up	Notes and Protocol Section
	Day –28 to –1	Day 1	Week 2 and Week 6 (± 3 Days)	Every 4 Weeks Through Week 48 (± 3 Days), (Week 4 included)	Every 12 Weeks From Week 48 (± 1 Week)		EOT + 30-35 Days	
Tumor biopsy	X			X*		X*		Participants must be willing to undergo an incisional, excisional or core needle lymph node or tissue biopsy or provide a lymph node or tissue biopsy after completion of the last therapy. *An optional biopsy at Week 4 and is encouraged. A lymph node or tissue biopsy is strongly encouraged at time of progression OR at time of relapse following response of PR or better. Tumor biopsy is not mandatory for participants who submit earlier archived lymph nodes or tissue biopsies. Section 8.5.3.

2. INTRODUCTION

2.1. Background

2.1.1. Follicular Lymphoma

Non-Hodgkin lymphoma is the most common hematologic malignancy, with over 385,000 new cases diagnosed in 2012 (Torre et al 2015). Follicular lymphoma, a subtype of NHL, is the second most prevalent form of NHLs overall, accounting for approximately 1 in 5 cases of NHL, and is the most common form of indolent (slow-growing) NHLs. More than 75,000 people are estimated to be diagnosed with FL annually worldwide (Shankland et al 2012).

Follicular lymphoma is defined as a lymphoma of germinal center B cells, including centrocytes and centroblasts, that has at least a partially follicular pattern. These bone marrow–derived cells undergo somatic hypermutation and class switching of the B-cell receptors, which leads to immunoglobulin diversity and selects B cells that produce high-affinity antibodies (Kahl and Yang 2016). Central to the early transformation and pathophysiology of FL is the t(14;18)(q32;18) translocation found in approximately 90% of FL and that leads to overexpression of BCL2 (Pastore et al 2015). Follicular lymphoma is also positive for the B-cell markers CD10, CD19, CD22, and usually CD20 but is always negative for CD5 (Barekman et al 2001).

The 2008 WHO classification system (Swerdlow et al 2016) divides FL into grades based on the proportion of centrocytes to centroblasts. Cases with more centroblasts tend to be more aggressive and are more likely to transform in to diffuse large-cell lymphoma (Kahl and Yang 2016). Grade 1 is defined as 0 to 5 centroblasts per HPF, Grade 2 is 6 to 15 centroblasts per HPF, and Grade 3 is > 15 centroblasts per HPF. Grade 3 can be subclassified into 3a and 3b, with the latter distinguished by an absence of centrocytes. FL3b appears to be biologically distinct compared with the other grades, with frequent absence of both t(14;18) and CD10 expression and increased p53 and MUM1/IRF4 expression. FL3b is commonly treated according to the treatment recommendations for DLBCL (NCCN 2020).

Although FL is a biologically heterogeneous disease with widely varying outcomes, the prognosis for individual patients can be made based on clinical and laboratory findings. The most widely used risk model for FL is the FLIPI, which includes 5 adverse prognostic factors: age older than 60 years, Ann Arbor Stage III to IV, hemoglobin less than 120 g/L, 4 or more involved nodal areas, and elevated serum lactate dehydrogenase (Solal-Céligny et al 2004; Appendix E). Following treatment, patients can be assessed for MRD, which refers to the small number or cancer cells that might remain after treatment and which may lead to relapse.

While effective treatments exist for FL, relapse is frequent and is followed by aggressive disease often leading to death within 1 to 2 years. Based on an analysis of 588 patients receiving R-CHOP as initial FL therapy, approximately 20% of patients experienced early PD, defined as PD within 2 years of diagnosis. The 5-year OS was 50% in the early PD group compared with 90% in patients without early PD (Casulo et al 2015). Thus, despite significant progress in the management of patients with FL, an unmet need exists.

2.1.2. Treatment of Follicular Lymphoma

Some patients with early stage FL (Ann Arbor Stage I or II) who develop symptoms may be treated with radiation therapy alone. Advanced stage (Ann Arbor Stage III-IV), Grade 1 to 3a FL is often treated according to the degree of tumor burden (low versus high) and the presence or absence of FL symptoms (eg, fever, night sweats, unexplained weight loss, etc). Asymptomatic patients with a low tumor burden may be candidates for watchful waiting, whereas those with a high tumor burden may receive R-chemo. Symptomatic patients with a low tumor burden may receive either single-agent rituximab or R-chemo, whereas patients with a high tumor burden may receive R-chemo with or without maintenance rituximab. Although the majority of patients will respond to these first-line therapies, the natural history of FL is characterized by continuous relapse (Izutsu 2019).

There are several options for patients with FL that relapse after initial treatment (Kahl and Yang 2016). Recent new option for relapsed FL is PI3K inhibitors. The PI3Kδ inhibitor idelalisib was approved for the treatment of patients in the United States with relapsed follicular B-cell NHL who have received at least 2 prior systemic therapies. The PI3K inhibitor copanlisib and duvelisib were also approved in the Unites States for the same patient population in September of 2017 and September of 2018, respectively (Aliqopa® 2020, Copiktra® 2019). Idelalisib was approved in the European Union for the treatment of adult patients with FL that is relapse or refractory to 2 prior lines of treatment. However, idelalisib, copanlisib, and duvelisib are not approved in Japan. The relapsed patient population is currently underserved by the available approved therapies in many countries and, like the double-refractory to rituximab (monotherapy or in combination) and to either chemotherapy or radioimmunotherapy population, represents an unmet medical need. This is especially true in patients that are ineligible for HSCT and relapse after high dose chemotherapy followed by ASCT and allogeneic SCT. To address the unmet medical need of these populations, and to enroll the study in a timely fashion, the study will allow participants who have either relapsed or refractory disease after at least 2 prior systemic therapies and who are ineligible for HSCT.

2.1.3. Parsaclisib

Phosphatidylinositol 3-kinases belong to a family of lipid signaling kinases that phosphorylate phosphoinositides of the inositol ring (Cantley 2002). Phosphatidylinositol 3 kinases are divided into 3 classes (Class I, II, and III) according to their structure, regulation, and substrate specificity. Class I PI3Ks, which include PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ, are dual-specificity lipid and protein kinases that catalyze the phosphorylation of phosphatidylinositol-4,5-bisphosphate, giving rise to phosphatidylinositol-3,4,5-trisphosphate. Phosphatidylinositol-3,4,5-trisphosphate functions as a second messenger that controls a number of cellular processes, including growth, survival, adhesion, and migration. The recognition that aberrant signal transduction occurs in malignant B-lymphocytes via the PI3K pathways resulting in disease progression has led to a focus on agents that modulate these signaling pathways.

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. Parsaclisib does not significantly inhibit (< 30% inhibition) a broad panel of kinases when tested at a concentration of 100 nM (refer to the parsaclisib IB). Parsaclisib is potent (IC_{50} values of ≤ 10 nM) in cell-based assays relevant to the pathogenesis of B-cell malignancies, such as PI3Kδ-mediated signaling and

growth of human B-cell lines. This effect is not due to general cytotoxicity. Compared with inhibition of B-cell proliferation, parsaclisib is similarly potent in blocking helper T-cell differentiation but is > 100 times less potent in assays that measure effects on human T-cell and natural killer cell proliferation or monocyte function. These data suggest that the impact of parsaclisib on the human immune system will largely be restricted to B-cell and helper T-cell differentiation. The IC_{90} for pAKT inhibition of Pfeiffer cells in human whole blood is 77 nM. Preclinical toxicology studies supported evaluation of parsaclisib in human clinical studies (parsaclisib IB).

A Phase1/2, dose-escalation and expansion study, INCB 50465-101, demonstrated the vast majority (93%) of responses occurred by the first assessment (~9 weeks) in participants with relapsed or refractory B-cell lymphoma who received parsaclisib monotherapy. The most common (≥ 30%) any-grade nonhematologic TEAEs in monotherapy patients were diarrhea/colitis (36%), nausea (36%), fatigue (31%) and rash (31%). Grade 3/4 neutropenia occurred in 19% of patients (Forero-Torres et al 2019). Refer to the parsaclisib IB for further details.

2.2. Study Rationale

This study is designed to evaluate the ORR of parsaclisib in participants with relapsed or refractory FL who have received at least 2 prior systemic therapies and who are ineligible for HSCT. Currently no PI3K inhibitor is approved in Japan and consequently there is not a relevant comparator for new PI3K inhibitors. Study INCB 50465-213 will therefore evaluate only parsaclisib.

2.2.1. Scientific Rationale for Study Design

Overall and CRRs usually can be assessed accurately in single-arm as well as randomized studies. Response rates are not considered as important as other endpoints except Phase 2 studies of novel new agents, in which identification of biologic activity is of interest (Cheson et al 2007). Incorporation of IRC aims to improve objectivity and reliability of clinical data that might be participant to observer bias and variability (Amit et al 2011). Overall survival and PFS will be assessed as secondary endpoints as well.

2.2.2. Justification for Dose

Parsaclisib will be self-administered at a dose of 20 mg QD for 8 weeks, followed by a dose of 2.5 mg QD until disease progression, death, HSCT (if become eligible), unacceptable toxicity or consent withdrawal. Based on an ex vivo whole blood assay, the 20 mg QD dose provides exposure ranging from approximately 2-fold above the IC_{90} at trough to 19-fold above the IC_{90} at peak. Furthermore, in the Phase1 Study INCB 50465-101 (Forero-Torres et al 2019) and 3 Phase 2 studies of participants with relapsed or refractory B-cell malignancies, the majority of participants who received this daily dosing regimen and achieved a tumor response did so at the first disease assessment (parsaclisib IB and Incyte unpublished data).

In the Japanese Phase1b dose-escalation Study INCB 50465-111, 14 participants received assigned cohort dose of 20 mg QD out of 17 participants) for 8 weeks followed by 20 mg QW. The AE profiles and PK parameters are comparable with Study INCB 50465-101.

The continuation of parsaclisib at a daily, but lower, dose (2.5 mg) is proposed to provide enough exposure (estimated to be approximately 1 × IC_{90} at peak) to maintain PI3K pathway inhibition while minimizing the frequency of late-onset AEs that may lead to study treatment withdrawal. Evaluation of this dosing regimen is ongoing in 3 Phase 2 studies in participants with FL (INCB 50465-203), MZL (INCB 50465-204), and mantle cell lymphoma (INCB 50465-205). These studies are done outside of Japan. Preliminary data from participants with FL receiving this regimen suggest that the continuous QD dosing has demonstrated benefits in both aggressive and indolent NHL. The emerging safety profile is consistent with that known for parsaclisib. Detail of dose modification is described in Section 6.5.

2.3. Benefit/Risk Assessment

Previous 2 Phase 1 studies, INCB 50465-101 and INCB 50465-111 suggested clinical efficacy of parsaclisib on participants with relapse and refractory FL. In Japanese Study INCB 50465-111, 9 of the 9 treated participants with FL had investigator-assessed CR or PR. Parsaclisib is expected to have reversible effects on immune function. Combined inhibition may adversely affect both B-cell and T-cell immune function with resultant increased risk of a variety of infections, including PJP, CMV, and COVID-19. PI3K inhibitors are known to be associated with diarrhea/colitis, pneumonitis, severe cutaneous reactions, and neutropenia. Similar events were observed on the INCB 50465-101 study and 50465-111 study. We expect to see the consistent efficacy and manageable AE with revised dosing regimen. Also, given the similar PK parameters on parsaclisib in Japanese vs non-Japanese participants, we would expect similar results of INCB 50465-203 study. 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 5 presents the objectives and endpoints.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of parsaclisib in terms of ORR in participants with relapsed or refractory FL.	ORR, defined as the percentage of participants with a CR or PR as defined by revised response criteria for lymphomas (Cheson et al 2014), as determined by an IRC.
Secondary	
To assess CRR.	CRR, defined as the percentage of participants with a CR as defined by revised response criteria for lymphomas (Cheson et al 2014), as determined by an IRC.
To assess DOR.	DOR, defined as the time from first documented evidence of CR or PR until disease progression or death from any cause among participants who achieve an objective response, as determined by radiographic disease assessment provided by an IRC.
To assess PFS.	PFS, defined as the time from the date of the first dose of study treatment until the earliest date of disease progression, as determined by radiographic disease assessment provided by an IRC, or death from any cause.
To assess OS.	OS, defined as the time from the date of the first dose of study treatment until death from any cause.
To assess best percentage change in target lesion size.	Best percentage change in target lesion size from baseline, where target lesion size is measured by the sum of the product of the diameters of all target lesion sizes.
To characterize the safety and tolerability of parsaclisib.	Safety and tolerability assessed by monitoring the frequency and severity of AEs; includes performing physical examinations and collecting vital signs, 12-lead ECGs, and clinical laboratory data.

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, multicenter, open-label study evaluating parsaclisib treatment based on the primary endpoint of ORR. Participants with relapsed or refractory FL (Grades 1, 2, or 3a) who have received at least 2 prior systemic therapies and who are ineligible for HSCT will be screened for eligibility. A total of approximately 40 participants will be enrolled. The study treatment will be administered orally. Participants will be evaluated for ORR by an IRC and followed for CRR, DOR, PFS, OS, and safety.

Participants may receive treatment until disease progression, death, HSCT (if become eligible) or unacceptable toxicity, or consent withdrawal. An interim futility analysis is planned when the first 20 participants have been treated and evaluated for response or have been followed for at least 9 weeks or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. The study will be terminated for futility if ≤ 7 of the 20 participants have responded (ie, CR or PR) based on assessments provided by the IRC; otherwise the study will continue. A timely assessment of response will be performed to avoid the risk of overenrollment. An IDMC will review safety data periodically as stated in the DMC charter.

After treatment discontinuation, participants will be followed for safety and survival. Participants who have discontinued study treatment due to reasons other than disease progression will be followed for either radiologic disease progression, the start of a new anti-lymphoma therapy, or death, whichever comes first. It is expected that the final analysis will occur no later than 2 years after the first dose of parsaclisib is administered to the last participant treated.

4.2. Overall Study Duration

The study begins when the first participant signs the ICF.

The end of the study (Section 8.9) will occur when all participants have discontinued from the study (see Section 7) **or** have completed at least 12 months of study participation (starting from the first dose of study treatment). It is estimated that the study will take approximately 1.0 year to accrue 40 participants, and that the final analysis will be performed no later than 2 years after the first dose of study treatment is administered to the last participant treated. If by the end of the study there remains at least 1 participant still on study treatment for at least 12 months, the participant(s) may continue treatment. At this point, a database lock of the study may occur to allow the analysis of the study data. See Section 6.7 for treatment after the end of the study.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator/head of study site 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 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 IDMC. If the study is terminated prematurely, the sponsor will notify the investigators/head of the study site, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study. The IDMC will recommend termination of the study if warranted, as described in IDMC charter.

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. Male or female Japanese participant who must be ≥ 18 years of age at the time of signing the ICF.
2. Ability to comprehend and willingness to sign a written ICF and comply with all study visits and procedures.

   Note: For participants under 20 years old, those whose parent/legal guardian is willing/able to comply with study requirements and understand/sign the ICF. Participants themselves must sign the ICF form.
3. Histologically confirmed, relapsed or refractory, FL Grade 1, 2, and 3a.
4. Ineligible for HSCT.
5. Must have been treated with at least 2 prior systemic therapies for FL.
6. Radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures > 1.5 cm in the LD and ≥ 1.0 cm in the LPD, respectively) as assessed by CT or MRI.
7. Participants must be willing to undergo an incisional, excisional, or core needle lymph node or tissue biopsy or provide a lymph node or tissue biopsy collected after the completion of last therapy. An earlier archived lymph node or tissue biopsy is acceptable if hospitalization is required for biopsy (eg, no superficial lymph node) and SUV_{max} by FDG-PET is < 14.
8. ECOG performance status 0 to 2.
9. Life expectancy ≥ 12 weeks.

10. Adequate hematologic, hepatic, and renal function (values must not be achieved with growth factors):
    a. ANC $\geq 1.0 \times 10^9$/L.
    b. Hemoglobin ≥ 8.0 g/dL.
    c. Platelet count $\geq 50 \times 10^9$/L.
    d. Total bilirubin $\leq 1.5 \times$ ULN. Participants with documented history of Gilbert's syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible.
    e. ALT/AST $\leq 2.5\times$ ULN or $\leq 5 \times$ ULN in the presence of liver involvement.
    f. Calculated creatinine clearance ≥ 40 mL/min by the Cockcroft-Gault Equation or the estimated glomerular filtration rate ≥ 40 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease formula.
11. Willingness to avoid pregnancy or fathering children based on the criteria below:
    a. Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and > 50 years of age after cessation of all exogenous hormonal treatments).
    b. Woman of childbearing potential who has a negative serum pregnancy test and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty, see Appendix A) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the participant and their understanding confirmed.
    c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty, see Appendix A) from screening through at least 93 days after the last dose of study treatment. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the participant and their understanding confirmed. Participant should refrain from donating sperm from the start of the study treatment administration until 93 days after discontinuing study treatment.

    Note: Approximately 18 participants with history of ASCT will be involved.

5.2. Exclusion Criteria

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

1. Known histological transformation from indolent NHL to DLBCL
2. History of central nervous system lymphoma (either primary or metastatic).
3. Prior treatment with the following:
    a. Selective PI3Kδ or pan-PI3K inhibitors (eg, idelalisib, copanlisib, duvelisib, etc).
    b. Bruton's tyrosine kinase inhibitor (eg, ibrutinib).
4. Allogeneic SCT within the last 6 months, or autologous SCT within the last 3 months before the date of study treatment administration.
5. Active graft-versus-host disease.

6. Use of immunosuppressive therapy within 28 days of the date of study treatment administration. Immunosuppressive therapy includes, but is not limited to, cyclosporine A, tacrolimus, or high-dose corticosteroids. Participants receiving corticosteroids must be at a dose level ≤ 10 mg/day (prednisolone or equivalent) within 7 days of the date of study treatment administration.
7. Receipt of anticancer medications or investigational drugs within the following intervals before the date of study treatment administration:
    a. < 10 weeks from completion of any radio- or toxin-immunoconjugates.
    b. < 6 weeks for mitomycin-C or nitrosoureas.
    c. < 4 weeks for immunotherapy.
    d. < 3 weeks for radiotherapy.
    e. < 2 weeks for any investigational agent or other anticancer medications.
8. Prior treatment-related toxicities have not resolved to ≤ Grade 1 prior to study treatment administration except for stable chronic toxicities (≤ Grade 2) not expected to resolve (eg, stable Grade 2 peripheral neurotoxicity).
9. Concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, investigational therapy, or tumor embolization).
10. Use or expected use during the study of any prohibited medications (see Section 6.6.3), including potent CYP3A4 inhibitors or inducers within 14 days or 5 half-lives (whichever is longer) before the date of study treatment administration.
11. Significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral, or psychiatric disease.
12. Current or previous other malignancy within 3 years of study entry, except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy without sponsor approval.
13. History of stroke or intracranial hemorrhage within 6 months of the date of study treatment administration.
14. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment, and exposure to a live vaccine within 30 days of study treatment administration.
15. Known HIV infection or positivity.
16. Hepatitis B (HBV) or HCV infection: Participants positive for HBsAg 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 positive for anti-HCV antibody will be eligible if they are negative for HCV-RNA.
17. Clinically significant cardiac disease, including unstable angina, acute myocardial infarction, and or cardiac conduction issues within 6 months of the date of study treatment administration.

18. Current New York Heart Association Class II to IV congestive heart failure or uncontrolled arrhythmia.
19. Presence of an abnormal ECG that is clinically meaningful. Screening QTc interval > 450 milliseconds is excluded (corrected by Fridericia). In the event that a single QTc is > 450 milliseconds, the participant may enroll if the average QTc for 3 ECGs is < 450 milliseconds.
20. Unable to swallow and retain 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.
21. Known hypersensitivity or severe reaction to parsaclisib (IB) or any of the excipients.
22. History of serious allergic reactions including anaphylaxis and toxic epidermal necrolysis.
23. Inadequate recovery from toxicity and/or complications from a major surgery before study treatment administration.
24. Currently pregnant or breastfeeding.
25. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

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

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. For screening assessments that are repeated, the most recent available result before treatment assignment will be used to determine eligibility. Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Replacement of Participants

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

5.6. Data Monitoring Committee

Preplanned analyses of safety will be provided to an independent DMC as specified in the DMC charter. The DMC will review safety data of the ongoing study approximately 8 weeks after the first 10 participants have been treated. In addition, the DMC will make recommendations to the

sponsor at the planned interim futility analysis. The DMC will use the guidelines provided in Section 10.5 for recommendation of either continuation or early termination of the study at the interim analysis. The process by which the DMC will make recommendations and decisions will be documented in the IDMC charter.

6. STUDY TREATMENT

6.1. Study Treatment Administered

Table 6 presents the study treatment information.

Table 6: Description and Administration of Parsaclisib

Compound name	Parsaclisib
Dosage strengths	1 mg, 2.5 mg, 5 mg, and 20 mg
Form	Tablet
Active compound	Parsaclisib
Route of administration	Oral
Dose and regimen	20 mg QD for 8 weeks followed by 2.5 mg QD
Instructions	Parsaclisib will be taken orally with water without regard to food [redacted] Parsaclisib should be taken at approximately the same time each day. If a dose is missed by more than 12 hours, the participant should skip the dose and take the next scheduled dose at the usual time. For QW dose regimen, if the dose is missed by more than 2 days, the participant should skip the dose and take the next scheduled dose.

6.2. Preparation, Handling, and Accountability

6.2.1. Supply, Packaging, and Labeling

Parsaclisib will be provided as 1 mg, 2.5 mg, 5 mg, and 20 mg tablets packaged in high-density polyethylene bottles. No preparation is required.

Each container will be labeled as required per country requirement.

6.2.2. Storage

Bottles of parsaclisib tablets should be stored at ambient conditions (15°C-30°C).

6.2.3. Instruction to Participants for Handling Parsaclisib

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

- To store study treatment at room temperature.
- To remove from the study treatment bottle only the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- To report any missed doses.
- To keep parsaclisib in a safe place and out of reach of children.
- To bring all used and unused study treatment kits to the site at each visit.

The investigator, investigational drug storage manager (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 be readily available for inspection by the study monitor and open to inspection at any time by any applicable regulatory authorities. The investigator, investigational drug storage manager, or designee must maintain records that document:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Participant use of the study drug, including 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. 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, 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, or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional SOPs. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable.

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 parsaclisib will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Participants will be instructed to keep a daily diary to record dosing compliance and bring the diary plus all study treatments with them to the study visits for site personnel to conduct tablet counts to assess study treatment accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

6.5. Dose Modifications

Dose modification guidance for AEs that have been previously observed in participants receiving parsaclisib or are potential class-effect AEs are provided (see Table 7). The starting dose and dose reduction levels of parsaclisib are provided (see Table 8). Individual decisions regarding dose interruption and reduction should be made using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study treatment and the participant's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction guidelines.

Table 7: Guidelines for Interruption and Restarting of Study Drug

ADVERSE EVENT	ACTION TAKEN
Chemistry	
• AST and/or ALT is Grade 3 (> 5.0 × ULN). *Note:* In participants with liver metastasis–related elevations at baseline, contact sponsor to discuss clinical management and possible dose reductions.	**Step 1:** Interrupt parsaclisib and monitor weekly until the toxicity has resolved to ≤ Grade 1. **Step 2:** Restart parsaclisib at next lower dose with medical monitor approval. Monitor as clinically indicated.

Table 7: Guidelines for Interruption and Restarting of Study Drug (Continued)

ADVERSE EVENT	ACTION TAKEN
Hematology	
• Grade 3 ANC (< 1.0×10^9/L). • Platelet count is Grade 2 (50 to < 75×10^9/L) for participants who enrolled with platelets > 100×10^9/L. • Platelet count is Grade 3 (< 50×10^9/L) for participants who enrolled with platelets ≤ 100×10^9/L.	**Step 1:** Interrupt parsaclisib up to 14 days until the toxicity has resolved to ≤ Grade 1 or pretherapy baseline. For Grade 3 ANC, monitor at least weekly. **Step 2:** Restart parsaclisib at same dose; monitor as clinically indicated.
• Grade 4 ANC (< 0.5×10^9/L). • Grade 3 or Grade 4 febrile neutropenia. • Platelet count is Grade 4 (< 25×10^9/L).	**Step 1:** Interrupt parsaclisib up to 14 days until the toxicity has resolved ≤ Grade 2. (Monitor ANC at least weekly.) **Step 2:** Restart parsaclisib at same dose. Monitor as clinically indicated. If recurs, start at next lower dose.
Other toxicities	
• Diarrhea (Grade 1).	**Step 1:** Treat with antimotility agents (eg, 2 mg loperamide followed by 2 mg every 4 hours or after every unformed stool) and initiate supportive care (see Section 6.5.1). Monitor approximately every 48 hours until resolved. If not improved after 48 hours, treat per guidance for Grade 2.
• Diarrhea (Grade 2).	**Step 1:** Interrupt parsaclisib. Perform work-up for infection (including CMV, *C. difficile*, etc) immediately. Initiate or continue supportive care (see Section 6.5.1). Monitor approximately every 48 hours until resolution. **Step 2:** If improved within 48 hours and/or infection* is confirmed, restart parsaclisib 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 according to clinical judgement 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 at the next lower dose with approval of the medical monitor (see Table 8 for dose levels). **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.

Table 7: Guidelines for Interruption and Restarting of Study Drug (Continued)

<table>
<tr><th>ADVERSE EVENT</th><th>ACTION TAKEN</th></tr>
<tr><td colspan="2">Other toxicities (continued)</td></tr>
<tr><td>• Diarrhea (≥ Grade 3).
• Noninfectious colitis (any grade; confirmed or suspected).</td><td>Step 1: Interrupt parsaclisib. Perform work-up for infection (including CMV, C. difficile, etc) immediately. Initiate or continue supportive care (see Section 6.5.1). Consider colonoscopy with biopsy for diarrhea ≥ Grade 3 and/or if symptoms[a] suggestive of colitis. Monitor every 48 hours until resolution.
Step 2: If infection* is ruled out, start oral steroids, or consider IV steroids if participant is being given IV fluids. If no improvement with oral steroids within 48 hours, switch to IV steroids.
*For infectious diarrhea/colitis, follow institutional standard of care guidelines and restart parsaclisib according to clinical judgement 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 as described herein and with approval of the medical monitor. Continue to monitor.
<table>
<tr><th>Parsaclisib</th><th>Dose Modification</th></tr>
<tr><td>Any dose with QD dosing</td><td>20 mg QW</td></tr>
<tr><td>20 mg QW</td><td>10 mg QW</td></tr>
</table>
Step 4: If ≥ Grade 3 diarrhea/colitis (any grade) reoccurs, permanently discontinue parsaclisib.</td></tr>
<tr><td>• Pneumonitis (Grade 1).</td><td>Step 1: Interrupt parsaclisib until the toxicity has resolved.
Step 2: Restart parsaclisib at next lower dose. Monitor as clinically indicated.</td></tr>
<tr><td>• Pneumonitis (≥ Grade 2).</td><td>Permanently discontinue parsaclisib.</td></tr>
<tr><td>• Skin toxicity (eg, rash, pruritus, etc, unless otherwise specified) (Grade 2-3).</td><td>Step 1: Interrupt parsaclisib until the toxicity has resolved to ≤ Grade 1.
Step 2: Restart parsaclisib at same dose. If assessed as related to parsaclisib, restart at next lower dose.</td></tr>
<tr><td>• Exfoliative dermatitis (Grade 1).</td><td>Step 1: Interrupt parsaclisib until the toxicity has resolved.
Step 2: Restart parsaclisib at next lower dose. Monitor as clinically indicated.</td></tr>
<tr><td>• Exfoliative dermatitis (≥ Grade 2).</td><td>Permanently discontinue parsaclisib.</td></tr>
<tr><td>• Intestinal perforation (any grade).</td><td>Permanently discontinue parsaclisib.</td></tr>
<tr><td>• Pneumocystis jiroveci pneumonia infection.</td><td>Interrupt parsaclisib. Permanently discontinue parsaclisib if Pneumocystis jiroveci pneumonia infection is confirmed.</td></tr>
</table>

Table 7: 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 for participants with CMV viremia and clinical signs of infection until the infection has resolved. Restart parsaclisib reduced by 1 dose level if approved by the medical monitor.
• Varicella zoster infection.	Interrupt parsaclisib. Restart parsaclisib only by approval of the medical monitor.
• Any Grade 1 or Grade 2 toxicity unless otherwise specified.	Continue parsaclisib and treat the toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care unless otherwise specified.	**Step 1:** Interrupt parsaclisib up to 14 days until the toxicity has resolved to ≤ Grade 1. **Step 2:** Restart parsaclisib at same dose. If assessed as related to parsaclisib, restart at next lower dose. If interrupted for > 14 days, contact the medical monitor for approval to restart parsaclisib. Monitor as clinically indicated.
• Any recurrent Grade 3 toxicity after 2 dose reductions.	Discontinue parsaclisib administration and follow-up per Protocol. Exceptions require approval of sponsor.
• Any other Grade 4 toxicity.	Discontinue parsaclisib administration and follow-up per Protocol. Exceptions require approval of sponsor.

CMV = cytomegalovirus; IV = intravenous; PCR = polymerase chain reaction.
[a] Diarrhea accompanied by abdominal pain and/or mucus or blood in stool.

Table 8: Dose Levels for Parsaclisib

Timepoint	Dose
Starting dose	20 mg QD for 8 weeks (Day 1 through Day 56)
First dose reduction	10 mg QD
Second dose reduction	5 mg QD
Week 8 (Day 57) onward	2.5 mg QD[a]
First dose reduction	1 mg QD
Second dose reduction	NA

[a] All participants will receive 2.5 mg QD at Week 8 (Day 57) regardless of prior dose level unless dose was modified due to diarrhea/colitis guidelines.

6.5.1. Supportive Care Guidelines for Diarrhea/Colitis

Participants should be informed to immediately report to the investigator any event of diarrhea. Treatment with parsaclisib may be interrupted or modified according to the guidelines in Table 7 to allow for resolution of diarrhea/colitis.

Participants should receive appropriate supportive care measures as deemed necessary by the investigator. For any Grade ≥ 1 diarrhea, participants should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. Participants should try to eat 5 to 6 small meals per day; low-fat, high-protein foods; and cooked instead of raw vegetables. Participants may supplement their diet with bananas, rice, applesauce, and toast to reduce the number of bowel movements and may also try crackers, gelatin, noodles, or oatmeal. Participants should avoid fried, fatty, greasy, or spicy foods; milk, milk products, and acidic drinks; high-fiber foods and foods that cause gas; and alcohol, caffeine, and herbal supplements (Coutré et al 2015).

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

It may be necessary to perform conditional procedures such as colonoscopy with biopsy as part of evaluation of the event. Note that several courses of steroid tapering may be necessary 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).

6.5.2. Supportive Care Guidelines for Neutropenia and Thrombocytopenia

Neutropenia and thrombocytopenia appear to be PI3Kδ class-effect toxicities. Investigators should ensure that participants understand the need to seek medical care when they have conditions that could become life-threatening in the presence of cytopenias (eg, neutropenic fever or bleeding with low platelets). Participants should be instructed to report immediately any signs of infection, unexpected bleeding, or sudden, extremely painful headaches.

6.5.3. Definition for Immune-Related Adverse Events

Adverse events of a potential immunologic etiology, or irAEs, may be defined as an AE consistent with an immune phenomenon associated with study treatment exposure after all other etiologies have been eliminated. Immune-related AEs may be expected based on previous experience with parsaclisib and other PI3K inhibitors. Special attention should be paid to AEs that may be suggestive of potential irAEs. Based on emerging data from the ongoing Study INCB 50465-101, most irAEs occur after the first 9 weeks of study treatment administration. However, an irAE could occur at any time. Suspected irAEs should be discussed with the medical monitor when possible.

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of drug-related AEs with potential immunologic etiology are outlined in Table 7 and Section 6.5.1. For each AE, attempts should be made to rule out other causes, including but not limited to metastatic disease or bacterial or viral infection, which might require specific supportive care.

6.5.4. Criteria and Procedures for Dose Interruptions

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

Treatment with parsaclisib may be delayed up to 14 days to allow for resolution of toxicity. Participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the case of any participant whose treatment has been delayed for more than 14 days before restarting treatment with parsaclisib.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments must be recorded in the eCRF. Any prior medication received up to 30 days before the date of study treatment administration (Day 1) will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant treatments and/or procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. *Pneumocystis Jirovecii* Prophylaxis

All participants are required to receive a standard PJP prophylaxis regimen determined by the investigator. Examples of standard PJP prophylaxis therapies for this population include trimethoprim-sulfamethoxazole, atovaquone, diaphenylsulfone with or without pyrimethamine, and pentamidine (diaphenylsulfone and pentamidine are not approved for PJP prophylaxis in Japan) (NCCN 2020). Due to reports of cross-sensitivity between sulfonamides and dapsone, all participants who have a known or suspected allergy to sulfonamides must receive atovaquone for PJP prophylaxis. Trimethoprim-sulfamethoxazole or atovaquone can be used for PJP prophylaxis in this study. Prophylaxis should be given while participants are receiving study treatment and should continue for 2 to 6 months after the last dose of study treatment.

The prophylactic agents will be obtained from commercial supplies and will be reimbursed by the sponsor. Investigators are responsible for ensuring that participants receive commercially available supplies of the selected prophylactic agents as required per Protocol. The sponsor may provide prophylactic agents where required by applicable law or regulation or under other limited circumstances when a participant may not otherwise have access to these therapies. The contents of the label will be in accordance with all applicable regulatory requirements. Further details are available in the Pharmacy Manual.

6.6.2. Restricted Medications and Procedures

- Use of systemic corticosteroid doses ≤ 10 mg/day prednisone (or equivalent) is permitted but discouraged from the screening visit through EOT.
- Short courses of systemic corticosteroid doses > 10 mg/day prednisolone or equivalent are permitted only in the case of severe or life-threatening complications that cannot be controlled with other drugs, but are otherwise discouraged from the screening visit through EOT.
- Use of weak or moderate inducers or inhibitors of CYP3A4 (see Appendix B and consult your local pharmacist) is discouraged, and investigators should seek other options where possible.
- For participants receiving parsaclisib, P-glycoprotein substrates of clinical relevance should be used with caution (ie, aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan).
- Localized radiotherapy will be permitted if administered as treatment for pain or impending compression fractures and with prior approval of the medical monitor.

6.6.3. Prohibited Medications and Procedures

- Use of potent inducers and inhibitors of CYP3A4 are prohibited (see Appendix B and consult your local pharmacist). Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole.
- Apart from the study treatments, the use of any anticancer medications as described (see Section 5.2) through the 30-day follow-up is prohibited.
- Exposure to a live vaccine within 30 days of study treatment through 3 months after the last dose of INCB050465.

6.7. Treatment After the End of the Study

At the end of the study as defined in Section 8.9, participants who have completed at least 12 months of study participation (starting from the first dose of study treatment), who remain on active study treatment, and who have no evidence of PD may continue treatment. Any remaining participants may continue to receive study treatment and be seen by the investigator per usual standard of care for this participant population. In addition, the investigator will be expected to monitor for and report any SAEs, ECIs, and pregnancies, as detailed in Section 9. The participants is considered on study until such time that they meet any of the discontinuation criteria and written notification is given to the sponsor.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

The decision to discontinue study treatment will not constitute study completion. In the event that study treatment is discontinued, the treatment period will be considered complete, and follow-up periods will begin.

7.1.1. Reasons for Discontinuation

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

- The participant has died.
- The participant has experienced an unacceptable toxicity defined as follows:
  - Occurrence of an AE that is related to study treatment that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
  - Persistent AE requiring a delay of therapy for more than 2 weeks (14 days) unless a greater delay has been approved by the sponsor.
- The participant is unable to tolerate study treatment.
- The participant has an objective radiographic tumor response of PD/PMD.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- The participant becomes pregnant.
- Informed consent is withdrawn. *Note:* Consent withdrawn means that the participant can no longer be followed. Participants may choose to discontinue study treatment and remain in the study to be followed for disease progression and survival per the schedule of assessments.
- The participant is considered lost-to-follow-up when they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site (eg, after 3 telephone calls and/or a certified letter or local equivalent).
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

Participants **may** be discontinued from study treatment in the following situation:

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

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 3 and Table 4. The last date of the last dose of study drug and the reason for discontinuation of study treatment will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record and the primary reason for withdrawal must be included in the eCRF.
- The EOT visit should be performed and date recorded.
- The status of the participant should be updated to EOT in the IWRS.
- Participants must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (safety 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 and survival per the schedule of assessments.

7.2. Participant Withdrawal From the Study

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

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

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

See Table 3 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

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. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the country 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(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

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

8.1.2. Screening Procedures

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

Procedures conducted as part of the participant 's routine clinical management (eg, blood count, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study. For participants who are enroll in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

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

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

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site staff should contact the IWRS to obtain the participant ID number during screening. Upon determining that the participant is eligible for enrollment, the IWRS will be contacted to obtain the treatment assignment. Additionally, the IWRS will be contacted at each regular study visit to update the study drug supply. Additional details are provided in the IWRS Manual.

8.1.4. Distribution of Reminder Cards

Participants will be provided with a reminder card at each visit. The reminder card will indicate the date/time of the next visit and will also remind the participant that they should not take their morning dose of study drug before coming to the clinic (see Section 8.4.1). [redacted]

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

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

8.1.5.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details including date of diagnosis, initial and current stage, histology, grade, sites of disease, prior anti-lymphoma systemic therapy, surgery, radiation, and other details related to the disease under study will be recorded.

For consideration of prior lines of therapy, a treatment is considered a new line of therapy if any of the following 3 conditions are met:

- Start of a new line of treatment after discontinuation of a previous line: If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. A regimen is considered to have been discontinued if all the drugs in that given regimen have been stopped. A regimen is not considered to have been discontinued if some of the drugs of the regimen, but not all, have been discontinued.
- The unplanned addition or substitution of 1 or more drugs in an existing regimen: Unplanned addition of a new drug or switching to a different drug (or combination of drugs) due to any reason is considered a new line of therapy.

- Stem cell transplant: In participants undergoing > 1 SCT, each SCT (autologous or allogeneic) should be considered a new line of therapy regardless of whether the conditioning regimen used is the same or different.

Note: A therapy administered before an SCT, the subsequent SCT, and planned maintenance therapy after the SCT is considered 1 line of therapy.

8.2. Efficacy Assessments

8.2.1. Computed Tomography Scan or Magnetic Resonance Imaging

Participants will undergo a diagnostic-quality CT or MRI to evaluate measurable disease. If CT is not available, is not practicable, or is contraindicated, then an MRI may be substituted. Every effort must be made to use the same modality for disease assessment throughout the study for each individual participant. Lesion assessment must be done for the neck, chest, abdomen, and pelvis.

If CT/MRI assessment was performed as standard of care before signing of the ICF but within 28 days of Day 1, then the results from that assessment must be recorded in the eCRF if used in lieu of a study-specific assessment.

The disease assessment schedule also applies to those participants who discontinue study treatment for reasons other than disease progression until disease progression, start of new anticancer therapy, withdrawal of consent, end of the study, or death, whichever occurs first. Imaging should not be delayed for interruption of study treatment.

No further CT/MRI is required as per Protocol-defined timepoint after all study participants have completed at least 12 months of study participation (starting from the first dose of study treatment).

8.2.2. Bone Marrow Examination

Bone marrow examination is required as a baseline assessment except in the following circumstances:

- Participant had a bone marrow examination performed as per standard of care within approximately 60 days from the first dose of study treatment.
- Participant had a bone marrow examination performed after the last treatment for NHL and the results showed lymphoma involvement of the bone marrow.

Subsequently, bone marrow examination will be performed and the sample(s) sent to a local histopathology laboratory to confirm CR, or as clinically indicated. If the bone marrow does not have lymphoma involvement at baseline, a repeat marrow examination is not required to confirm indication of CR on imaging.

All bone marrow examinations should include a unilateral aspiration and biopsy, when feasible.

The pathology report result from the bone marrow examination will be captured in the eCRF.

Note: Bone marrow biopsies and aspirates collected at screening should be evaluated locally. These materials are not to be sent to the central laboratory or the sponsor.

[redacted]

8.2.4. Independent Review Committee

All imaging (CT or MRI) will be submitted to the central radiology vendor for review. Imaging data and applicable clinical data will be reviewed and response assessed using the CT-based response criteria of the Lugano Classification (Cheson et al 2014; see Appendix D) by independent reviewers as described in the Imaging Charter.

8.2.5. Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.3. Safety Assessments

See Section 6.5 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

8.3.1. Adverse Events

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious AESI (as defined in Section 9.5.1) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.2. Physical Examinations

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

At the screening and EOT visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include height 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.

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

8.3.3. 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. Weight will also be assessed at each study visit. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.3.4. Electrocardiograms

12-lead ECG will be obtained as outlined in the SoA (see Table 3). All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest. Baseline ECGs will be obtained during screening using a single measurement but can be performed in triplicate if the single QTc measurement is > 450 milliseconds (corrected by Fridericia; see Section 5.2).

Electrocardiograms will also be obtained during the Day 1 visit (triplicate measurements) before the participant receives the first dose of study drug. Triplicate ECGs will be performed predose

and 1.5 hours (± 15 minutes) after receiving study treatment at the Week 4 visit. When triplicate ECGs are being obtained, individual measurements should be performed 5 minutes (± 3 minutes) apart. All 12-lead ECGs obtained at subsequent timepoints (single measurements) will be compared with the baseline 12-lead ECGs as follows:

- For ECG morphology, all postdose ECG recordings will be compared with Day 1 predose ECGs.
- For the calculation of changes in cardiac intervals (eg, QT interval), the intervals from the screening and Day 1 predose (triplicate) ECGs will be computed and averaged and used as the baseline for comparison of all postdose intervals.

If a single measurement demonstrates a QTc interval > 500 milliseconds, 2 more ECGs should be obtained over a brief period, and the averaged QTc intervals should be used to determine whether the study treatment should be interrupted.

Twelve-lead ECGs will be acquired using an ECG analysis system with analysis and printing capabilities. The 12-lead ECGs will be interpreted by the investigator at the site and will be used for immediate participant management. The decision to include or exclude a participant or discontinue a participant's participation in the study based on an ECG is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Twelve-lead ECGs that are identified by the investigator as "Abnormal, Clinically Significant" will be sent to the sponsor's medical monitor for review.

Electrocardiogram abnormalities where study exclusion, further cardiovascular investigation, and/or prompt action may be necessary depending on the clinical context.

8.3.5. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status (Oken et al 1982; see Appendix C) will be assessed. Performance status must be assessed by a medically qualified individual and recorded in the eCRF.

8.3.6. Laboratory Assessments

Blood draws for laboratory assessments will occur at study visits indicated (see Table 4). Specific laboratory assessments are provided (see Table 9).

See Section 9.1 for information regarding laboratory abnormalities that should be recorded as an AE in the eCRF. Additionally, if laboratory values from laboratory assessments performed at the institution's local laboratory require a change in participant management (eg, require treatment), or are considered clinically significant by the investigator (eg, SAE or AE or dose modification, see Section 6.5), then the result(s) of the **specific laboratory assessment(s)** must be recorded in the eCRF.

Table 9: Required Laboratory Analytes

Serum Chemistries	Hematology	Serology	Pregnancy Testing (Performed Locally)
Albumin Alkaline phosphatase ALT AST Bicarbonate (if applicable) Blood urea nitrogen C-reactive protein Calcium Chloride Creatinine Glucose Lactate dehydrogenase Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is > ULN) Indirect bilirubin (if total bilirubin is > ULN) Total protein Uric acid	Complete blood count, including: Hemoglobin Hematocrit Platelet count (absolute) 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: Lymphocytes Neutrophils	HBsAg HBsAg antibody Hepatitis B core antibody HBV-DNA (serology positive only) HCV antibody HCV-RNA CMV DNA HIV antibody	Only for female participants of childbearing potential (see Table 4). Pregnancy tests (serum or urine)

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

8.3.6.1. Chemistry and Hematology

All chemistry and hematology assessments (see Table 3 and Table 4) will be performed from blood samples collected using institutional best practices.

8.3.6.2. Pregnancy Testing

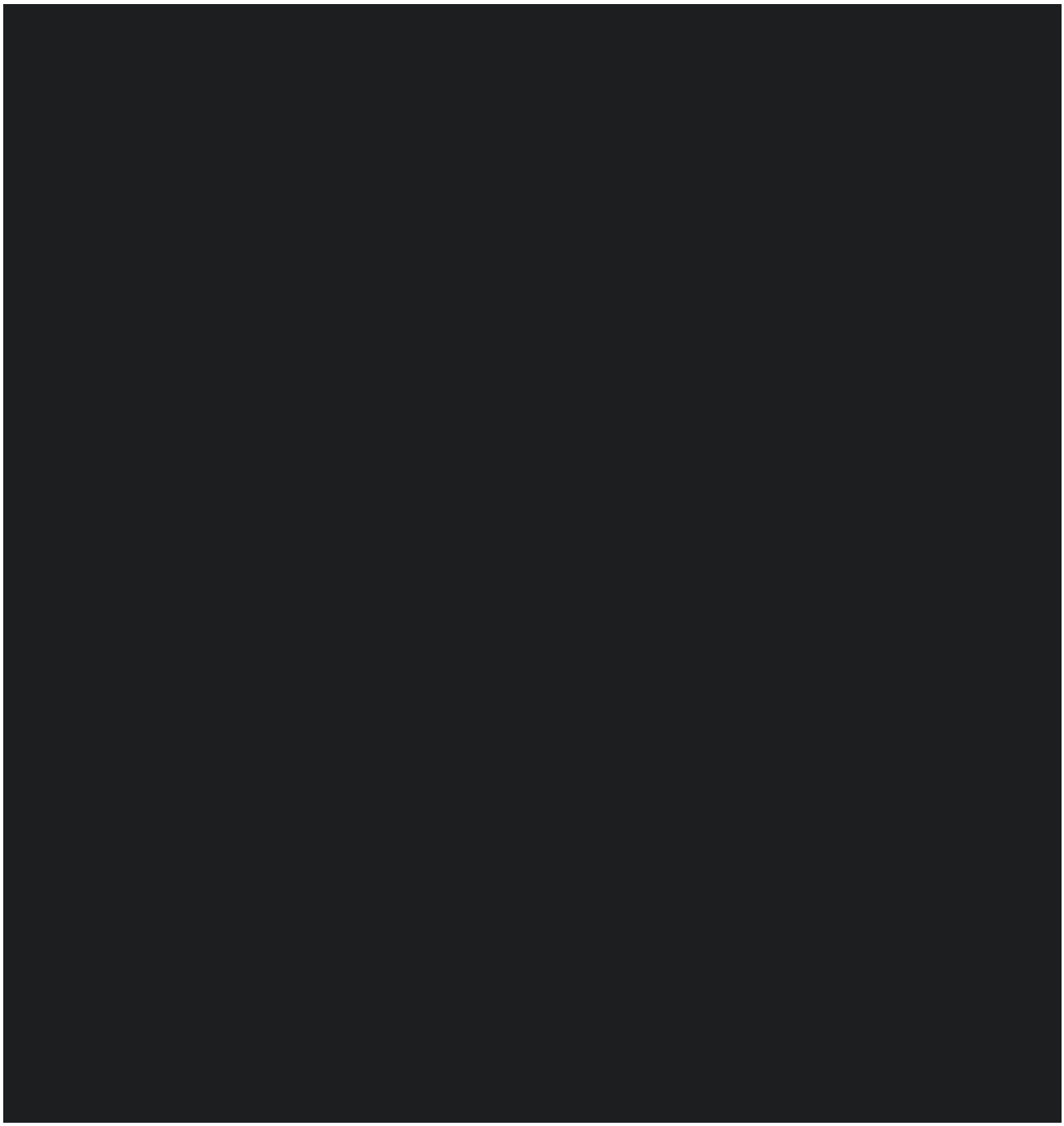
A serum pregnancy test will be required for all women of childbearing potential (see Section 5.1) as shown (see Table 4). Serum pregnancy and urine pregnancy tests will be performed locally as outlined in Table 4. If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy 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, see Section 9.7 for reporting requirements.

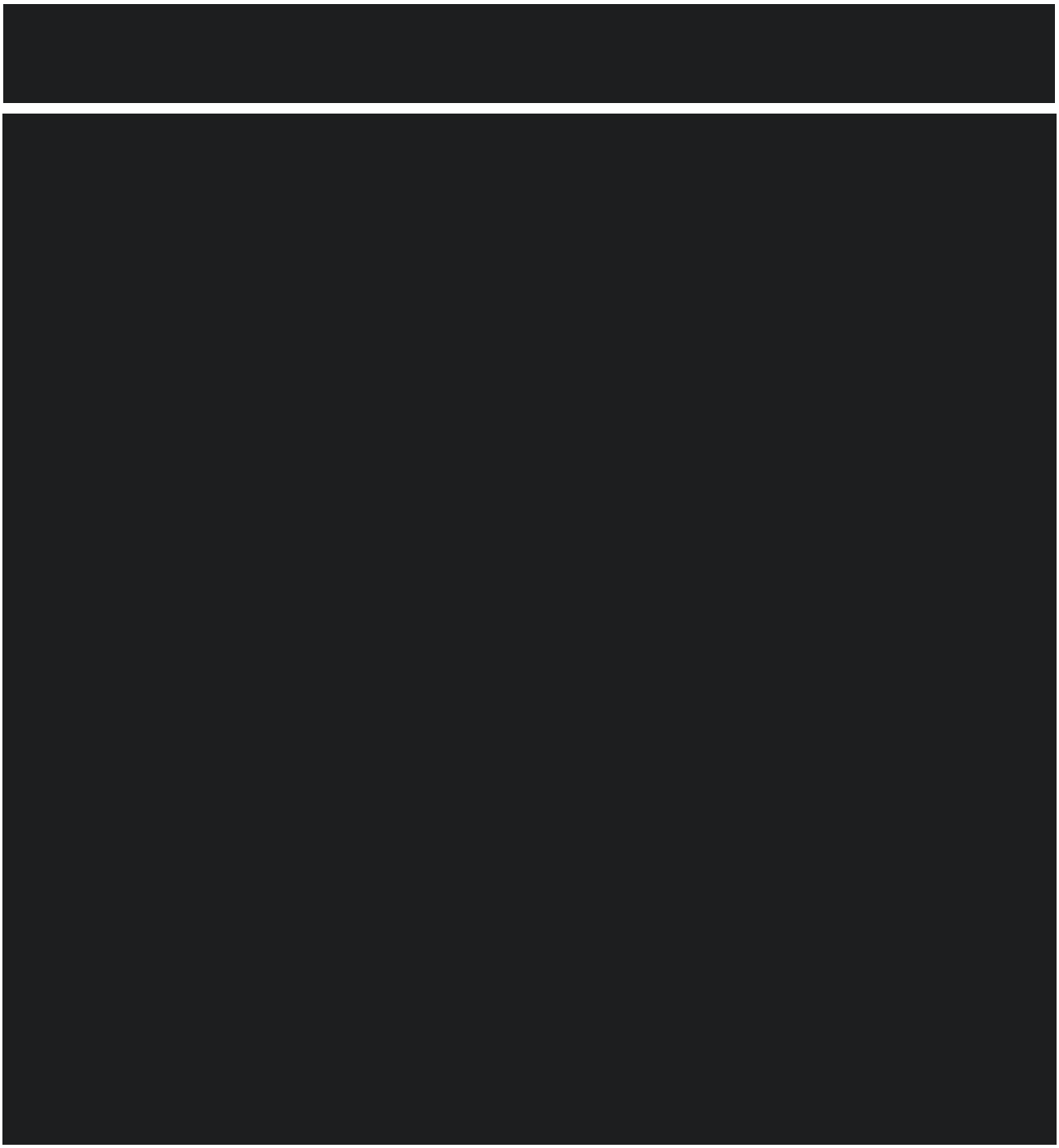
8.3.6.3. Serology

Hepatitis screening assessments will be performed at the screening visit to rule out hepatitis infection; required analytes are shown in Table 9. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.



8.4.2. Bioanalytical Methodology and Analysis

The plasma samples will be analyzed for parsaclisib by a validated liquid chromatography–tandem mass spectrometry assay. These samples will be analyzed by Incyte Corporation (Wilmington, DE) or its designee.



8.5.3. Tissue Biopsies

Participants must have an available tissue biopsy after the completion of last therapy or be willing to undergo a pretreatment tumor biopsy at baseline. [redacted]

If a participant doesn't have a superficial lymph node or tumor and needs hospitalization for the purpose of a tissue biopsy, submitting the most recent archived tumor tissue sample is allowed.

8.6. 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.

8.7. End of Treatment

There is no predefined EOT. When the participant permanently discontinues study drug, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The participant should be encouraged to return for the follow-up visit.

8.8. Follow-Up

8.8.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 35 days after the EOT visit (or after the last dose of study drug/treatment if the EOT visit was not performed). Adverse events and SAEs must be reported up until 1) at least 30 days after the last dose of study drug or the start of a new anti-lymphoma therapy or 2) until toxicities resolve, return to baseline, or are deemed irreversible. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period.

If a participant is scheduled to begin a new anti-lymphoma therapy before the end of the safety follow-up period, the safety follow-up visit should be performed before a new anti-lymphoma therapy is started. Once a new anti-lymphoma therapy has been initiated, the participant will move into the survival follow-up period.

8.8.2. Post-Treatment Disease Follow-Up

Participants who discontinue study treatment for a reason other than disease progression will continue to be followed for disease assessments by radiologic imaging [redacted] per the schedule of assessments (see timepoints for CT/MRI [redacted] in Table 3. Every effort should be made to collect information regarding disease status until any 1 of the following occurs:

- The start of new antineoplastic therapy.
- Disease progression.
- Consent withdrawal
- Death.
- The end of the study.

8.8.3. Survival Follow-Up

Once a participant has received the last dose of study drug, confirmed disease progression, or started a new anti-lymphoma therapy, the participant moves into the survival follow-up period. The site will use continuing participant records to supply data on subsequent treatment regimens, tumor assessments (if discontinued treatment for a reason other than progression), and OS in the eCRF.

For participants who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

8.9. End of Study

The end of the study will be when all participants have met any of the study withdrawal criteria in Section 7.2 or have completed at least 12 months of study participation (starting from first dose of parsaclisib).

At the end of the study, participants who have completed at least 12 months of study participation, who remain on active study treatment, and who have no evidence of PD will have the option to continue on monotherapy with parsaclisib. See Section 6.7 for treatment after the end of the study.

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

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) are to be reported as an AE. • Abnormal laboratory test results constitute 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 including either an increase in frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from dosing errors of a study treatment (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy," "disease progression," or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. • A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after obtaining informed consent. If the condition is present before entering the study, then it should be captured as medical history. • Pre-existing diseases or conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected 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. Other situations (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 (excluding the disease[s] under study, FL or MZL); intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; development of drug dependency or drug abuse; or suspected transmission of an infectious agent via a medicinal product. Secondary malignancies should always be considered SAEs.

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

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

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Event Form in the eCRF. AEs/SAEs should be reported for enrolled participants, but only SAEs need to be reported for screen failure participants. For enrolled participants, conditions that were present at the time informed consent was given should be recorded on the Medical History eCRF. For detailed information refer to the eCRF guidelines.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the Adverse Event Form in the eCRF.
- There may be rare instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted by the site staff on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the 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 treatment: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at final safety follow-up (30 to 35 days after the EOT visit).
- The action taken with regard to study treatment as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

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

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive treatment indicated; limiting age appropriate activities of daily living.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4:** Life-threatening consequences; urgent treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

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

Follow-Up of Adverse Events and Serious Adverse Events

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

- Once an AE is detected, it should be followed until the end of safety follow-up periods. All SAEs and nonserious AESIs should be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. 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.
- 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 of receipt of the information.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drugs, reference therapy, or study procedure), all SAEs occurring after the participant has signed the ICF through the last safety study visit, or until the participant starts a new anticancer therapy must be reported to the sponsor (or designee) immediately, without undue delay but not later than within **24 hours** of obtaining knowledge of its occurrence unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available. This information must also be reported immediately to the head of the study site.

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 9.5.1) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

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

If the SAE is not documented in the RSI of the parsaclisib IB for the study treatment (new occurrence) and is thought to be related to the sponsor's study treatment, the sponsor or its designee may urgently require further information from the investigator for expedited reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. The sponsor will report suspected expected deaths and life-threatening events to the PMDA as per local regulatory requirements.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The

sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

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

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

Serious Adverse Event Reporting

- Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF.
- The investigator must report within 24 hours of learning of its occurrence any SAEs via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if EDC system is not available. The contact information for Incyte Pharmacovigilance by email/fax is listed in the Incyte Reference Guide for Completing the Serious Adverse Event Report Form).
- In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor within 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form. Once the EDC system is functional, the SAE report should be retrospectively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form for details and for the email address or fax number).
- Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, 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. Events of Clinical Interest

9.5.1. Adverse Events of Special Interest

Specific AEs, or groups of AEs, will be followed as part of standard safety monitoring activities.

- ALT ≥ 5 × ULN
- AST ≥ 5 × ULN
- Colitis
- Diarrhea ≥ Grade 2
- Rash ≥ Grade 2
- Intestinal perforation
- Pneumonitis
- *Pneumocystis jirovecii* infection
- CMV infection

- Herpes simplex virus infection
- Varicella zoster virus infection
- Exfoliative dermatitis

9.6. Emergency Unblinding of Treatment Assignment

Not applicable.

9.7. Pregnancy

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

- The study drug must be discontinued immediately (female participants only; see Section 6.5.4 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

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

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

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

9.8. Warnings and Precautions

Infection with SARS-CoV-2, the coronavirus that causes COVID-19, is more frequent and severe in patients with hematologic dysfunction (Jee et al 2022). The presence of hematologic malignancy, baseline neutropenia and lymphopenia, B-cell depletion, and other factors have been identified as risk factors for loss of humoral immunity to COVID-19, poor vaccine response, viral persistence, and severe disease (Lee et al 2022, Lyudovyk et al 2022, Shree et al 2022). Targeting B-cell function, proliferation, and survival with various therapies are current strategies

for improving the outcome of several hematologic malignancies. Pi3Kδ inhibition with parsaclisib alone or in combination with other therapies, which may also suppress humoral immunity, has the potential to negatively impact SARS-CoV-2 infection risk, vaccine effectiveness, recovery from COVID-19, and disease severity (Cheson 2022). Investigators and participants 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, and infection management of COVID-19.

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

9.9. Product Complaints

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

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

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

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

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

9.10. Treatment of Overdose

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

10. STATISTICS

10.1. Sample Size Determination

Approximately 40 participants will be enrolled, including approximately 18 participants who have history of ASCT. If the true ORR is 62%, then with 40 total participants, there is approximately 90% probability of observing the lower bound of the 95% CI of ORR ≥ 35%.

A historical examination of efficacy in the subgroup of patients with FL who received R-CHOP (or the equivalent) as their first therapy and experienced early relapse showed and ORR of 33% (Flinn et al 2019). And previous studies of PI3K inhibitor for relapse or refractory FL set ORR of 30% to 40% as target. Thus ORR of 35% is a clinically relevant target of patients with relapse or refractory FL (Flinn et al 2019, Dreyling et al 2017).

10.2. Populations for Analysis

Table 11 presents the populations for analysis.

Table 11: Populations for Analysis

Population	Description
All screened	The all screened population includes all participants who signed the ICF.
FAS	The FAS includes all participants enrolled in the study who received at least 1 dose of parsaclisib. The FAS will be used for the summary of demographics, baseline characteristics, participants disposition, and analyses of all efficacy data.
Safety	The safety population includes all enrolled participants who received at least 1 dose of parsaclisib. All safety analyses will be conducted using the safety population.
[redacted]	

10.3. Level of Significance

No formal statistical tests will be performed. Two-sided 95% CIs will be reported for all analyses when appropriate.

10.4. Statistical Analyses

10.4.1. Analyses of Primary Endpoint

The primary endpoint ORR is the percentage of participants with a CR or PR as defined by revised response criteria for lymphomas (Cheson et al 2014) per IRC. The ORR as determined by the IRC and its 95% exact binomial CIs will be calculated. Participants whose baseline disease assessment or on-study response assessments cannot be adequately assessed for response will be considered as nonresponders. These participants will be included in the denominators in the calculations of ORR.

Subgroups will be formed based on the following participant characteristics and baseline variables:

- Age: ≤ 65 years, > 65 years
- Gender: male, female
- Prior ASCT: yes, no

Subgroups may be further divided or combined based on emerging data. The ORR and its 95% CIs will be provided for each subgroup. A forest plot will be created to summarize the variability in ORRs across subgroups.

10.4.2. Analyses of Secondary Efficacy Endpoints

Complete response rate is the percentage of participants with a CR as defined by revised response criteria for lymphomas, as determined by an IRC. The CRR determined by the IRC and its 95% exact binomial CIs will be calculated.

Duration of response is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among participants who achieve an overall response, as determined by IRC. For participants who have not progressed and are still alive at the time of the analysis, DOR will be censored on the day of last evaluable disease assessment. For participants who have discontinued study or have started other anti-lymphoma treatment, DOR will be censored on the day of last evaluable disease assessment documenting absence of PD before the discontinuation or the start of the new anti-lymphoma treatment. Kaplan-Meier estimation of median DOR per IRC and its 95% CIs will be provided.

Progression-free survival is defined as the time from the date of the first dose of study drug to the first documented disease progression as determined by IRC, or death due to any cause, whichever occurs first. For participants who have not progressed and are still alive at the time of the analysis, PFS will be censored on the day of last evaluable disease assessment. For participants who have discontinued study or have started other anti-lymphoma treatment, PFS will be censored on the day of last evaluable disease assessment documenting absence of PD before the discontinuation or the start of the new anti-lymphoma treatment. For participants who have no baseline or no postbaseline disease assessment, PFS will be censored with duration of 1 day. Kaplan-Meier estimation of median PFS per IRC and its 95% CIs will be provided.

Overall survival is defined as the time from the date of the first dose of study drug to death due to any cause. For participants who are still alive at the time of the analysis, OS will be censored on the date the participant is last known to be alive. The Kaplan-Meier estimation of median OS and its 95% CIs will be provided.

For participants with measurable lesions at baseline, target lesion sizes will be measured by sum of the product of the diameters of all target lesions. The best percentage change from baseline, defined as the largest decrease in target lesion sizes during the study, will be summarized descriptively. Note that for participants who only have increases in target lesion sizes from baseline, the smallest increase will be considered as the best change from baseline. Target lesions considered "too small to measure" will be assigned a default value of 5 mm × 5 mm for purposes of this analysis. Likewise, target lesions identified as "not present" at postbaseline assessments will be assigned 0 mm for this analysis. In the event that a target lesion is

unaccounted for in a particular postbaseline timepoint (ie, the assessment is missing or NE), then the overall sum of target lesions will not be evaluable for that postbaseline timepoint.

10.4.4. Safety Analyses

Safety analyses will be conducted for the safety population.

Quantitative safety variables and their changes from baseline (laboratory, vital signs, and ECG values) will be summarized with descriptive statistics. Abnormal values outside of established ranges will be flagged and tabulated based on predefined criteria.

Measures of exposure (eg, days of exposure, etc) of parsaclisib will be summarized by means of summary statistics.

10.4.4.1. Adverse Events

Adverse events will be coded by the MedDRA dictionary and severity of AEs will be based on the NCI CTCAE v5.0 (NCI 2017) using Grades 1 through 5. A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study treatment and within 30 days of the last administration of study drug.

Number (%) of participants reporting any TEAEs, any serious TEAEs, any Grade 3 or higher TEAEs, any treatment-related TEAEs, any treatment-related serious TEAEs, any treatment-related Grade 3 or higher TEAEs, any fatal TEAEs, and any TEAEs leading to treatment interruption/dose reduction/discontinuation will be tabulated by MedDRA system organ class and preferred term. Data listings will include all AEs regardless of their timing to study treatment administration.

Adverse events of special interest will be summarized as detailed in the Statistical Analysis Plan.

10.4.4.2. Clinical Laboratory Tests

The clinical laboratory data will be analyzed using summary statistics. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into Grades 1 through 4 using CTCAE v5.0 (NCI 2017) when applicable and tabulated.

10.4.4.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Normal ranges for vital sign results are defined in Table 12), and participants exhibiting vital sign abnormalities

will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% absolute percentage change from baseline (except body temperature).

Table 12: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38ºC	< 35ºC
Respiratory rate	> 24 breaths/min	< 12 breaths/min

10.4.4.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. ECG values will also be considered abnormal if the absolute percentage change from baseline is more than 25% (30% for QRS interval). Normal ranges for ECG values are defined in Table 13. Participants exhibiting ECG abnormalities will be listed.

Table 13: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 450 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.

[redacted]

10.5. Interim Analysis

An interim futility analysis is planned when the first 20 participants have been evaluated for response or have been followed for at least 9 weeks or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. The study will be terminated for futility [redacted] on assessments provided by the IRC; otherwise the study will continue. A timely assessment of response will be performed to avoid the risk of overenrollment. The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

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.
- 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 study drug(s)/treatment or at least 3 years after the discontinuation or completion of the study conduct, whichever is later. If the sponsor requires retention of these documents for a longer period of time, the duration and method of retention will be decided upon through discussion between the sponsor and the study site. It is the responsibility of the sponsor to inform the head of the study site as to when the documents no longer need to be retained.

- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study during the retention period without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
- All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

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

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

11.3. Data Quality Assurance

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

Quality tolerance limits will be predefined in the Incyte's SOPs and work instructions 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 Biosciences Japan GK (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. Compliance With Trial Registration and Results Posting Requirements

The sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to https://www.clinicaltrials.gov, https://www.clinicaltrialsregister.eu, or other local registries. The results of the study endpoints will be posted for the public and participants in national and local clinical trial registries such as https://www.clinicaltrials.gov and https://www.japic.or.jp/ as per requirements and format from registries. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information. These websites will not include information that can identify participants. [redacted]

11.8. 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.

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For male participants in the study:

Male participants should use a condom from screening through 93 days after the end of systemic exposure. If the male participant has a partner that is of child-bearing potential, the partner should also use contraception through 93 days after the end of relevant systemic exposure. In addition, male participants must refrain from donating sperm from screening through 93 days after the end of relevant systemic exposure. Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

For female participants in the study:

The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a]
  - oral
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - injectable
  - implantable[b]
- Intrauterine device[b]
- Intrauterine hormone-releasing system[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[bc]

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

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

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

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

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

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

Source: Clinical Trial Facilitation and Coordination Group 2014.

APPENDIX B. 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
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
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
evacetrapid	CETP inhibitors
linagliptin	Dipeptidyl Peptidase 4 Inhibitors
grazoprevir *(ingredient of Zepatier)*	Antivirals
lacidipine	Calcium Channel Blockers
cranberry juice	Food Products
pazopanib	Kinase Inhibitors
fostamatinib	Other
everolimus	Immunosuppressants
blueberry juice	Food Products
flibanserin	Central Nervous System Agents
lapatinib	Kinase Inhibitors
brodalumab	Immunomodulators Biologics
AMD070	Fusion Inhibitors
alprazolam	Benzodiazepines
Tong Xin Luo	Herbal Medications
glecaprevir and pibrentasvir	Antivirals
bicalutamide	Antiandrogens
sitaxentan	Endothelin Receptor Antagonists
azithromycin	Antibiotics
obeticholic acid	Miscellaneous Agents
ginkgo	Herbal Medications
teriflunomide	Other Immunomodulators

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 Johns 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
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
dexamethasone	Corticosteroids
terbinafine	Antifungals
quercetin	Food Products
glycyrrhizin	Herbal Medications
aprepitant	Neurokinin-1 Receptor Antagonists
pretomanib (PA-824)	Antibiotics
safinamide	MAO-B Inhibitors
oritavancin	Antibiotics
AZD 7325	Anxiolytics
methylprednisolone	Corticosteroids
topiramate	Anticonvulsants

APPENDIX C. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Eastern Cooperative Oncology Group Performance Scores

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

Source: Oken et al 1982.

APPENDIX D. LUGANO CLASSIFICATION FOR RESPONSE ASSESSMENT (CT-BASED ONLY)

Site	CT-Based Response
	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi.
Nonmeasured lesion	Absent.
Organ enlargement	Regress to normal.
New lesions	None.
Bone marrow	Normal by morphology; if indeterminate, immunohistochemistry negative.
	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	• ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default. • When no longer visible, 0 × 0 mm. For a node > 5 mm × 5 mm but smaller than normal, use actual measurement.
Nonmeasured lesions	Absent/regressed, but no increase.
Organ enlargement	Spleen must have regressed by > 50% in length beyond normal.
New lesions	None.
Bone marrow	Not applicable.
	Stable disease
Target nodes/nodal masses, extranodal lesions	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for PD are met.
Nonmeasured lesions	No increase consistent with progression.
Organ enlargement	No increase consistent with progression.
New lesions	None.
Bone marrow	Not applicable.

Site	CT-Based Response
	Progressive disease (requires at least 1 of the following)
Individual target nodes/nodal lesions	PPD progression: • An individual node/lesion must be abnormal with all of the following: – LDi > 1.5 cm. – Increase by ≥ 50% from PPD nadir. – Increase in LDi or SDi from nadir: ○ 0.5 cm for lesions ≤ 2 cm. ○ 1.0 cm for lesions > 2 cm. • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. • New or recurrent splenomegaly. • New or clear progression of pre-existing nonmeasured lesions. • Regrowth of any previously resolved lesions. • A new node > 1.5 cm in any axis. • A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. • Assessable disease of any size unequivocally attributable to lymphoma. • New or recurrent involvement of the bone marrow.

CT = computed tomography; EOT = end of treatment; LDi = longest transverse diameter of lesion; MRI = magnetic resonance imaging; PPD = cross-product of the longest transverse diameter and perpendicular diameter; SDi = shortest axis perpendicular to the longest transverse diameter; SPD = sum of the product of the perpendicular diameters for multiple lesions.

APPENDIX E. FOLLICULAR LYMPHOMA INERNATIONAL PROGNOSTIC INDEX

Scoring System		
Parameter	**Value**	**Point Score**
Age	> 60 years of age	1
Ann Arbor stage	Stage III or IV	1
Hemoglobin level	< 120 g/L (12.0 g/dL or 6.37 mmol/L)	1
Serum LDH	> ULN	1
Number of Nodal Sites	> 5	1

Risk Group by FLIPI Total Point Score	
Risk Group	**Total Point Score**
Low	≤ 1
Intermediate	2
High	≥ 3

APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 1 (Version 2):	25 JUN 2020
Amendment 2 (Version 3):	19 MAY 2021
Amendment 3 (Version 4):	07 OCT 2022
Amendment 4 (Version 5):	24 JAN 2023

Amendment 4 (24 JAN 2023)

Overall Rationale for the Amendment:

The primary purpose to this amendment is to enable the study to close ahead of the original plan by updating the minimum study participation period.

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

   Description of change: Changed the estimated duration of study participation from 25 months to 16 months.

   Rationale for change: Consistency with the change in the minimum study participation period.

[redacted]

3. **Section 4.2, Overall Study Duration; Section 6.7, Treatment After the End of the Study; Section 8.9, End of Study**

   Description of change: Changed the minimum study participation period from 24 months to 12 months to trigger the end of the study.

   Rationale for change: Based on the time to response data from a non-Japanese study, the minimum observation period required for evaluation of the primary endpoint (ORR) was updated.

4. **Section 8.2.1, Computed Tomography Scan or Magnetic Resonance Imaging**

   Description of change: Added text that no further imaging is required once all participants complete at least 12 months of study participation.

   Rationale for change: To clarify the required period for CT/MRI.

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

Amendment 3 (07 OCT 2022)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to describe risks associated with COVID-19.

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

   Description of change: Added language to address possible risks of serious infection events.

   Rationale for change: Clarify the possible risk of infection.

2. **Section 9.8, Warnings and Precautions**

   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.

3. **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 2 (19 MAY 2021)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to change inclusion criteria for the purpose of stimulating enrollment and to align with Japan GCP requirement(s).

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

   Description of change: Added "after EOT" to survival follow-up and the test item of FDG-PET to the list of procedures.

   Rationale for change: Clarified the timing of survival follow-up and added FDG-PET due to the modification of inclusion criteria.

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

   Description of change: Added explanation that a tumor biopsy is not mandatory for participants who submit earlier archived lymph nodes or tissue biopsies to notes for tumor biopsy.

   Rationale for change: Due to the modification of inclusion criteria.

3. **Section 4.3, Study Termination; Section 6.2.3, Instruction to Participants for Handling Parsaclisib**

   Description of change: Added and modified descriptions specific to Japan.

   Rationale for change: Added based on Japan GCP requirement(s).

4. **Section 5.1, Inclusion Criteria (Criterion 7); Section 8.5.3, Tissue Biopsies**

   Description of change: Added a sentence to allow enrollment without biopsy sample collected after the completion of last therapy.

   Rationale for change: Modified to stimulate enrollment.

5. **Section 5.1, Inclusion Criteria (Criterion 11c); Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: Changed the duration for avoiding fathering children from 90 to 93 days.

   Rationale for change: Modified to be consistent with the duration of refraining from donating sperm discussed in Inclusion Criterion 11C.

6. **Section 8.4.1, Blood Sample Collection**

   Description of change: Added explanation of meal information during [redacted] sample visits in the eCRF.

   Rationale for change: To obtain the information of meal.

7. **Section 9.1, Definition of Adverse Event; Section 9.2, Definition of Serious Adverse Event; Section 9.3, Recording and Follow-Up of Adverse Events and/or Serious Adverse Events; Section 9.4, Reporting of Serious Adverse Events; Section 9.9, Product Complaints**

   Description of change: Modified language to align with the most updated protocol template.

   Rationale for change: Updated based on current protocol template.

8. **Section 10.4.4.4, Electrocardiograms (Table 13: Criteria for Clinically Notable Electrocardiogram Abnormalities)**

   Description of change: QTcB was deleted from table.

   Rationale for change: QTcB was deleted to align with Exclusion Criterion 19.

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

Amendment 1 (25 JUN 2020)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to clarify the PJP prophylaxis situation in Japan and the follow-up period of AEs.

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

   Description of change: Removed the note that pregnancy test may be performed by the central laboratory.

   Rationale for change: Pregnancy test will be performed locally.

[redacted]

5. **Section 6.5, Dose Modifications (Table 7: Guidelines for Interruption and Restarting of Study Drug)**

   Description of change: Removed the 5 mg QW dose regimen from Step 3 for diarrhea/colitis toxicities, and updated the parsaclisib 20 mg QW dose modification to 10 mg QW.

   Rationale for change: There will be no 5 mg QW regimen in this study.

6. **Section 6.6.1, *Pneumocystis Jirovecii* Prophylaxis**

   Description of change: Described the unapproved drugs in Japan and drugs used for PJP prophylaxis in this study.

   Rationale for change: Clarify the drugs used for PJP prophylaxis in this study.

7. **Section 8.2.2, Bone Marrow Examination**

   Description of change: Removed the MRD evaluation information.

   Rationale for change: MRD evaluation will not be conducted in this study in consideration of feasibility.

8. **Section 8.3.1, Adverse Events**

   Description of change: Added nonserious AESIs to the follow-up details.

   Rationale for change: Clarify the follow-up period of nonserious AESI.

9. **Section 8.3.6, Laboratory Assessments**

   Description of change: Removed statement regarding central laboratory assessments.

   Rationale for change: Most laboratory testing will be performed locally in this study.

10. **Section 8.3.6.2, Pregnancy Testing**

    Description of change: Updated the description of pregnancy testing for location to be performed locally.

    Rationale for change: Pregnancy test will be performed locally in this study.

11. **Section 8.3.6.3, Serology**

    Description of change: Deleted the statement regarding serology to be performed by a central laboratory.

    Rationale for change: Serology assessment will be performed locally in this study.

12. **Section 9.3, Recording and Follow-Up of Adverse Events and/or Serious Adverse Events**

    Description of change: Updated the follow-up of AE details to be consistent with Section 8.3.1.

    Rationale for change: Clarification and keep consistency with Section 8.3.1.

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

    Description of change: Changed description of SAE reporting method to be provided by EDC.

    Rationale for change: Change in SAE reporting method.

14. **Section 10.2, Population for Analysis (Table 11: Populations for Analysis)**

    Description of change: Deleted information regarding pharmacodynamics.

    Rationale for change: No pharmacodynamics will be evaluated in this study.

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

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