SECURA BIO™

CLINICAL STUDY PROTOCOL

Protocol No. VS-0145-225

Title: A Multi-Center, Phase 2, Open-label, Parallel Cohort Study of Efficacy and Safety of Duvelisib in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)

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Sponsor: Secura Bio, Inc.
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Sponsor Signatory:

I have read this protocol for Study VS-0145-225, Version 7.1 and I approve the design of this study:

[redacted]

30-NOV-2021

Date

Secura Bio, Inc.

Medical Monitor Contact Information:

Medical Monitor contact information will be provided separately in a study contact list.

INVESTIGATOR AGREEMENT

Secura Bio, Inc.
Protocol No. VS-0145-225, Version No. 7.1

I have read Protocol VS-0145-225, A Multi-Center, Phase 2, Open-label, Parallel Cohort Study of Efficacy and Safety of Duvelisib in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL).

I will conduct the study as detailed herein and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

Principal Investigator	Date

Printed Name:

Institution:

Address:

PROTOCOL SYNOPSIS

Study Title:	A Multi-Center, Phase 2, Open-label, Parallel Cohort Study of Efficacy and Safety of Duvelisib in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)
Protocol Number:	VS-0145-225
Study Phase:	Phase 2
Investigational Agent:	Duvelisib (IPI-145, VS-0145)
Study Objectives:	**Dose Optimization Phase** Primary Objective: • To determine the optimal duvelisib dose for utilization in the Expansion Phase by evaluating the overall response rate (ORR) of duvelisib supported by safety, additional efficacy, and pharmacokinetic (PK) parameters as well as any other available data in the population of patients receiving the optimal dose of duvelisib for at least one cycle in patients with relapsed or refractory PTCL Secondary Objectives: • To evaluate additional efficacy parameters for duvelisib in the population of patients receiving duvelisib for at least one cycle in patients with relapsed or refractory PTCL • To characterize the tolerability and safety of duvelisib in patients with relapsed or refractory PTCL • To evaluate pharmacokinetics (PK) of duvelisib and if applicable, its metabolite(s) Exploratory Objective: • To evaluate pharmacodynamic and prognostic biomarkers **Expansion Phase** Primary Objective: • To determine the efficacy of duvelisib at an optimal dose in patients with relapsed or refractory PTCL Secondary Objectives: • To evaluate additional efficacy parameters for duvelisib • To characterize the tolerability and safety of duvelisib in patients with relapsed or refractory PTCL • To evaluate PK of duvelisib and if applicable, its metabolite(s) Exploratory Objective:

	• To evaluate pharmacodynamic and prognostic biomarkers
Study Treatment:	All patients will receive duvelisib orally (PO) twice daily (BID) continuously in 28-day cycles. In the Dose Optimization phase, duvelisib will be administered at doses of 25 mg, 50 mg, and 75 mg BID; the duvelisib dose administered to individual patients is dependent on the cohort allocation as well as the patient's response to and tolerance of therapy (see **Study Design**).
Study Design:	This is a multi-center, parallel cohort, open-label, Phase 2 study of duvelisib, an oral dual inhibitor of PI3K-δ,γ, in patients with relapsed/refractory PTCL. The study has 2 phases, a Dose Optimization Phase and an Expansion Phase. Regardless of study phase, all patients will undergo screening assessments up to 30 days before the first study drug dose (Cycle 1, Day 1 [C1D1]). Patients meeting all of the entrance criteria, based on Screening assessments, will be enrolled in the study and receive the first study drug dose on C1D1. Thereafter, patients will attend study center visits as per the Schedule of Events (Table 1 or Table 2). At screening, disease will be measured using ^{18}F-fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET)-computed tomography (CT) scanning (PET-CT) (CT images along with PET should be diagnostic with contrast unless contraindicated). Where PET-CT is not feasible, CT with contrast or magnetic resonance imaging (MRI) may be used after discussion with the Medical Monitor. Subsequently, for FDG-avid PTCL, PET-CT will be used to assess disease status, and for FDG-non-avid PTCL, CT with contrast or MRI will be appropriate substitutes. The modality chosen to evaluate response in each individual patient should be the same throughout the duration of the study. For the purposes of patient management during the conduct of the study, the Investigator's assessment of disease response will be used. Images also will be centrally stored, and disease response will be determined by an Independent Review Committee (IRC) for futility and at the end of the study. **Dose Optimization Phase** In the Dose Optimization Phase, patients will be randomly assigned to 1 of 2 study cohorts, as follows: • Cohort 1: Duvelisib PO BID at a starting dose of 25 mg, with potential escalation on a per-patient basis to 50 mg BID and then 75 mg BID, based on the patient's response to and tolerance of therapy, in 28-day cycles • Cohort 2: Duvelisib 75 mg PO BID, administered in 28-day cycles Approximately10 patients each will be enrolled in Cohorts 1 and 2. Patients in the Dose Optimization Phase who discontinue before receiving at least 1 cycle of study drug may be replaced. Enrollment into the Dose Optimization Phase may continue until the initiation of the Expansion Phase.

	For both cohorts, dose modification criteria for duvelisib will be applied if the starting dose or a subsequent dose of duvelisib is deemed intolerable. Dose Optimization patients will complete treatment as defined for their cohort. ***Cohort 1*** All patients will receive duvelisib at a starting dose of 25 mg PO BID (Level 1), with potential sequential escalation to 50 mg PO BID (Level 2), and then to 75 mg PO BID (Level 3). Intra-patient dosing decisions will occur as follows: After completion of Cycle 1 and every 2 cycles thereafter: • Patients with complete response (CR) or partial response (PR) will have their duvelisib dose maintained at the current dose level • Patients with stable disease (SD) who are, in the Investigator's opinion, tolerating and otherwise suitable to continue receiving therapy, will have the duvelisib dose increased to the next level until the next response assessment or development of progressive disease (PD) or intolerance, as determined by the Investigator Patients with PD, who are not tolerating therapy, or otherwise not suitable to continue receiving therapy, will discontinue duvelisib In no case will the duvelisib dose be increased to a level > 75 mg BID (total daily dose 150 mg). All patients in Cohort 1 will receive duvelisib until development of PD or unacceptable toxicity, as determined by the Investigator. ***Cohort 2*** All patients in Cohort 2 will receive duvelisib 75 mg PO BID in 28-day cycles until development of PD or unacceptable toxicity, as determined by the Investigator. **Expansion Phase** After a sufficient number of patients from the Dose Optimization Phase are evaluable, all available data will be reviewed and an optimal dose for the Expansion Phase will be selected. (Note: the optimal dose for the Expansion Phase has been selected and documented in Protocol Amendment 2 V3, 14 March 2019 – see Expansion Phase Dose Selection below and Section 1.3). The interim results of the Dose Optimization Phase may also drive changes to the Expansion Phase of the study, such as modification to the study patient population, other aspects of entry criteria, and the inclusion of patients from geographic regions outside the United States (US); any such changes will be documented in an amendment to the protocol. The Secura Bio study team, in collaboration with the Investigators, will make the determination of duvelisib dose for the Expansion Phase of the study based on the safety and activity data (see Section 1.3). Patients will have disease assessment after Cycle 2 and every 2 cycles thereafter until the follow-up stage is reached. All patients in the Expansion Phase will receive duvelisib until development of PD or unacceptable toxicity, as determined by the Investigator. **Expansion Phase Dose Selection:**

	As of 02 January 2019, 20 patients met the criteria for the Dose Optimization efficacy population and available data as of 11 February 2019 were reviewed. A dosage of 75 mg BID for the first 2 cycles, followed by a mandatory reduction to 25 mg BID thereafter for those patients with CR, PR or SD, will be used for the Expansion Phase. The dose may be re-escalated to 75 mg BID based on response assessment and safety (see Sections 1.3 and 9.1.2).
Number of Patients:	**Dose Optimization Phase** Approximately 20 patients with relapsed/refractory PTCL will be enrolled in the Dose Optimization Phase, with approximately 10 evaluable patients per cohort. Patients in the Dose Optimization Phase who discontinue before receiving at least 1 cycle of study drug may be replaced. Enrollment into the Dose Optimization Phase may continue until the initiation of the Expansion Phase. **Expansion Phase** Approximately 100-130 patients may be enrolled, for a total of approximately 130-160 patients across both phases. After the first 100 patients are enrolled in the expansion phase an additional 20-30 patients may be enrolled with a target of 8-10 patients having an ALCL or NK cell subtype.
Duration of Study:	The total duration of this study is anticipated to be 3.2 years.
Study Centers:	The Dose Optimization Phase will be conducted at up to approximately 15 centers in the US. The Expansion Phase will be conducted at approximately 40-50 centers globally.
Inclusion Criteria:	Inclusion Criteria: Patients meeting all of the following criteria are eligible for study participation: 1. ≥ 18 years of age 2. Pathologically-confirmed PTCL, as defined by the World Health Organization. Slides must be submitted for central pathology review. Results of central pathology review are not required prior to initiation of treatment. 3. Received at least 2 cycles of one standard regimen for newly diagnosed advanced PTCL, and one of the following: (a) failed to achieve at least a partial response after 2 or more cycles of standard therapy; (b) failed to achieve a complete response after completion of standard therapy; and/or (c) persistent or progressive disease after an initial response 4. For patients with CD30+ anaplastic large cell lymphoma (ALCL), failed or are ineligible or intolerant to brentuximab vedotin

	5. Measurable disease as defined by Lugano (Cheson et al, 2014) for PTCL, i.e., at least 1 measurable disease lesion > 1.5 cm in at least one dimension by conventional techniques (^{18}FDG-PET-CT, CT with contrast, MRI) 6. Must have the following laboratory parameters: • Hemoglobin ≥ 8.0 g/dL with or without transfusion support • Platelet count ≥ 25 × 10^9/L • Serum creatinine ≤ 2.0 × the upper limit of normal (ULN) • Total bilirubin ≤ 1.5 × ULN (in patients with Gilbert's Syndrome a bilirubin > 1.5 × ULN may be allowed) • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 × ULN • Expansion Phase Only: CD4 lymphocyte count ≥ 50/mm^3 (0.05 x 10^9/L) 7. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 8. Recovery to ≤ Grade 1 or baseline for any toxicities due to prior treatments, with the exception of peripheral neuropathy (recovery to ≤ Grade 2) or alopecia 9. Washout of at least 14 days or 5 half-lives, whichever is longer, from PTCL-directed therapy. If previously treated with lenalidomide, must have completed treatment 4 weeks prior to C1D1. 10. For women of childbearing potential (WCBP): negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test within 1 week before first treatment (WCBP defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally post-menopausal for at least 12 consecutive months for women > 55 years of age) 11. Male and female patients of reproductive potential (i.e., not surgically sterile or female patients who are not postmenopausal) must be willing to use a highly effective method of contraception for the duration of study treatment and for at least 3 months after the last dose of duvelisib 12. Signed and dated institutional review board (IRB)/independent ethics committee (IEC)/central ethics committee (CEC)-approved informed consent form before any Screening procedures are performed

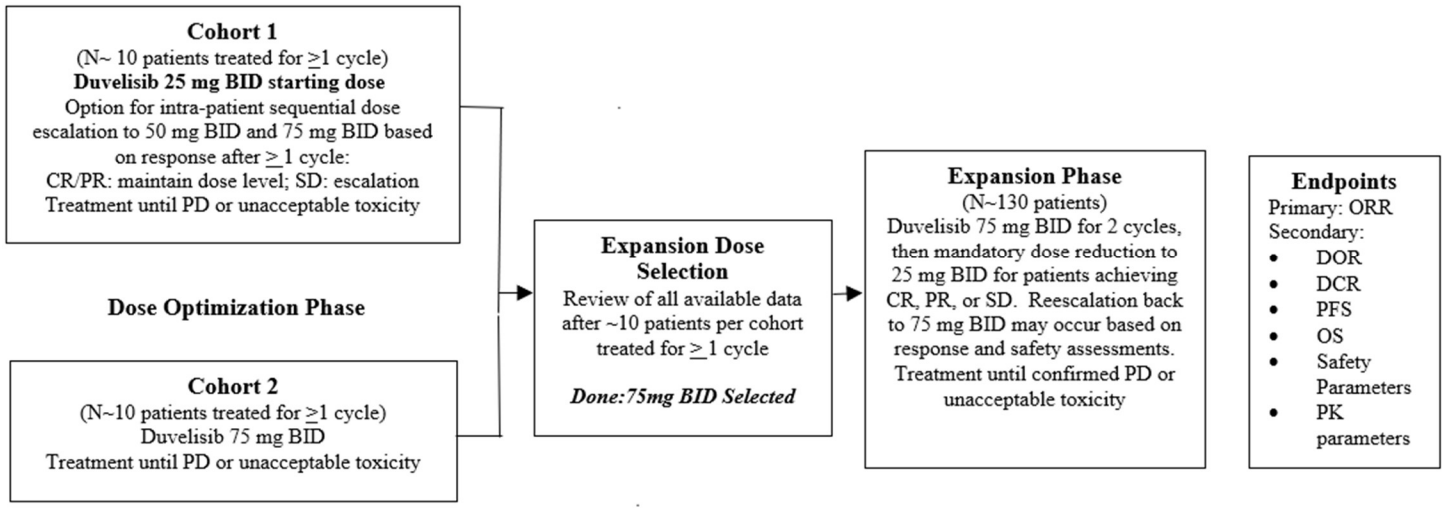
Exclusion Criteria:	Exclusion Criteria: Patients meeting any of the following criteria are not eligible for study participation: 1. Primary leukemic PTCL subtypes (i.e., T-cell prolymphocytic leukemia, T-cell large granular lymphocytic leukemia, adult T-cell leukemia/lymphoma and aggressive NK-cell leukemia) or transformed mycosis fungoides 2. Received prior allogeneic transplant 3. Received prior treatment with a phosphoinositide-3-kinase (PI3K) inhibitor 4. Major surgery within 4 weeks prior to Screening 5. Known central nervous system involvement by PTCL 6. Infection with hepatitis B, hepatitis C, human immunodeficiency virus (HIV) or human T-lymphotropic virus type 1. (Patients with a positive hepatitis B surface antigen [HBsAg] or hepatitis C antibody [HCVAb] will be excluded. Patients with a positive hepatitis B core antibody [HBcAb] must have negative hepatitis B virus [HBV] deoxyribonucleic acid (DNA) to be eligible, must receive prophylaxis with entecavir [or equivalent] concomitant with duvelisib treatment, and must be periodically monitored for HBV reactivation by institutional guidelines. Investigators who strongly believe that a positive HBcAb is false due to passive immunization from previous immunoglobulin infusion therapy should discuss the potential to defer HBV prophylaxis with the Medical Monitor.) 7. Active cytomegalovirus (CMV) infection (patients with detectable viral load) 8. History of tuberculosis treatment within 2 years prior to C1D1 9. History of chronic liver disease, veno-occlusive disease, or alcohol abuse 10. Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids > 20 mg of prednisone (or equivalent) once daily (QD) 11. Ongoing treatment for systemic bacterial, fungal, or viral infection at Screening NOTE: Patients on antimicrobial, antifungal, or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met 12. Administration of a live vaccine within 6 weeks of C1D1 13. Concurrent administration of medications or foods that are strong inhibitors or inducers of cytochrome P450 3A (CYP3A) 14. Unable to receive prophylactic treatment for pneumocystis at Screening 15. Baseline left ventricular ejection fraction (LVEF) < 50% (or below institution's normal limit) 16. Baseline QT interval corrected with Fridericia's method (QTcF) >480 ms

	NOTE: criterion does not apply to patients with a right or left bundle branch block 17. Prior surgery or condition with gastrointestinal dysfunction that may significantly affect drug absorption (e.g., gastric bypass surgery, gastrectomy, etc., see Section 5.2) 18. If female, pregnant or breastfeeding 19. Concurrent active malignancy other than nonmelanoma skin cancer, carcinoma in situ of the cervix NOTE: Patients with previous malignancies are eligible if disease-free for >2 years. 20. History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or a pacemaker within the last 6 months prior to Screening 21. Unstable or severe uncontrolled medical condition (e.g., unstable cardiac function, unstable pulmonary condition, uncontrolled diabetes) or any important medical illness or abnormal laboratory finding that would, in the Investigator's judgment, increase the risk to the patient associated with his or her participation in the study 22. Known hypersensitivity to duvelisib and/or its excipients
Study Endpoints:	**Primary Endpoint(s):** **Dose Optimization Phase** • Objective response rate (ORR [CR + PR]), as assessed by the Investigator, as determined using the Lugano criteria (Cheson et al, 2014) supported by secondary efficacy, safety and PK parameters **Expansion Phase** • ORR (CR + PR), according to Lugano criteria (Cheson et al, 2014) as assessed by IRC **Secondary Endpoints** **Dose Optimization Phase and Expansion Phase** • DOR, for those patients with CR or PR, defined as the time from the first documentation of response to the first documentation of PD, or death due to any cause • Treatment-emergent adverse events (TEAEs) and changes in laboratory values • PFS, defined as the time from the first study drug dose to the first documentation of PD, or death from any cause • Disease control rate (DCR), defined as CR + PR + stable disease ≥ 8 weeks • Overall survival (OS)

	• PK parameters derived from blood concentrations of duvelisib and its metabolites **Exploratory Endpoints:** **Dose Optimization and Expansion Phases** • Analysis of PTCL tumor pharmacodynamic markers • Analysis of PTCL tumor prognostic markers • Analysis of cytokines and non-tumor immune populations NOTE: Additional exploratory analyses identified by the Sponsor may be performed on study samples
Statistical Methodology:	**Dose Optimization Phase:** <u>Sample Size Considerations:</u> This phase of the study will enroll approximately 20 evaluable patients. However, enrollment may discontinue in either cohort if no CR/PR is noted in the first 5 evaluable patients per cohort. This stopping rule is based on the first stage decision rule of a Simon 2-stage design, with assumptions of a hypothesized ORR of 50% and a null rate of 15% with a one-sided alpha of 0.05 and a power of 85%. <u>Response Assessment:</u> The Investigator's determination of response to study treatment will be used in primary and secondary efficacy analyses. The IRC's determination of disease response will be used in supportive efficacy analyses. For both the IRC and Investigator response determinations, response will not require confirmation by second assessment. <u>Analysis Sets:</u> The Dose Optimization Efficacy Set will include patients who 1) receive at least one dose of study drug and 2) complete at least one cycle of treatment and 3) have at least one scan to assess disease response after completion of one cycle of treatment. The Modified Intent-to-Treat (mITT) Set will include patients who receive at least one dose of study drug. <u>Efficacy Analyses:</u> The Dose Optimization Efficacy Set will be used for all primary and secondary efficacy analyses. Statistical analyses of safety and response will be primarily descriptive in nature. Summary statistics will be produced by dose level, patients with dose changes and for the overall study population for both safety and biological effect parameters. At the conclusion of the Dose Optimization Phase, activity, PK, and safety data as well as any other available data will be taken into consideration to recommend the optimal dose for the Expansion Phase. **Expansion Phase:**

	Sample Size Considerations: One-hundred patients at the optimal duvelisib dose will provide 99.2% power to distinguish between a null ORR of 20% and an alternative ORR of 40% with a two-sided alpha of 0.05. The obtained ORR will have 95% confidence bounds of no greater than ± 10% when the normal approximation method is employed (assumes 50% ORR). If the observed ORR is greater or less than 50%, the confidence bounds will be less than ± 10%. These bounds around the obtained ORR are thought to adequately characterize the effect of the optimal dose of duvelisib in this PTCL population. With protocol amendment 7.0, 20-30 additional patients will be enrolled in the Expansion Phase. Assuming a total of 120 or 130 patients the power to distinguish between a null hypothesis of ORR of 20% and an alternative ORR of 40% will be 99.4% or 99.6% respectively. The primary analysis for the Expansion Phase will be performed once approximately 100 patients with a centrally confirmed diagnosis of PTCL have been enrolled and evaluated for the primary endpoint. In the event that enrollment in the expansion phase exceeds 110% of the planned sample size, a sensitivity analysis will be performed on the first 100 patients enrolled in the Expansion Phase. The final analysis for the Expansion phase will be performed once all patients with a centrally confirmed diagnosis of PTCL have been enrolled and evaluated for the primary endpoint. The total number of patients (up to 130) will be determined by the Sponsor. An important driver of the final sample size may be the number of additional patients needed to add an additional 8-10 patients having PTCL subtype of either ALCL or NK cell. Response Assessment: The IRC's determination of response to study treatment will be used in primary and secondary efficacy analyses. Investigator's determination of disease response will be used in supportive efficacy analyses. For both the IRC and Investigator response determinations, response will not require confirmation by second assessment. Analysis Set: The mITT Set will include patients who receive at least one dose of study drug. Efficacy Analysis: Efficacy analyses will be performed using the mITT population for all primary and secondary efficacy analyses using the response determined by the IRC. An assessment of ORR will be conducted after 40 patients from the Expansion Phase have been followed for a minimum of 4 months from the last patient's first dose. Enrollment in the Expansion Phase may be held if ORR as assessed by IRC, is less than 20%. At that time, the efficacy data (including durability of response) will be reviewed in combination with safety and PK and upon review, the study may be fully stopped for futility.

Figure 1 Study Overview



Abbreviations: BID: twice daily; CR: complete response; DLT: dose-limiting toxicity; DOR: duration of response; DCR: disease control rate; N: number; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PK: pharmacokinetic; PR: partial response; SD: stable disease

The study is being conducted in two phases, with the Dose Optimization Phase (DOP) used to identify a dose for further evaluation in the Expansion Phase. The DOP has been completed and 75 mg BID with a mandatory dose reduction after 2 cycles to 25 mg BID was selected for the Expansion Phase. The primary overall response rate (ORR) endpoint will be assessed according to the Lugano criteria (Cheson et al, 2014). ORR in the DOP was based on investigator assessment, while ORR in the Expansion Phase will be determined by an Independent Review Committee.

Table 1: Dose Optimization Phase Schedule of Events

Procedure[1]	Screening D-30 to -1[2]	Cycle / Day						End of Treatment (EOT)[5]	Safety Follow-up	PD Follow-Up[6]	Survival Follow-up[7]
		Cycle 1			Cycle 2		Cycle 4 and then every 2 cycles[4]				
		D1[2,3]	D8 ± 3	D15 ± 3	D1 ± 3	D15 ± 3	D1 ± 4	≤ 7 d from last dose	30 + 7 d from last dose	Q2M (± 1M)	Q3M (± 1M)
Provision of written informed consent	X										
Demographics	X										
Medical History, including cancer history	X										
12-lead electrocardiogram	X										
Echocardiogram	X										
Complete physical examination	X							X			
Targeted physical examination		X			X		X		X	See Table 3	
Vital signs[8]	X	X			X		X	X	X		
Screening serology[9]	X										
Blood chemistry	X	X	X	X	X	X	X	X	X		
Hematology	X	X	X	X	X	X	X	X	X		
β-hCG pregnancy test[10]	X	X			X		X	X	X		
Serum Immunoglobulins	X	X					X	X			
Tumor tissue	X[11]										
Blood for pharmacodynamic assessment		X[12]			X[12]	X[12]					

Procedure[1]	**Screening D-30 to -1**[2]	**Cycle / Day**						**End of Treatment (EOT)**[5]	**Safety Follow-up**	**PD Follow-Up**[6]	**Survival Follow-up**[7]
		Cycle 1			**Cycle 2**		**Cycle 4 and then every 2 cycles**[4]				
		D1[2,3]	**D8 ± 3**	**D15 ± 3**	**D1 ± 3**	**D15 ± 3**	**D1 ± 4**	**≤ 7 d from last dose**	**30 + 7 d from last dose**	**Q2M (± 1M)**	**Q3M (± 1M)**
Blood for pharmacokinetic assessment	See Table 5										
Blood for exploratory biomarkers[13]	X	X			X		X			X	
Response Assessments	See Table 3										
ECOG Performance Status											
Concomitant medications & Procedures	All concomitant medications and procedures are to be documented from 30 days before the Screening visit through 30 days after the last study drug dose									X	
AE/SAE assessment	All AEs are to be documented the time written informed consent is provided through 30 days after the last study drug dose										
Study Drug Administration		Duvelisib is to be administered PO BID continuously in 28-day cycles									
Survival status											X

Abbreviations: AE = adverse event; BID = twice daily; CMV = cytomegalovirus; d = day; D = Study Day; ECOG = Eastern Cooperative Oncology Group; EOT = End-of-Treatment; HIV = human immunodeficiency virus; HTLV-1 = human T-lymphotropic virus type 1; M = month; PD = progressive disease; PO = orally; Q2M = every 2 months; SAE = serious adverse event; β-hCG = β-human chorionic gonadotropin.

1. See Section 6 for additional information on each assessment.
2. Screening evaluations other than clinical laboratory tests performed within 7 days of C1D1 do not need to be repeated at C1D1 (predose). C1D1 laboratory tests do not need to be repeated if performed within 72 hours prior to Screening.
3. All laboratory samples on C1D1 should be collected predose.
4. Additional visits may be scheduled / procedures may be performed at the Investigator's discretion, as clinically indicated.
5. The End-of-Treatment (EOT) visit is to be performed within 7 days after the last study drug dose. If safety assessments were performed within the previous 2 weeks, they need not be performed at the EOT visit. If disease response assessments were performed within the previous 4 weeks, they need not be performed at the EOT visit.
6. Patients who discontinue treatment from duvelisib for reasons other than PD are to have disease response assessments performed Q2M per Table 3 until the development of PD, as determined by the Investigator, death, or initiation of alternate anti-cancer therapy.
7. After development of PD, as determined by the Investigator, patients are to be followed Q3M for survival; this follow-up may be conducted via telephone.
8. Vital signs, including temperature, blood pressure, and heart rate, are to be measured only if clinically indicated.

9. Screening serology includes assessment of CMV serologies and a liver serology panel. HIV and HTLV-1 tests are to be performed during Screening for all patients without documentation of prior negative results (see Section 6.10.1 for details).
10. Urine or serum β-human chorionic gonadotropin pregnancy testing is to be performed for women of childbearing potential. Pregnancy testing is to be repeated as deemed necessary by the Investigator.
11. Tumor biopsy from Screening or archival tumor tissue will be collected to evaluate prognostic markers. In the event a bone marrow biopsy is collected at Screening please provide a sample.
12. Blood collected at C1D1 (predose), C1D1 (1 hour postdose), C1D1 (4 hour postdose), C2D1 (predose), C2D15 (1 hour), C2D15 (4 hour) (Cohort 1, for patients receiving 50 mg on C2D15) and sent to the central laboratory.
13. To be sent to the central laboratory. Blood collected at predose on C1D1, C2D1, C4D1, and predose every 2 cycles thereafter.

Table 2: Expansion Phase Schedule of Events

Procedure[1]	Screening D-30 to -1[2]	Cycle / Day								End of Treatment (EOT)[5]	Safety Follow-up	PD Follow-Up[6]	Survival Follow-up[7]
		Cycle 1			Cycle 2		Cycle 3	Cycle 4 and then every 2 cycles (WCBP only)[13]	Cycle 5 and then every 2 cycles[4]				
		D1[2,3]	D8 ± 3	D15 ± 3	D1 ± 3	D15 ± 3	D1 ± 3		D1 ± 4	≤ 7 d from last dose	30 + 7 d from last dose	Q2M (± 1M)	Q3M (± 1M)
Provision of written informed consent	X												
Demographics	X												
Medical History, including cancer history	X												
Archival Slides, initial pathological diagnosis	X[8]												
12-lead electrocardiogram[9]	X												
Echocardiogram[10]	X												
Complete physical examination	X									X			
Targeted physical examination		X			X		X		X		X	See Table 4	
Vital signs[11]	X	X	X	X	X	X	X		X	X	X		
Screening serology[12]	X												
CD4 lymphocyte cell count (local laboratory)	X												
Blood chemistry	X	X	X	X	X	X	X		X	X	X		
Hematology	X	X	X	X	X	X	X		X	X	X		
β-hCG pregnancy test[13]	X	X			X		X	X	X	X	X		

Procedure[1]	Screening D-30 to -1[2]	Cycle / Day								End of Treatment (EOT)[5]	Safety Follow-up	PD Follow-Up[6]	Survival Follow-up[7]
		Cycle 1			Cycle 2		Cycle 3	Cycle 4 and then every 2 cycles (WCBP only)13	Cycle 5 and then every 2 cycles[4]				
		D1[2,3]	D8 ± 3	D15 ± 3	D1 ± 3	D15 ± 3	D1 ± 3		D1 ± 4	≤ 7 d from last dose	30 + 7 d from last dose	Q2M (± 1M)	Q3M (± 1M)
Serum Immunoglobulins	X	X					X		X	X			
Tumor tissue	X[14]												
Blood for pharmacodynamic assessment		X[15]				X[15]							
Blood for pharmacokinetic assessment			See Table 5										
Blood for exploratory biomarkers[16]	X	X			X		X		X			X	
Response Assessments			See Table 4										
ECOG Performance Status													
Concomitant medications & Procedures			All concomitant medications and procedures are to be documented from 30 days before the Screening visit through 30 days after the last study drug dose									X	
AE/SAE assessment			All AEs are to be documented at the time written informed consent is provided through 30 days after the last study drug dose										
Study Drug Administration				Duvelisib is to be administered PO BID continuously in 28-day cycles									
Survival status													X

Abbreviations: AE = adverse event; BID = twice daily; CMV = cytomegalovirus; d = day; D = Study Day; ECOG = Eastern Cooperative Oncology Group; EOT = End-of-Treatment; HIV = human immunodeficiency virus; HTLV-1 = human T-lymphotropic virus type 1; M = month; PD = progressive disease; PO = orally; Q2M = every 2 months; SAE = serious adverse event; β-hCG = β-human chorionic gonadotropin.

1. See Section 6 for additional information on each assessment.
2. Screening evaluations other than clinical laboratory tests performed within 7 days of C1D1 do not need to be repeated at C1D1 (predose). C1D1 laboratory tests do not need to be repeated if performed within 72 hours prior to Screening.
3. All laboratory samples on C1D1 should be collected predose.
4. Additional visits may be scheduled / procedures may be performed at the Investigator's discretion, as clinically indicated.

5. The End-of-Treatment (EOT) visit is to be performed within 7 days after the last study drug dose. If safety assessments were performed within the previous 2 weeks, they need not be performed at the EOT visit. If disease response assessments were performed within the previous 4 weeks, they need not be performed at the EOT visit.
6. Patients who discontinue treatment from duvelisib for reasons other than PD are to have disease response assessments performed Q2M per Table 4 until the development of PD, as determined by the Investigator, death, or initiation of alternate anti-cancer therapy.
7. After development of PD, as determined by the Investigator, patients are to be followed Q3M for survival; this follow-up may be conducted via telephone.
8. Stained Formalin-fixed, paraffin-embedded (FFPE) slides used for PTCL diagnosis must be collected for all patients enrolled and submitted for central pathology review. See lab manual for details.
9. Additional on-treatment or follow-up electrocardiograms should be performed at the Investigator's discretion as clinically indicated.
10. Additional on-treatment or follow-up echocardiograms should be performed at the Investigator's discretion as clinically indicated.
11. Vital signs, including temperature, blood pressure, pulse, and respiration rate, and weight (kg) are to be measured. Height (cm) to be measured only at Screening.
12. Screening serology includes assessment of CMV serologies and a liver serology panel. HIV and HTLV-1 tests are to be performed during Screening for all patients without documentation of prior negative results (see Section 6.10.1 for details).
13. Urine or serum β-human chorionic gonadotropin pregnancy testing is to be performed for women of childbearing potential. Pregnancy testing is to performed monthly and may be repeated as deemed necessary by the Investigator. For cycles where pregnancy testing is the only requirement, the patient may have this done locally.
14. Tumor biopsy from Screening or archival tumor tissue will be collected to evaluate prognostic markers. In the event a bone marrow biopsy is collected at Screening please provide a sample.
15. Blood collected at C1D1 (predose), C1D1 (1 hour postdose), C1D1 (4 hour postdose), C2D15 (predose), C2D15 (1 hour), C2D15 (4 hour) and sent to the central laboratory. The collection of PD samples will occur for patients in the US only.
16. To be sent to the central laboratory. Blood collected at predose on C1D1, C2D1, C3D1, and predose every 2 cycles thereafter up to Cycle 11.

Table 3: Dose Optimization Phase Disease Response and Follow-up Assessments

Procedure[1]	Screening D-30 to -1	Cycle / Day						End of Treatment (EOT)[3]	PD Follow-up[4]	Survival Follow-up[5]
		Cycle 1			Cycle 2		Cycle 4 and then every 2 cycles[2]			
		D1	D8 ± 3	D15 ± 3	D1 ± 3	D15 ± 3	D1 ± 4	≤ 7 d from last dose	Q2M (± 1M)	Q3M (± 1M)
PET-CT or CT or MRI[6]	X[7]				X[8]		X	X	X	
ECOG performance status	X						X	X	X	
Survival status										X

Abbreviations: C = cycle; CT = d = day; D = Study Day; ECOG = Eastern Cooperative Oncology Group; EOT = End-of-Treatment; FDG = fluorodeoxyglucose ; IRC = independent review committee; M = month; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography; PTCL = peripheral T-cell lymphoma; Q2M = every 2 months.

1. See Section 6.11 for additional information on disease response assessments.
2. Additional visits may be scheduled / procedures may be performed at the Investigator's discretion, as clinically indicated.
3. The EOT visit is to be performed within 7 days after the last study drug dose.
4. Patients who discontinue treatment from duvelisib for reasons other than PD are to have disease response assessments performed Q2M until the development of PD, as determined by the Investigator, death, or initiation of alternate anti-cancer therapy.
5. After development of PD, as determined by the Investigator, patients are to be followed Q3M for survival until closure of the study by the Sponsor; this follow-up may be conducted via telephone.
6. PET-CT is the preferred method of assessment. The modality chosen to evaluate response in each individual patient should be the same throughout the duration of the study. PET images are to be assessed using the 5-point scale (5PS). At each scheduled timepoint, the Investigator will be asked to provide a PET-CT-based response, based on the Lugano (Cheson et al, 2014) response criteria. Images will be centrally stored and read, with disease response determined by the IRC using the central image assessments.
7. To be performed within 14 days before C1D1. At Screening, disease will be assessed with PET-CT. Where PET-CT is not feasible, CT with contrast or MRI may be used after discussion with the Medical Monitor. Subsequently, for FDG-avid PTCL, PET-CT will be used to assess disease status and for FDG-non-avid PTCL, CT with contrast or MRI will be appropriate substitutes.
8. To be performed within 7 days prior to starting Cycle 2.

Table 4: Expansion Phase Disease Response and Follow-up Assessments

Procedure[1]	Screening D-30 to -1	Cycle / Day						End of Treatment (EOT)[3]	PD Follow-up[4]	Survival Follow-up[5]
		Cycle 1			Cycle 3		Cycle 5 and then every 2 cycles[2]			
		D1	D8 ± 3	D15 ± 3	D1 ± 3	D15 ± 3	D1 ± 4	≤ 7 d from last dose	Q2M (± 1M)	Q3M (± 1M)
PET-CT or CT or MRI[6]	X[7]				X[8]		X	X	X	
ECOG performance status	X						X	X	X	
Survival status										X

Abbreviations: C = cycle; CT = d = day; D = Study Day; ECOG = Eastern Cooperative Oncology Group; EOT = End-of-Treatment; FDG = fluorodeoxyglucose ; IRC = independent review committee; M = month; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography; PTCL = peripheral T-cell lymphoma; Q2M = every 2 months.

1. See Section 6.11 for additional information on disease response assessments.
2. Additional visits may be scheduled / procedures may be performed at the Investigator's discretion, as clinically indicated.
3. The EOT visit is to be performed within 7 days after the last study drug dose.
4. Patients who discontinue treatment from duvelisib for reasons other than PD are to have disease response assessments performed Q2M until the development of PD, as determined by the Investigator, death, or initiation of alternate anti-cancer therapy.
5. After development of PD, as determined by the Investigator, patients are to be followed Q3M for survival until closure of the study by the Sponsor; this follow-up may be conducted via telephone.
6. PET-CT is the preferred method of assessment. The modality chosen to evaluate response in each individual patient should be the same throughout the duration of the study. PET images are to be assessed using the 5-point scale (5PS). At each scheduled timepoint, the Investigator will be asked to provide a PET-CT-based response, based on the Lugano (Cheson et al, 2014) response criteria. Images will be centrally stored and read, with disease response determined by the IRC using the central image assessments.
7. To be performed within 14 days before C1D1. At Screening, disease will be assessed with PET-CT. Where PET-CT is not feasible, CT with contrast or MRI may be used after discussion with the Medical Monitor. Subsequently, for FDG-avid PTCL, PET-CT will be used to assess disease status and for FDG-non-avid PTCL, CT with contrast or MRI will be appropriate substitutes.
8. To be performed within 7 days prior to starting Cycle 3.

Table 5: Dose Optimization and Expansion Phase Pharmacokinetic Assessment

	Cycle / Day						
	Cycle 1			Cycle 2		Cycle 3	Cycle 5
Procedure[1]	**D1**	**D8 ± 3**	**D15 ± 3**	**D1 ± 3**	**D15 ± 3**	**D1 ± 3**	**D1 ± 4**
Dose Optimization Phase[2]	X[3]	X[4]	X[3]	X[4]	X[5]		
Expansion Phase[2]			X[6]		X[6]	X[4]	X[4]

Abbreviations: AE = adverse event; BID = twice daily; PK = pharmacokinetic.

1. On the PK sampling days, duvelisib will be administered in clinic in the morning after predose PK sampling.
2. An additional blood sample(s) for PK is requested at the start and end of any drug interruptions for an AE, when feasible.
3. PK blood samples will be collected from all patients on C1D1 and C1D15 at predose (within 30 minutes prior to the morning dosing) and 0.5, 1, 1.5, 2, 3, 4, and 6 hours postdose.
4. Predose sample is drawn within 30-minutes prior to the morning dosing.
5. PK blood samples will be collected only from patients receiving 50 mg BID on C2D15 at predose (within 30 minutes prior to the morning dosing) and 0.5, 1, 1.5, 2, 3, 4, and 6 hours postdose.
6. PK blood samples will be collected from all patients on C1D15 and C2D15 at predose (within 30 minutes prior to the morning dosing) and 1, 2, and 4 hours postdose.

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Abbreviation	Definition
^{18}FDG-PET	[^{18}F] Fluorodeoxyglucose-positron emission tomography
5PS	5-point scale
AE	Adverse event
ALC	Absolute lymphocyte count
ALCL	Anaplastic large cell lymphoma
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	Twice daily
CEC	Central ethics committee
CMV	Cytomegalovirus
CR	Complete response
CRO	Contract Research Organization
CT	Computed tomography
CX	Cycle X
CYP3A	Cytochrome P450 3A
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DOR	Duration of response
DX	Day X
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End-of-Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
Gi	Giga (1 x 10^9) or 1 billion
GI	Gastrointestinal
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCV Ab	Hepatitis C Ab
HIV	Human immunodeficiency virus

Abbreviation	Definition
HSV	Herpes simplex virus
HTLV-1	Human T-lymphotropic virus type 1
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IRB	Institutional review board
IRC	Independent Review Committee
ITT	Intent-to-treat
IV	Intravenous(ly)
IWG	International Working Group
LDi	Longest transverse diameter of a lesion
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NKTL	Natural-killer/T-cell lymphoma
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
P-gp	P-glycoprotein
PI3K	Phosphoinositide-3-kinase
PO	Oral(ly)
PPD	Cross product of the LDi and perpendicular diameter
PR	Partial response
PTCL	Peripheral T-cell lymphoma
QD	Once daily
QTcF	QT interval corrected with Fridericia's method
SAE	Serious adverse event

Abbreviation	Definition
sALCL	Systemic anaplastic large cell lymphoma
SAP	Statistical Analysis Plan
SCT	Stem cell transplantation
SD	Stable disease
SDi	Shortest axis perpendicular to the LDi
SPD	Sum of the product of the perpendicular diameters for multiple lesions
SPTCL	Subcutaneous panniculitis-like T-cell lymphoma
SUV	Standardized uptake value
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
VZV	Herpes zoster virus
WBC	White blood cell count
WCBP	Women/woman of childbearing potential
β-hCG	β-human chorionic gonadotropin

1. BACKGROUND AND STUDY RATIONALE

1.1. Peripheral T-cell Lymphoma

Peripheral T-cell lymphoma (PTCL) is a rare, aggressive type of non-Hodgkin lymphoma with an incidence of < 1 in 100,000 in the United States (US). The incidence varies geographically, with higher incidences in Asian countries than in Western countries (Park et al, 2014). PTCL generally affects people aged 60 years and older and is diagnosed slightly more often in men than in women. In addition to the incidence, there is a geographic difference in the PTCL subtypes. For example, PTCL-not otherwise specified (NOS) is the most common subtype in North American and Europe, while adult T-cell leukemia/lymphoma (ATLL) is most common in Asia (Vose et al, 2008).

Patients with newly diagnosed PTCL are most commonly treated with combination chemotherapy regimens, often followed by consolidation with high-dose chemotherapy and stem cell transplantation (SCT). However, the majority of patients develop relapsed or refractory disease (Zinzani et al, 2016). In addition, co-existing co-morbidities often preclude SCT consolidation in older PTCL patients.

Historically, patients with relapsed disease have had a dismal prognosis, with a median overall survival (OS) of less than 6 months. Pralatrexate, a folate analog, and belinostat and romidepsin, both intravenously (IV)-administered histone deacetylase inhibitors, were approved by the US Food and Drug Administration (FDA) for the treatment of relapsed or refractory PTCL patients based on objective response rates (ORR) ranging from 25% to 27% in single-arm studies. Brentuximab vedotin, a CD30-directed antibody-drug conjugate, also administered IV, is indicated for systemic anaplastic large cell lymphoma (sALCL), a sub-type of PTCL, also on the basis of a single-arm study. To date, no agent has been shown to improve OS. However, these treatments are associated with toxicities and only one to date is globally available (Laribi et al, 2018). Apart from a few patients who achieve complete response (CR), response durations remain brief. Therefore, PTCL remains a condition of high unmet medical need.

1.2. Duvelisib (IPI-145; VS-0145)

Phosphoinositide-3-kinase (PI3K) is a lipid kinase involved in intracellular signal transduction in many cells. The isoforms of PI3K's catalytic subunit (p110) exist as α, β, δ, and γ, the δ and γ isoforms being preferentially expressed in leukocytes and involved in innate and adaptive immune function (Clayton et al, 2002; Okkenhaug et al, 2002; Vanhaesebroeck et al, 2010; Fung-Leung et al, 2011). For patients with advanced hematologic malignancies, including T-cell lymphomas, the pathways mediated by PI3K-δ,γ contribute to survival, proliferation, and differentiation of cancer cells. It is well recognized that cancer cells, through the expression of various cytokines, growth factors, and chemokines, recruit multiple cell types, including myeloid cells capable of differentiating into tumor-associated macrophages that promote angiogenesis and augment tumor growth (Lewis et al, 2006). PI3K-δ and PI3K-γ also have roles in the establishment and maintenance of the tumor microenvironment that plays an important role in

the development and maintenance of cancer cells (Hanahan et al, 2011). Accordingly, PI3K-δ,γ inhibition would be expected to disrupt tumor maintenance and progression (Schmid et al, 2011).

Duvelisib is a potent PI3K-δ,γ inhibitor being developed by Secura Bio, Inc. (Secura Bio) as an orally administered therapeutic in hematologic malignancies, including PTCL. Duvelisib is mechanistically distinct from other agents either currently available or being developed for PTCL and has demonstrated encouraging clinical activity in heavily pre-treated PTCL patients treated at doses of 60 mg twice daily (BID) (n = 2), 75 mg BID (n = 13), or 100 mg BID (n = 1). Among these 16 patients, the Investigator-assessed ORR per International Working Group (IWG) criteria was 50% (8/16), which included 2 CRs and 5 partial responses (PRs) in the 75 mg BID dose group and 1 CR in the 60 mg BID dose group. Responses were seen across the spectrum of PTCL subtypes, with CRs in patients with enteropathy-associated T-cell lymphoma (EATL), angioimmunoblastic T-cell lymphoma (AITL), and PTCL-NOS, and PRs in those with subcutaneous panniculitis-like T-cell lymphoma (SPTCL), ALCL, AITL and PTCL-NOS. Responses were observed in patients who had relapsed from prior treatment with approved therapies for PTCL. The median time to response was 1.9 months and the median duration of response was not estimable, as only 1 patient had progression or death after response. The median OS was 8.4 months, and the estimated probability of survival at 24 months was 34.4%.

Furthermore, duvelisib demonstrated an acceptable safety profile in this relapsed and refractory patient population. In the combined population of patients with PTCL or cutaneous T-cell lymphoma (n = 35), the most frequently observed ≥ Grade 3 adverse events (AEs) were elevated transaminase (11 patients; 31% alanine aminotransferase [ALT]/aspartate aminotransferase [AST]), maculopapular rash (6 patients;17%), neutropenia (3 patients; 9%) pneumonia (5 patients;14%), and lung infection (3 patients; 9%), which were generally manageable with dose modifications and standard of care interventions (Horwitz et al, 2018).

For additional preclinical information on the antitumor activity of duvelisib, please see the Investigator's Brochure (IB).

1.3. Study Rationale

The activity and evidence of response durability in 16 patients with heavily pre-treated PTCL observed in the Phase 1 study suggest that duvelisib is an active single agent for relapsed or refractory PTCL, an indication with a high unmet therapeutic need.

The Phase 2/3 clinical dose of duvelisib has been identified as 25 mg BID for patients with indolent non-Hodgkin lymphoma and chronic lymphocytic leukemia. Duvelisib (COPIKTRA™) was approved in the US in September 2018 with a dosage of 25 mg orally BID and is indicated for the treatment of adult patients with relapsed or refractory CLL or SLL after at least two prior therapies and accelerated approval for the treatment of adult patients with relapsed or refractory FL after at least two prior systemic therapies. In the Phase 1, dose-escalation study in patients with hematologic malignancies, including PTCL, duvelisib was administered BID at escalating doses of 8 mg, 15 mg, 25 mg, 35 mg, 50 mg, 60 mg, 75 mg, and 100 mg, with the maximum

tolerated dose identified as 75 mg BID. Patients with PTCL received dose levels ≥ 60 mg; therefore, the activity of duvelisib in patients with PTCL at lower dose levels has not been evaluated. Accordingly, the current study will employ a Dose Optimization Phase, in which patients will initially start treatment with duvelisib 25 mg BID, with potential sequential escalation on a per-patient basis to 50 mg BID and then 75 mg BID, based on disease response and tolerability. The optimal dose, as identified in the Dose Optimization Phase will then be selected for use in the subsequent Expansion Phase.

As described in Section 11.13 a review of preliminary indications of response in each cohort was conducted when 5 patients had completed the first cycle in each cohort of the Dose Optimization Phase. Responses had been reported by the investigators for at least one patient in each cohort and enrollment was allowed to continue.

The interim analysis from the Dose Optimization Phase demonstrated the following:

- Sixteen patients on Cohort 1 and 11 patients on Cohort 2 received at least one dose of duvelisib. Ten patients from each cohort were evaluable for response. Six patients discontinued treatment prior to reaching the first assessment, all of whom were on Cohort 1. Premature discontinuations were due primarily to disease progression and/or toxicities.

- Five patients per cohort demonstrated radiographic responses, including 4 CRs on Cohort 1 and 2 CRs on Cohort 2. Not all responses have been confirmed. Responses were not limited to a particular subtype of PTCL.

- With a mean follow-up time of 4 weeks for Cohort 1 and 8 weeks for Cohort 2, there appeared to be a numerically greater number of adverse events in Cohort 1. Among the 16 patients in Cohort 1 and 11 in Cohort 2, 68.8% and 36.4%, respectively, had ≥ Grade 3 AE's. Similarly, the incidence of serious adverse events in Cohort 1 and Cohort 2 was 43.8% and 18.2%, respectively. However, 2 patients in Cohort 1 had more than 1 AE. No new safety signals were identified. Infections and neutropenia appeared to account for the majority of the differences in the incidence of AEs between the two cohorts.

- Area Under the Curve (AUC) increased with dose, and the mean steady state AUC at 75 mg BID was approximately 2 times that at 25 mg BID.

- Exploratory biomarker analysis revealed a difference in the baseline CD4 lymphocyte counts between evaluable patients (mean CD4 count of 398/mm^3) and non-evaluable patients (mean CD4 count of 230/mm^3). CD8 lymphocyte counts also showed a similar difference. The reasons for these differences are unclear.

In summary, the preliminary data from the Dose Optimization Phase support continuation to the Expansion Phase (see Section 4.1.2 and Section 11). While both starting doses are active, it appears that more patients discontinued prematurely on Cohort 1 because of more rapid disease progression and toxicity. This observation suggests that the higher starting dosage of 75 mg BID may result in a more rapid debulking of tumor and more rapid disease control. However, the

longer-term toxicities with the 75 mg BID dosage have not yet been assessed during this phase of the study. It is likely that toxicities with longer times of onset, such as colitis, may be disproportionately greater with the 75 mg BID starting dosage. Therefore, to achieve both a rapid remission and ameliorate longer-term toxicities, the dosage will be 75 mg BID until the first response assessment (2 cycles) at which the dose will be reduced to 25 mg BID. As it is now known that the 25 mg BID dosage can be active in PTCL, and later-onset toxicities may be prevented, a proactive decrease in the dose is justified.

Response assessments will continue at approximately 8-week intervals. If a subsequent assessment demonstrates progression and the patient did not require a dose modification due to toxicity, the dose can be re-escalated to 75 mg BID with a confirmatory scan after approximately 4 weeks of therapy. Patients that re-escalate to 75 mg BID may remain at this dose level until the need for dose modification or the criteria for discontinuation is met. The rationale for re-escalation in the absence of clinically significant toxicities is justified by the prior clinical benefit on the higher dose.

Responses in the Phase 1 were seen in SPTCL (n=2 of 3 patients; PRs) and EATL (n=1 of 1 patient; CR) which were additional subtypes of PTCL not included initially in this study. Therefore, the inclusion criterion number 1 was broadened.

Lastly, the rationale for the requirement of CD4 lymphocyte count of $\geq 50/mm^3$ ($0.05 \times 10^9/L$) is based on the emerging data from the Dose Optimization Phase that non-evaluable patients were more likely to be immunodeficient with respect to CD4 lymphocyte cell count. By using the Grade 4 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) definition for decreased CD4+ lymphocytes as the cut off, the patient population could be enriched for patients who are more likely to stay on treatment to allow sufficient time to achieve a response. This cut-off was chosen on the basis of above data, input from investigators, and aligned with the NCI CTCAE definition of life-threatening lymphopenia.

1.4. Benefit/Risk Assessment

Clinical study results to date support a favorable benefit-risk of duvelisib for patients with hematologic malignancies. The risks are consistent with the AE profile for the PI3K inhibitor drug class and AEs experienced by patients undergoing treatment for advanced cancers. Important identified risks include infections, diarrhea/colitis, cutaneous reactions, pneumonitis, neutropenia, and ALT/AST elevation. Potential risks include hepatotoxicity, drug-drug interaction (DDI) and reproductive toxicity. These toxicities are managed using a combination of prophylaxis, supportive care and dose modifications. Duvelisib monotherapy has demonstrated encouraging activity in relapsed and refractory PTCL seen in this study and the Phase 1 study in hematologic malignancies. The starting dosage will be 75 mg BID until the first response assessment (2 cycles) in an attempt to debulk the tumor more efficiently. Subsequently, the dose will be reduced to 25 mg BID to anticipate and reduce toxicities of later times of onset. As both dose levels have demonstrated preliminary responses, this strategy is designed to reduce the risk of toxicity while maintaining clinical benefit. Overall, the potential benefit to a patient

with relapsed/refractory PTCL with few treatment options and historically a dismal prognosis, appears at this time, to outweigh any potential risks.

2. STUDY OBJECTIVES

2.1. Dose Optimization Phase

2.1.1. Primary Objective

The primary objective of the Dose Optimization Phase is:

- To determine the optimal duvelisib dose for utilization in the Expansion Phase by evaluating the ORR supported by safety, additional efficacy, and pharmacokinetics (PK) parameters as well as any other available data in the population of patients receiving the optimal dose of duvelisib for at least one cycle in patients with relapsed or refractory PTCL

2.1.2. Secondary Objectives

The secondary objectives of the Dose Optimization Phase are:

- To evaluate additional efficacy parameters for duvelisib in the population of patients receiving duvelisib for at least one cycle in patients with relapsed or refractory PTCL
- To characterize the tolerability and safety of duvelisib in patients with relapsed or refractory PTCL
- To evaluate the PK of duvelisib and if applicable, its metabolite(s)

2.1.3. Exploratory Objective

The exploratory objective of the Dose Optimization Phase is:

- To evaluate pharmacodynamic and prognostic biomarkers

2.2. Expansion Phase

2.2.1. Primary Objective

The primary objective of the Expansion Phase is:

- To determine the efficacy of the optimal dose of duvelisib in patients with relapsed or refractory PTCL

2.2.2. Secondary Objectives

The secondary objectives of the Expansion Phase are:

- To evaluate additional efficacy parameters for duvelisib
- To characterize the tolerability and safety of duvelisib in patients with relapsed or refractory PTCL
- To evaluate the PK of duvelisib and if applicable, its metabolite(s)

2.2.3. Exploratory Objective

The exploratory objective of the Expansion Phase is:

- To evaluate pharmacodynamic and prognostic biomarkers

3. STUDY ENDPOINTS

3.1. Dose Optimization Phase

The evaluation of the primary and secondary efficacy endpoints based upon Lugano criteria (Cheson et al, 2014), will be performed using Investigator assessments unless otherwise noted, with results from Independent Review Committee (IRC) assessments used as supportive analyses.

3.1.1. Primary Endpoint

The primary endpoint is:

- ORR (CR + PR), as assessed by the Investigator, as determined using the Lugano criteria (Cheson et al, 2014), supported by secondary efficacy, safety and PK in the population of patients receiving the optimal dose of duvelisib for at least one cycle of study therapy

3.1.2. Secondary Endpoints

The secondary endpoints are:

- Duration of response (DOR), for those patients with CR or PR, defined as the time from the first documentation of response to the first documentation of progressive disease (PD), or death due to any cause
- Treatment-emergent adverse events (TEAEs) and changes in laboratory values
- Progression-free survival (PFS), defined as the time from the first study drug dose to the first documentation of PD, or death from any cause
- Disease control rate (DCR), defined as CR + PR + stable disease ≥ 8 weeks
- Overall survival (OS)
- PK parameters derived from blood concentrations of duvelisib and its metabolites

3.1.3. Exploratory Endpoints

The exploratory endpoints are:

- Analysis of PTCL tumor pharmacodynamic markers
- Analysis of PTCL tumor prognostic markers
- Analysis of cytokines and non-tumor immune populations

NOTE: Additional exploratory analyses identified by the Sponsor may be performed on study samples

3.2. Expansion Phase

The evaluation of the primary and secondary efficacy endpoints based upon Lugano criteria (Cheson et al, 2014) will be performed using IRC assessments, with results from Investigator-assessed response used as supportive analyses.

3.2.1. Primary Endpoint

The primary endpoint is:

- ORR (CR+PR), as assessed by the IRC, according to Lugano criteria (Cheson et al, 2014)

3.2.2. Secondary Endpoints

The secondary endpoints are:

- TEAEs and changes in laboratory values
- DOR, for those patients with CR or PR, defined as the time from the first documentation of response to the first documentation of PD, or death due to any cause
- PFS, defined as the time from the first dose of study treatment to the first documentation of PD, or death from any cause
- DCR, defined as CR + PR + SD $\geq$ 8 weeks
- OS
- PK parameters derived from blood concentrations of duvelisib and its metabolites

3.2.3. Exploratory Endpoints

The exploratory endpoints are:

- Analysis of PTCL tumor pharmacodynamic markers
- Analysis of PTCL tumor prognostic markers
- Analysis of cytokines and non-tumor immune populations

NOTE: Additional exploratory analyses identified by the Sponsor may be performed on study samples

4. STUDY DESIGN

4.1. Overview of Study Design

This is a multi-center, parallel cohort, open-label, Phase 2 study of duvelisib, an oral dual inhibitor of PI3K-δ,γ, in patients with relapsed/refractory PTCL. The study has 2 phases, a Dose Optimization Phase and an Expansion Phase.

Regardless of study phase, all patients will undergo screening assessments up to 30 days before the first study drug dose (Cycle 1, Day 1 [C1D1]). Patients meeting all of the entrance criteria, based on Screening assessments, will be enrolled in the study and receive the first study drug dose on C1D1. Thereafter, patients will attend study center visits as per the applicable Phase Schedule of Events (Dose Optimization: Table 1, Expansion Phase: Table 2). At screening, disease will be measured using ^{18}F-fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET)-computed tomography (CT) scanning (PET-CT) (CT images along with PET should be diagnostic with contrast unless contraindicated). Where PET-CT is not feasible, CT with contrast or magnetic resonance imaging (MRI) may be used after discussion with the Medical Monitor. Subsequently, for FDG-avid PTCL, PET-CT will be used to assess disease status and for FDG-non-avid PTCL, CT with contrast or MRI will be appropriate substitutes. The modality chosen to evaluate response in each individual patient should be the same throughout the duration of the study. For the purposes of patient management during the conduct of the study, the Investigator's assessment of disease response will be used. Images also will be centrally stored, and disease response will be determined by an IRC for futility and at the end of the study.

4.1.1. Dose Optimization Phase

The Dose Optimization Phase will be conducted at up to approximately 15 centers in the US.

In the Dose Optimization Phase, patients will be randomly assigned at a 1:1 ratio to 1 of 2 study cohorts, as follows:

- Cohort 1: Duvelisib orally (PO) BID at a starting dose of 25 mg, with potential escalation on a per-patient basis to 50 mg BID and then to 75 mg BID, based on the patient's response to and tolerance of therapy, in 28-day cycles
- Cohort 2: Duvelisib 75 mg PO BID, administered in 28-day cycles

Approximately 10 patients each will be enrolled in Cohorts 1 and 2. Patients in the Dose Optimization Phase who discontinue before receiving at least 1 cycle of study drug may be replaced. Enrollment into the Dose Optimization Phase may continue until the initiation of the Expansion Phase.

For both cohorts, dose modification criteria for duvelisib will be applied if the starting dose or a subsequent dose of duvelisib is deemed intolerable (see Section 9.4.2). Dose Optimization Phase patients will complete treatment as defined for their cohort.

Cohort 1

All patients will receive duvelisib at a starting dose of 25 mg PO BID (Level 1), with potential sequential escalation to 50 mg PO BID (Level 2), and then to 75 mg PO BID (Level 3). Intra-patient dosing decisions will occur as follows:

After completion of Cycle 1 and every 2 cycles thereafter:

- Patients with complete response (CR) or partial response (PR) will have their duvelisib dose maintained at the current dose level
- Patients with stable disease (SD) who are, in the Investigator's opinion, tolerating and otherwise suitable to continue receiving therapy, will have the duvelisib dose increased to the next level until the next response assessment or development of PD or intolerance, as determined by the Investigator

Patients with PD, who are not tolerating therapy, or otherwise not suitable to continue receiving therapy will discontinue duvelisib

In no case will the duvelisib dose be increased to a level > 75 mg BID (total daily dose 150 mg).

All patients in Cohort 1 will receive duvelisib until development of PD or unacceptable toxicity, as determined by the Investigator.

Cohort 2

All patients in Cohort 2 will receive duvelisib 75 mg PO BID in 28-day cycles until development of PD or unacceptable toxicity, as determined by the Investigator.

4.1.2. Expansion Phase

The Expansion Phase will be conducted at approximately 40-50 centers globally.

After a sufficient number of patients from the Dose Optimization Phase are evaluable, efficacy, PK, and safety data as well as any other available data will be taken into consideration to recommend the optimal dose for the Expansion Phase (Note: the optimal dose for the Expansion Phase has been selected and documented in Protocol Amendment 2 V3, 14 March 2019 –see Expansion Phase Dose Selection below and Section 1.3). The interim results of the Optimization Phase may also drive changes to the Expansion Phase of the study such as modification to the study patient population, other aspects of entry criteria, and the inclusion of patients from geographic regions outside the US; any such changes will be documented in an amendment to the protocol. Patients will have disease assessment after Cycle 2 and every 2 cycles thereafter until the follow-up stage is reached and assessment will occur according to Table 4.

Expansion Phase Dose Selection:

As of 02 January 2019, 20 patients met the criteria for the Dose Optimization efficacy population and available data as of 11 February 2019 were reviewed. A dosage of 75 mg BID for the first 2 cycles, followed by a mandatory reduction to 25 mg BID thereafter for those patients with CR, PR or SD, will be used for the Expansion Phase. The dose may be re-escalated to 75 mg BID based on response assessment and safety (see Sections 1.3 and 9.1.2).

4.1.3. Independent Review Committee

An IRC will be established to provide a blinded review of imaging and pertinent clinical data in order to provide expert interpretation of treatment response. The IRC will be composed of independent clinicians not otherwise involved in the study. The specifics of the IRC composition and processes will be described in a separate IRC charter.

4.2. Number of Patients

Approximately 20 patients with relapsed/refractory PTCL will be enrolled in the Dose Optimization Phase, with approximately 10 evaluable patients each in Cohorts 1 and 2. Patients in the Dose Optimization Phase who discontinue before receiving at least 1 cycle of study drug may be replaced.

Approximately 100-130 patients are anticipated to participate in the Expansion Phase, for a total of 130-160 patients across both phases.

After the first 100 patients are enrolled in the expansion phase an additional 20-30 patients may be enrolled with a target of 8-10 patients have an ALCL or NK cell subtype.

4.3. Duration of Patient Participation

The duration of patient participation is dependent on the patient's tolerance of and response to duvelisib; it is anticipated that patients will participate in the study for a minimum of ~3 months.

All patients will be screened for study eligibility within 30 days before the first study drug dose (i.e., Baseline, C1D1). Patients who are determined to be eligible will be enrolled in the study at Baseline and will receive duvelisib continuously in 28-day cycles. For the Dose Optimization Phase, it is anticipated that patients will receive at least 1 cycle of therapy. For the Expansion Phase, it is anticipated that patients will receive at least 2 cycles of therapy. Unlike the Dose Optimization Phase if the patient demonstrates progression and no dose modification was required for toxicity, the patient may re-escalate to 75 mg BID with a confirmatory scan after approximately 4 weeks of therapy. Patients will continue duvelisib until development of PD or intolerance or another discontinuation criterion is met, as determined by the Investigator; no maximum duration of therapy has been set. After discontinuation of duvelisib, all patients are to attend an End-of-Treatment (EOT) visit within 7 days after the last study drug dose and then a Safety Follow-up visit 30 days after the last study drug dose. Patients who have not experienced PD will continue to be followed for disease response as per Table 3 or Table 4 until development

of PD, as determined by the Investigator. Patients with documented PD, as determined by the Investigator, will be followed on an every 3-month basis for survival until closure of the study by the Sponsor; follow-up for survival may be conducted via telephone.

5. STUDY POPULATION

5.1. Inclusion Criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. ≥ 18 years of age
2. Pathologically-confirmed PTCL, as defined by the World Health Organization. Slides must be submitted for central pathology review. Results of central pathology review are not required prior to initiation of treatment.
3. Received at least 2 cycles of one standard regimen for newly diagnosed advanced PTCL, and one of the following:
    (a) failed to achieve at least a PR after 2 or more cycles of standard therapy;
    (b) failed to achieve a CR after completion of standard therapy; and/or
    (c) persistent or progressive disease after an initial response
4. For patients with CD30+ ALCL, failed or are ineligible or intolerant to brentuximab vedotin
5. Measurable disease as defined by Lugano for PTCL, i.e., at least 1 measurable disease lesion > 1.5 cm in at least one dimension by conventional techniques (^{18}FDG-PET-CT, CT with contrast, MRI)
6. Must have the following laboratory parameters:
    - Hemoglobin ≥ 8.0 g/dL with or without transfusion support
    - Platelet count ≥ 25×10^9/L
    - Serum creatinine ≤ 2.0 × the upper limit of normal (ULN)
    - Total bilirubin ≤ 1.5 × ULN (in patients with Gilbert's Syndrome a bilirubin > 1.5 × ULN may be allowed)
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 × ULN
    - CD4 lymphocyte count ≥ 50/mm^3 (0.05 x 10^9/L) (Expansion Phase)
7. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
8. Recovery to ≤ Grade 1 or baseline for any toxicities due to prior treatments, with the exception of peripheral neuropathy (recovery to ≤ Grade 2) or alopecia

9. Washout of at least 14 days or 5 half-lives, whichever is longer, from PTCL-directed therapy. If previously treated with lenalidomide, must have completed treatment 4 weeks prior to C1D1

10. For women of childbearing potential (WCBP): negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test within 1 week before first treatment (WCBP defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally post-menopausal for at least 12 consecutive months for women > 55 years of age)

11. Male and female patients of reproductive potential (i.e., not surgically sterile or female patients who are not postmenopausal) must be willing to use a highly effective method of contraception for the duration of study treatment and for at least 3 months after the last dose of duvelisib

12. Signed and dated institutional review board (IRB)/independent ethics committee (IEC)/central ethics committee (CEC)-approved informed consent form before any Screening procedures are performed

5.2. Exclusion Criteria

Patients who fulfill 1 or more of the following criteria will not be eligible for inclusion in this study:

1. Primary leukemic PTCL subtypes (i.e., T-cell prolymphocytic leukemia, T-cell large granular lymphocytic leukemia, adult T-cell leukemia/lymphoma and aggressive NK-cell leukemia) or transformed mycosis fungoides

2. Received prior allogeneic transplant

3. Received prior treatment with a PI3K inhibitor

4. Major surgery within 4 weeks prior to Screening

5. Known central nervous system involvement by PTCL

6. Infection with hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or Human T-lymphotropic virus type 1 (HTLV-1). (Patients with a positive hepatitis B surface antigen [HBsAg] or hepatitis C antibody [HCV Ab] will be excluded. Patients with a positive hepatitis B core antibody [HBcAb] must have negative hepatitis B virus [HBV] deoxyribonucleic acid (DNA) to be eligible, must receive prophylaxis with entecavir [or equivalent] concomitant with duvelisib treatment, and must be periodically monitored for HBV reactivation by institutional guidelines. Investigators who strongly believe that that a positive HBcAb is false due to passive immunization from previous immunoglobulin

infusion therapy should discuss the potential to defer HBV prophylaxis with the Medical Monitor.)

7. Active cytomegalovirus (CMV) infection (patients with detectable viral load)

8. History of tuberculosis treatment within 2 years prior to C1D1

9. History of chronic liver disease, veno-occlusive disease, or alcohol abuse

10. Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids > 20 mg of prednisone (or equivalent) once daily (QD)

11. Ongoing treatment for systemic bacterial, fungal, or viral infection at Screening

    NOTE: Patients on antimicrobial, antifungal, or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met

12. Administration of a live vaccine within 6 weeks of C1D1

13. Concurrent administration of medications or foods that are strong inhibitors or inducers of cytochrome P450 3A (CYP3A)

14. Unable to receive prophylactic treatment for pneumocystis at Screening

15. Baseline left ventricular ejection fraction (LVEF) < 50% (or below institution's normal limit)

16. Baseline QT interval corrected with Fridericia's method (QTcF) > 480 ms

    NOTE: criterion does not apply to patients with a right or left bundle branch block

17. Prior surgery or condition with gastrointestinal dysfunction that may significantly affect drug absorption (e.g., gastric bypass surgery, gastrectomy, clinically significant medical condition of malabsorption, inflammatory bowel disease, chronic conditions which manifest with diarrhea, refractory nausea, vomiting)

18. If female, pregnant or breastfeeding

19. Concurrent active malignancy other than nonmelanoma skin cancer, carcinoma in situ of the cervix

    NOTE: Patients with previous malignancies are eligible if disease-free for > 2 years

20. History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or a pacemaker within the last 6 months prior to Screening

21. Unstable or severe uncontrolled medical condition (e.g., unstable cardiac function, unstable pulmonary condition, uncontrolled diabetes) or any important medical illness or abnormal laboratory finding that would, in the Investigator's judgment, increase the risk to the patient associated with his or her participation in the study

22. Known hypersensitivity to duvelisib and/or its excipients

6. STUDY CONDUCT

This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Council for Harmonisation (ICH) guidelines.

6.1. Study Procedures

Patients will be evaluated at scheduled visits over 6 study periods: Screening, Treatment, End of Treatment, Safety Follow-up, PD Follow-up, and Survival Follow-Up. Tests and procedures should be performed in accordance with the Schedule of Events provided in Table 1 and Table 2. Additional details are provided in the sections that follow.

6.2. Informed Consent

Each patient must sign a written informed consent form (ICF) prior to performing any study-specific procedure unless the procedure is performed as part of standard of care.

6.3. Inclusion and Exclusion Criteria

All patients must meet the inclusion and exclusion criteria prior to being enrolled in the study. Eligibility criteria will be reviewed during Screening and again prior to dosing on C1D1.

6.4. Medical and Medication History

During Screening, a complete medical history will be obtained from each patient including relevant medical history, current medications, current primary cancer diagnosis, prior cancer treatments (chemo and immunotherapies, radiation therapy, surgeries) including duration of prior response, and disease-specific characteristics such as tumor stage and histology. Current medications and all medications used within 30 days prior to Screening will be documented.

6.4.1. Disease Confirmation by Central Pathology Review

As part of the patient's medical history, pathology reports from the time of diagnosis are to be collected. In addition, stained formalin-fixed, paraffin-embedded (FFPE) slides used for PTCL diagnosis must be collected for all patients enrolled and submitted for central pathology review. Refer to lab manual for more details.

6.5. Demography

At Screening, patient demographic data will be collected, including date of birth, gender, race, and ethnicity, as allowable according to local law.

6.6. Physical Examination

A complete physical examination per standard of care will be conducted at the Screening and EOT visits. Targeted physical examinations should be performed at time points specified in the Schedule of Events (Table 1 and Table 2).

Any physical examination abnormality deemed clinically significant by the Investigator during Screening will be reported as medical history. Any physical examination abnormality that emerges or has worsened after signing of the ICF and that is assessed as clinically significant by the Investigator will be reported as an AE.

6.7. Electrocardiogram

A twelve-lead electrocardiogram (ECG) will be conducted during Screening and assessed by the Investigator to confirm eligibility. A single ECG tracing is sufficient unless there is an abnormality, such as prolonged QTcF ≥ 480 msec, new arrhythmia, or other clinically significant finding. If an abnormality is observed, the ECG is to be performed in triplicate at least 2 minutes apart. Additional on-treatment or follow-up ECGs should be performed at the Investigator's discretion as clinically indicated.

6.8. Echocardiogram

An echocardiogram will be conducted during Screening and assessed by the Investigator to confirm eligibility (patients with baseline LVEF < 50% [or below institution's normal limit] are excluded). Additional on-treatment or follow-up echocardiograms should be performed at the Investigator's discretion as clinically indicated.

6.9. Vital Signs, Height and Weight

Vital signs, including temperature (°C), blood pressure, pulse, and respiration rate, as well as weight (kg) will be measured at the time points specified in the Schedule of Events (Table 1 and Table 2). Height (cm) will be measured during Screening only.

Systolic and diastolic blood pressure and pulse will be measured with the patient in a supine or sitting position; the same position will be used for a patient throughout the study. Blood pressure should be assessed on the same arm throughout the study.

6.10. Clinical Laboratory Tests

6.10.1. Screening Serology

Laboratory studies to assess the status of prior or current CMV infection include CMV serologies, CMV immunoglobulin (Ig) G and IgM, and viral load, are to be conducted during Screening. Patients with a detectable viral load will not be eligible for enrollment. During

duvelisib treatment, periodic CMV viral load monitoring is recommended in patients with a history of CMV reactivation or other opportunistic infections.

Furthermore, a liver serology panel, including HBsAg, HBcAb, and HCV Ab, is to be performed during Screening. Patients with a positive HBsAg or HCV Ab will be excluded. Patients with a positive HBcAb must have negative HBV DNA to be eligible, must receive prophylaxis with entecavir (or equivalent) concomitant with duvelisib treatment, and must be periodically monitored for HBV reactivation by institutional guidelines. Investigators who strongly believe that that a positive HBcAb is false due to passive immunization from previous immunoglobulin infusion therapy should discuss the potential to defer HBV prophylaxis with the Medical Monitor.

HIV and HTLV-1 tests are to be performed during Screening for all patients without documentation of prior negative results.

6.10.2. Pregnancy Test

A serum or urine pregnancy test will be done during Screening and repeated predose on C1D1 for WCBP; results must be available and confirmed to be negative before administration of the first study drug dose. If the Screening pregnancy test is performed within 1 week before C1D1, it need not be repeated on C1D1.

For the Dose Optimization Phase, pregnancy tests are to be repeated during the Treatment Period at the time points designated in the Schedule of Events (Table 1). For the Expansion Phase, pregnancy tests are to be repeated monthly (see Table 2). For cycles where pregnancy testing is the only requirement in the Schedule of Events, the patient may have this done locally. For both phases, the pregnancy test may be repeated as deemed necessary by the Investigator.

6.10.3. Clinical Laboratory Tests

Clinical laboratory tests will be performed by the investigative site's local laboratory. Samples will be collected from patients at scheduled study visits before the administration of study drug unless otherwise noted.

Blood samples for evaluation of the following clinical laboratory tests will be collected at the time points specified in the Schedule of Events (Table 1 and Table 2). Samples may be collected up to 24 hours from the visit. C1D1 laboratory tests do not need to be repeated if performed within 72 hours prior to Screening. All safety Screening/C1D1 laboratory results will be reviewed prior to dosing to ensure patient is eligible.

- **Hematology:** Hemoglobin, hematocrit, platelets, white blood cell count (WBC) with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), such that an absolute neutrophil count and an absolute lymphocyte count (ALC) can be derived, if it is not already provided as part of the laboratory analysis.

- **Clinical Chemistries:** Sodium, potassium, chloride, bicarbonate, albumin, total protein, creatinine, blood urea nitrogen or urea, lipase, amylase, uric acid, calcium, phosphorus, magnesium, glucose, lactic dehydrogenase, serum ALT, serum AST, total and direct bilirubin, and alkaline phosphatase.
- **Serum Quantitative Immunoglobulins (Ig)**: IgA, IgM, and IgG.
- **CD4 Lymphocyte Cell Count (at Screening)**

6.11. Disease and Response Assessment

At Screening, disease will be measured using PET-CT (CT images with PET should be diagnostic with contrast unless contraindicated). Where PET-CT is not feasible, CT with contrast or magnetic resonance imaging (MRI) may be used after discussion with the Medical Monitor. Subsequently, for FDG-avid PTCL, PET-CT will be used to assess disease status and for FDG-non-avid PTCL, CT with contrast or MRI will be appropriate substitutes. In all cases, disease status will be assessed using the Lugano criteria (Cheson et al, 2014). The modality chosen to evaluate each individual patient should be the same throughout the duration of the study, if feasible. Response and progression will be assessed as indicated in Table 7.

PET images are to be assessed using the 5-point scale (5PS), a semi-quantitative analysis that is a pragmatic yet robust predictor of patient outcome (Table 6).

Table 6: 5-Point Scale (Lugano Classification)

Score	Criterion
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum, but ≤ liver
4	Uptake moderately > liver*
5	Uptake markedly higher than liver and/or new lesions*
X	(New) areas of uptake unlikely to be related to lymphoma

*It is suggested according to published data that score 4 be applied to uptake greater than the maximum standardized uptake value (SUV) in a large region of normal liver and score 5 to uptake 2× to 3× greater than the maximum SUV in the liver.
Source: Barrington et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group Clin Oncol. 2014 Sep 20; 32(27): 3048–3058.

At each scheduled disease response assessment (Table 3 or Table 4), a PET-CT- or CT-based response will be determined, based on the Lugano response criteria for patients with malignant lymphoma (Table 7).

Table 7: Response Criteria for Malignant Lymphoma

Response and Site	PET-CT-based Response	CT-Based Response
Complete Response	**Complete metabolic response**	**Complete radiologic response (requires all of the following)**

Response and Site	PET-CT-based Response	CT-Based Response
Lymph nodes and extralymphatic sites	Score of 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Non-measured lesions	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in bone marrow	Normal by morphology; if indeterminate, IHC negative
Partial Response	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	5PS score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size During treatment, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 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 value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by ≥ 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to	Not applicable

Response and Site	PET-CT-based Response	CT-Based Response
	further evaluation with MRI or biopsy or an interval scan	
Stable disease (no response)	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	5PS score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive Disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following:**
Individual target nodes/nodal masses	5PS score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An 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 (e.g., 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
Non-measured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of 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

Response and Site	PET-CT-based Response	CT-Based Response
		Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS=5-point scale; CT=computed tomography; FDG=fluorodeoxyglucose; IHC=immunohistochemistry; LDi=longest transverse diameter of a lesion; MRI=magnetic resonance imaging; PET=positron emission tomography; PPD=cross product of the LDi and perpendicular diameter; SDi=shortest axis perpendicular to the LDi; SPD=sum of the product of the perpendicular diameters for multiple lesions.
*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in studies involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), gastrointestinal (GI) involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

Source: Cheson, BD, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32(27):3059-3067.

6.11.1. ECOG Performance Status

Performance status will be assessed using the ECOG Scale (see Appendix 2) at the time points specified in the Schedule of Events (Table 1 and Table 2).

6.12. Pharmacokinetic Assessment

Blood samples for PK analyses will be collected in both the Dose Optimization (Cohort 1 and Cohort 2) and Expansion Phases, as described in Table 5.

6.13. Exploratory Biomarkers

Blood and tissue specimens are to be collected at the times designated in the Schedule of Events for exploratory biomarker analysis (Table 1 and Table 2). In addition, whenever a bone marrow specimen is collected during Screening, an aliquot is to be reserved for exploratory biomarker assessments. Each of the specimens listed may be analyzed at a central laboratory or at a specialized laboratory vendor as determined by the Sponsor, for the various biomarkers outlined below:

- Pharmacodynamic markers of target inhibition in PTCL and immune populations (only for the US)

- Immunophenotypes and functional tests of major immune populations in the blood (only for the US)
- Cytokines and other circulating biomarkers
- Prognostic markers assessed by DNA, ribonucleic acid, and protein analysis from tissue and blood specimens

6.14. Unscheduled Visits

Unscheduled visits and assessments may occur at the Investigator's discretion, as clinically warranted.

7. COMPLETION OF TREATMENT

Patients will be considered to have completed study treatment if they receive the study drug until PD or until discontinuation for unacceptable toxicity, withdrawal of consent, or death. Patients will attend an EOT visit within 7 days after receiving the last dose of study drug and will continue to be followed for other follow-up assessments specified in the Schedule of Events (Table 3 or Table 4).

7.1. Completion of Study

Patients will be considered to have completed the study at the time of documented PD or death or closure of the study by the Sponsor.

7.2. Concomitant Medications

Medications received on or after the start of duvelisib therapy through the Safety Follow-up visit will be documented.

7.3. Adverse Events

AEs, including serious adverse events (SAEs) will be reported from the time the patient signs the ICF through 30 calendar days after last administration of study drug. The severity of AE will be assessed using the NCI CTCAE version 5.0 (see web page at http://ctep.cancer.gov for details). Study treatment related AE/SAE should continue to be followed until resolution or stabilization. See Section 10, Adverse Event Management, for additional details regarding AE reporting and recording.

8. DISCONTINUATION CRITERIA

8.1. Withdrawal of Individual Patients from Study Drug

Duvelisib will be discontinued for any of the following reasons:

- Patient withdrawal of informed consent
- Disease progression (NOTE: In the Expansion Phase, patients may stay on therapy if PD occurs following mandatory dose reduction if criteria are met. See Sections 1.3 and 9.1.2)
- Clinical deterioration due to PD (at the discretion of the Investigator)
- Study drug interruption for > 42 days due to duvelisib-related toxicity (unless approved by study Medical Monitor).
- AE, such as unacceptable toxicity
- Pregnancy
- Termination of the study by the Sponsor
- Death
- Other reasons, including major protocol violation, noncompliance

The Investigator must determine the primary reason for a duvelisib withdrawal and record this information on the electronic case report form (eCRF). The patient will be observed after discontinuation according to the Schedule of Assessments and Events.

8.2. Withdrawal of Individual Patients from the Study

A patient may be discontinued from the study at any time. Patients will be withdrawn from the study for any of the following reasons:

- Patient withdrawal of informed consent
- Termination of the study by the Sponsor
- Death
- Lost to follow-up
- Other reasons, including major protocol violation and noncompliance with study procedures, as specified by the Investigator

The Investigator must determine the primary reason for a patient's withdrawal from the study and record this information on the eCRF.

8.3. Early Discontinuation of the Study

The Sponsor may terminate this study at any time, provided a written notice is submitted at a reasonable time in advance of the intended termination.

8.4. End of Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Events (Table 2, Table 4 and Table 5) for the last patient in the study or closure of the study by the Sponsor.

9. STUDY DRUG REGIMEN

9.1. Dosing and Administration of Study Drug

All eligibility criteria must be met and documented prior to study drug administration. The study drug will be administered only to eligible patients under the supervision of the Investigator or identified Sub-Investigator(s).

Duvelisib is to be self-administered by patients as an oral capsule supplied by the Sponsor. Patients will receive duvelisib PO BID continuously in 28-day cycles.

On C1D1, the morning dose will be administered in the clinic. Duvelisib also will be administered in the clinic on PK sample collection days (see Table 5). An attempt should be made to enable each dose to be taken at approximately the same time of day. Missed doses outside the windows defined above or vomited doses should not be taken or repeated.

Duvelisib should be swallowed whole with a glass of water (approximately 8 ounces or 240 mL). Duvelisib may be administered without regard to meals, however, patients must avoid grapefruit and grapefruit juice while on duvelisib.

Dose reductions and interruptions for individual patients because of toxicity may be made based on the clinical judgment of the Investigator (see Section 9.4). In the event of a dose reduction, doses of less than 25 mg will utilize the 5 mg capsules.

Refer to the Pharmacy Manual for additional instructions regarding study drug administration.

9.1.1. Dose Optimization Phase

In the Dose Optimization Phase, the duvelisib dose schedule is dependent on the cohort allocation, as follows:

- Cohort 1: Duvelisib PO BID at a starting dose of 25 mg, with potential escalation on a per-patient basis to 50 mg and then 75 mg, based on the patient's response to and tolerance of therapy, in 28-day cycles
- Cohort 2: Duvelisib 75 mg PO BID, administered in 28-day cycles

In Cohort 1, all patients will receive duvelisib at a starting dose of 25 mg PO BID (Level 1), with potential sequential escalation to 50 mg PO BID (Level 2), and then to 75 mg PO BID (Level 3). The duvelisib dose will be escalated on a per-patient basis in 25-mg increments as follows.

After completion of Cycle 1 and every 2 cycles thereafter:

- Patients with CR or PR will have their duvelisib dose maintained at the current dose level
- Patients with SD will have the duvelisib dose increased to the next level until the next response assessment or development of PD or intolerance

Patients with PD, who are not tolerating therapy, or not otherwise suitable to continue receiving therapy, will have duvelisib discontinued

In no case will the duvelisib dose be increased to a level > 75 mg BID (total daily dose 150 mg).

All patients in the Dose Optimization Phase will receive duvelisib until development of PD or unacceptable toxicity, as determined by the Investigator. Note that for the purposes of patient management during the conduct of the study, the Investigator's assessment of disease response will be used. Dose Optimization Phase patients will complete treatment as defined for their cohort.

9.1.2. Expansion Phase

The duvelisib dose in the Expansion Phase will be:

Duvelisib PO at 75 mg BID for the first 2 cycles (cycle = 28 days) until the first response assessment (See Table 4). Then, dose will be reduced to 25 mg BID and administered in 28-day cycles.

If a subsequent assessment demonstrates progression and the patient did not require a dose modification due to toxicity, the dose can be re-escalated to 75 mg BID with a confirmatory scan after approximately 4 weeks of therapy. If the patient has progressive disease at the confirmatory scan, then the patient should be discontinued. Patients that re-escalate to 75 mg BID may remain at this dose level until the need for dose modification or the criteria for discontinuation is met.

9.2. Description

Duvelisib drug substance is a white to off-white crystalline powder. The duvelisib drug product is formulated in 2 different capsule strengths (5 mg and 25 mg; percent active drug in capsules are identical) for oral delivery with excipients (diluent, glidant, disintegrant, and lubricant) that are listed in the US FDA Inactive Ingredients Database for approved drug products and/or Generally Recognized as Safe.

Additional information is provided in the Pharmacy Manual.

9.3. Packaging and Labeling

Duvelisib packaging and labeling will be prepared to meet all regulatory requirements.

9.3.1. Dispensing and Storage Instructions

Dispensing and storage instructions for duvelisib will be provided in the Pharmacy Manual.

On receipt at the investigative site, duvelisib should remain in the blister cards provided until use or dispensation. The blister cards should be stored at the investigative site at room temperature (15 to 30°C or 59 to 86°F). All excursions should be brought to Secura Bio's attention for assessment and authorization for continued use. Expired drug is not to be dispensed.

9.3.2. Drug Accountability

Accountability for study drug at the site is the responsibility of the Investigator. The Investigator or delegated study staff will verify the integrity of the clinical study supplies (storage conditions, correct amount received, condition of shipment, kit numbers, etc.).

Records of duvelisib (used, lost, destroyed, and returned blister cards) must be maintained. Drug accountability records will indicate the drug's delivery to and receipt by the site, inventory at the site, dispensing to patients, use by each patient, and amount returned and/or disposed. Drug accountability records will be checked routinely by the study monitor.

Unused duvelisib will be destroyed locally per site standard operation procedures or returned to a location designated by Secura Bio. Destruction of duvelisib should not occur until the end of the study, unless otherwise authorized by Secura Bio.

9.4. Toxicity Management

9.4.1. Toxicity Grading Criteria

Toxicity grading will be assessed by the Investigator using the NCI CTCAE version 5.0: http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

9.4.2. Dose Modifications and Discontinuation

If a patient has an AE at least possibly related to duvelisib, then dose interruptions with possible modifications and toxicity management may be implemented as noted in Table 8. Adjustments to these guidelines may occur based on the clinical judgment of the Investigator with notification to the Medical Monitor/Sponsor. Additional information on the management of toxicities can be found in the Summary of Data and Guidance to the Investigator section of the Investigator's Brochure.

Table 8: Duvelisib Dose Modification and Toxicity Management

Treatment Related Toxicity[1,2]	Adverse Reaction Grade	Duvelisib Dose Modification and Toxicity Management
Nonhematologic Adverse Reactions		
Infections	Grade 3 or higher infection	• Withhold until resolved • Resume at the same or reduced dose (see Table 9)
	Clinical CMV infection or viremia (positive PCR or antigen test)	• Withhold until resolved • Resume at the same or reduced dose (see Table 9) • If duvelisib is resumed, monitor patients for CMV reactivation (by PCR or antigen test) at least monthly
	PJP	• For suspected PJP, withhold duvelisib until evaluated • For confirmed PJP, discontinue duvelisib
Non-infectious Diarrhea or colitis	Mild/moderate diarrhea (Grade 1-2, up to 6 stools per day over baseline) and responsive to antidiarrheal agents, OR Asymptomatic (Grade 1) colitis	• No change in dose • Initiate supportive therapy with antidiarrheal agents as appropriate • Monitor at least weekly until resolved
	Mild/moderate diarrhea (Grade 1-2, up to 6 stools per day over baseline) and unresponsive to antidiarrheal agents	Withhold until resolved • Initiate supportive therapy with enteric acting steroids (e.g., budesonide) • Monitor at least weekly until resolved • Resume at a reduced dose (see Table 9)
	Abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs, OR Severe diarrhea (Grade 3, > 6 stools per day over baseline)	• Withhold until resolved • Initiate supportive therapy with enteric acting steroids (e.g., budesonide) or systemic steroids • Monitor at least weekly until resolved • Resume at a reduced dose (see Table 9) • For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue
	Life-threatening	• Discontinue

Treatment Related Toxicity[1,2]	**Adverse Reaction Grade**	**Duvelisib Dose Modification and Toxicity Management**
Cutaneous reactions	Grade 1-2	• No change in dose • Initiate supportive care with emollients, anti-histamines (for pruritus), or topical steroids • Monitor closely
	Grade 3	• Withhold until resolved • Initiate supportive care with emollients, anti-histamines (for pruritus), or topical steroids • Monitor at least weekly until resolved • Resume at reduced dose (see Table 9) • If severe cutaneous reaction does not improve, worsens, or recurs, discontinue
	Life-threatening	• Discontinue
	SJS, TEN, DRESS (any grade)	• Discontinue
Pneumonitis without suspected infectious cause	Moderate (Grade 2) symptomatic pneumonitis	• Withhold • Treat with systemic steroid therapy • If pneumonitis recovers to Grade 0 or 1, duvelisib may be resumed at reduced dose (see Table 9) • If non-infectious pneumonitis recurs or patient does not respond to steroid therapy, discontinue
	Severe (Grade 3) or life-threatening pneumonitis	• Discontinue • Treat with systemic steroid therapy
ALT/AST elevation	3 to 5 × upper limit of normal (ULN) (Grade 2)	• Maintain duvelisib dose • Monitor at least weekly until return to < 3 × ULN
	> 5 to 20 × ULN (Grade 3)	• Withhold duvelisib and monitor at least weekly until return to < 3 × ULN • Resume duvelisib at same dose (first occurrence) or at a reduced dose for subsequent occurrence (see Table 9)
	> 20 × ULN (Grade 4)	• Discontinue duvelisib
Hematologic Adverse Reactions		
Febrile neutropenia	Grade 3-4	• Withhold duvelisib until afebrile and resolution of Grade 3 or Grade 4 neutropenia to Grade ≤ 2 (ANC > 1.0 Gi/L) • Monitor ANC at least weekly until > 1.0 Gi/L • Resume at same dose (first occurrence) or at a reduced dose for subsequent occurrence

Treatment Related Toxicity[1,2]	Adverse Reaction Grade	Duvelisib Dose Modification and Toxicity Management
Neutropenia	Absolute neutrophil count (ANC) 0.5 to 1.0 Gi/L	• Maintain duvelisib dose • Monitor ANC at least weekly
	ANC less than 0.5 Gi/L	• Withhold duvelisib • Monitor ANC until > 0.5 Gi/L • Resume at same dose (first occurrence) or at a reduced dose for subsequent occurrence (see Table 9)
Thrombocytopenia	Platelet count 25 to < 50 Gi/L (Grade 3) with Grade 1 bleeding	• No change in dose • Monitor platelet counts at least weekly
	Platelet count 25 to < 50 Gi/L (Grade 3) with Grade 2 bleeding or Platelet count < 25 Gi/L (Grade 4)	• Withhold duvelisib • Monitor platelet counts until ≥ 25 Gi/L and resolution of bleeding (if applicable) • Resume at same dose (first occurrence) or resume at a reduced dose for subsequent occurrence (see Table 9)

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CMV = cytomegalovirus; DRESS = drug reaction with eosinophilia and systemic systems; Gi = 1 x 10^9; PCR = polymerase chain reaction; PJP = *Pneumocystis jirovecii;* pneumonia; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; ULN = upper limit of normal

1. Treatment-related toxicity: possible, probable, or definite relationship to study treatment
2. Toxicity grades are defined per CTCAE version 5.0. Note if parameter is not defined by CTCAE, then AE grading criteria (Section 10.4) should be utilized.

Duvelisib may be held up to 42 days for toxicity. Doses held for > 42 days due to treatment-related toxicity will result in permanent discontinuation from duvelisib unless Sponsor Medical Monitor approves resuming treatment after Investigator confirmation of acceptable benefit-risk assessment. Any patient who requires a dose-level reduction to below dose level -3 (see Table 9) due to treatment-related toxicities will be permanently discontinued from duvelisib treatment.

In the event that study drug is discontinued due to any reason other than PD (e.g., AE), patients should continue disease response assessments until documentation of PD, as determined by the Investigator, death, or new anticancer treatment as outlined in Table 3 or Table 5.

Dose reduction levels, based on the patient's initial assigned dose optimization dose level, are shown in Table 9.

Table 9: Duvelisib Dose Reduction Levels for Patients Receiving 25 mg or 75 mg BID

Dose Level	Duvelisib (mg)	
Starting Dose	25 BID	75 BID

-1	15 BID	50 BID
-2	10 BID	25 BID
-3	5 BID	15 BID

Abbreviations: BID = twice daily

In the Dose Optimization Phase, patients in Cohort 1 will start treatment with duvelisib 25 mg BID; however, by design, a patient's assigned dose may be increased to 50 mg BID, based on the dose escalation scheme; dose reduction levels for such patients are shown in Table 10.

Table 10: Duvelisib Dose Reduction Levels for Patients Receiving 50 mg BID

Dose Level	Duvelisib (mg)
Starting Dose	50 BID
-1	25 BID
-2	15 BID
-3	10 BID

Abbreviations: BID = twice daily

For dosing requirements in the Expansion Phase, please refer to Section 9.1.2.

9.5. Permitted Concomitant Medications and Procedures

Patients should receive full supportive care (including transfusion of blood and blood products and antibiotics, etc.) according to local standards and guidelines. Treatment for nausea, vomiting, and diarrhea is permitted according to institutional guidelines. Concomitant medications received from 30 days before the Screening visit through the Safety Follow-up visit will be recorded in the eCRF.

9.5.1. Antimicrobial Prophylaxis

Based on the duvelisib clinical experience to date, the following are recommended:

- Patients are required to receive pneumocystis prophylaxis concomitant with study drug treatment. Selection of pneumocystis prophylaxis agent is per Investigator discretion. Patients who are found to be intolerant of all available pneumocystis prophylaxis may continue with study treatment at the discretion of the Investigator

- Herpes simplex virus (HSV) and varicella zoster virus (VZV) infections have been observed with duvelisib; therefore, herpes (HSV/VZV) prophylaxis concomitant with treatment is recommended, per Investigator discretion according to institutional guidelines

- Patients with a history of CMV infection or reactivation that required treatment, or history of other opportunistic infections, should be monitored for reactivation per

Investigator standard practice. Prophylactic treatment per institutional guidelines is recommended for patients considered by Investigator to be at high risk for CMV reactivation

- Antimicrobial prophylaxis is recommended for patients with history of or considered at high risk for opportunistic infections and during periods of severe neutropenia. Choice of antimicrobial agent (antifungal, antibiotic, antiviral) is per the Investigator's discretion

- Investigators may consider administration of pneumococcal pneumonia vaccine prior to C1D1

9.5.2. Transfusion and Growth Factor Support (Prophylaxis or Supportive Care)

During any time on treatment, blood cell transfusion (packed red blood cells or platelets) to maintain a patient's hemoglobin ≥ 8.0 mg/dL or platelets ≥ 10,000 per μL is recommended. Transfusions may be used at any time, as clinically indicated.

Prophylactic use of growth factors such as granulocyte-colony stimulating factor (G-CSF) or pegylated G-CSF may be implemented if clinically indicated, in accordance with institutional guidelines and/or according to the National Comprehensive Cancer Network or ASCO practice guidelines for myeloid factors). Patients on a stable dose of erythropoietin to treat baseline anemia may continue on this therapy at this dose.

9.5.3. Contraception and Pregnancy

The effects of duvelisib on conception, pregnancy, and lactation are unknown.

At Screening, male and female patients of reproductive potential (i.e., not surgically sterile or female patients who are not postmenopausal) must be willing to use a highly effective method of contraception for the duration of study treatment and for at least 3 months after the last dose of duvelisib. See Appendix 1 for Contraceptive Guidance including examples of highly effective contraceptive methods. Pregnancy testing will be performed throughout the study as shown in the Schedule of Events (Table 1 and Table 2).

9.6. Excluded Concomitant Medications and Procedures

9.6.1. Vaccines

For all patients, the use of live or live attenuated vaccines is prohibited within 6 weeks prior to C1D1during the treatment with duvelisib, and for 3 months after the last dose of study drug. Investigators may consider administration of pneumococcal pneumonia vaccine prior to C1D1

The use of inactivated (or killed) vaccines is allowed during the study, however patients and their physicians should be aware that the effectiveness of any vaccine administered concomitantly

with duvelisib may be diminished. The ability to generate an immune response to any vaccine following the administration of duvelisib has not been studied.

9.6.2. Immunosuppressants

Patients are not to receive ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids for > 1 week at doses > the equivalent of 20 mg prednisone QD, unless being used to treat treatment-emergent toxicity.

NOTE: Acute treatment for underlying autoimmune disorders (e.g., reactive airway disease, rheumatoid arthritis) with corticosteroid doses > 20 mg prednisone or equivalent QD for ≤ 1 week is permitted during the study. Corticosteroid doses of ≤ 20 mg prednisone or equivalent QD are permitted during the study for physiological replacement or chronic treatment for underlying autoimmune disorders (e.g., reactive airway disease, rheumatoid arthritis).

9.6.3. Other Anticancer Therapy or Investigational Agents

During study treatment period, additional anticancer therapy or other investigational agents are prohibited during the study treatment period.

9.6.4. Medications or Food that Inhibit or Induce CYP3A

In vitro data indicate that duvelisib is mostly metabolized by CYP3A4. Therefore, concomitant use of drugs or foods that are strong inhibitors or inducers of CYP3A are not allowed during study treatment with duvelisib.

Appendix 3 provides a list of medications known to be strong inhibitors or inducers of CYP3A. Please note that Appendix 3 is not a comprehensive list of all medications that may modulate CYP3A activity.

Patients should avoid eating grapefruits or grapefruit-containing products. In addition, patients should avoid herbal supplements including, but not limited to, St. John's Wort throughout the study as this is known to be a strong inducer of CYP3A.

The Sponsor should be contacted with any questions regarding concomitant use of medications that are thought to modulate CYP3A activity. The concomitant use of moderate or weak inhibitors may be allowed in selected circumstances after consultation with the medical monitor.

9.7. Concomitant Medications to be Used with Caution

9.7.1. Medications that are Substrates of CYP3A or CYP2C8

In vitro studies have demonstrated duvelisib is an inhibitor of CYP3A4. Coadministration of duvelisib with midazolam, a sensitive CYP3A substrate, resulted in an approximate 4-fold increase in the midazolam AUC. Systemic exposure to other medications that are substrates for CYP3A may be increased in patients receiving duvelisib. Caution should be used if duvelisib is

administered concomitantly with drugs that are substrates for CYP3A, particularly those with a narrow therapeutic range. Drugs that are substrates for CYP3A should be used only if medically necessary and therapeutic alternatives are not available.

Duvelisib is an inhibitor of CYP2C8 in vitro. Physiologically based pharmacokinetic modeling indicates the inhibitory effect of duvelisib on CYP2C8 substrates is not expected to be clinically meaningful at a duvelisib dose of 25 mg BID. The predicted mean area under the curve ratio for rosiglitazone (a CYP2C8 substrate) with and without duvelisib at 25 mg BID was 1.02. Inhibition of CYP2C8 metabolism appears to be negligible and only minor changes in the systemic exposure to CYP2C8 substrates are anticipated in the presence of duvelisib. Medications that are metabolized via CYP2C8 may be used as medically indicated but with caution.

Appendix 4 provides a list of medications known to be substrates of CYP3A or CYP2C8. Please note that Appendix 4 is not an exhaustive list of all medications which may be substrates of CYP3A or CYP2C8. The Sponsor should be contacted with any questions regarding concomitant use of medications that are CYP3A or CYP2C8 substrates.

9.7.2. Medications that are Substrates or Inhibitors of P-glycoprotein

In vitro data indicate duvelisib is a substrate for P-glycoprotein (P-gp) and may have the potential to inhibit the activity of P-gp. P-gp substrates or inhibitors may be used as medically indicated but with caution.

Appendix 5 provides a list of medications that are substrates or inhibitors of P-gp. Please note that Appendix 5 is not a comprehensive list of all medications which may be substrates of P-gp or may modulate P-gp activity. The Sponsor should be contacted with any questions regarding concomitant use of medications that are thought to modulate P-gp activity.

9.8. Other Concomitant Therapies

Any other medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of duvelisib may be given at the discretion of the Investigator.

9.8.1. Photo Safety

Duvelisib was determined to have the potential for phototoxicity in an in vitro phototoxicity assay and in a follow-up in vivo phototoxicity study. Patients should be advised to use appropriate protective measures to minimize exposure to direct sunlight or ultraviolet light sources during the treatment period and for at least 30 days after the last dose of duvelisib.

9.9. Blinding and Unblinding

Treatment assignment is not blinded.

9.10. Treatment Compliance

The Investigator will dispense the study drug only for use by patients enrolled in the study as described in this protocol. The study drug is not to be used for reasons other than those described in this protocol.

The Investigator or other study staff will supervise study drug given in the clinic and instruct the patient on duvelisib self-administration. Patients will be asked to bring their duvelisib blister cards with them at each visit. Compliance with protocol-defined duvelisib intake will be checked by pill count.

10. ADVERSE EVENT MANAGEMENT

10.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the study (investigational) product. This includes an exacerbation of pre-existing conditions or events, concurrent illnesses, drug interaction, or the significant worsening of the indication under investigation. Anticipated fluctuations of pre-existing conditions, including the disease under study that does not represent a clinically significant exacerbation or worsening, need not be considered AEs.

Symptoms of the disease under study / lack of efficacy / disease progression should not be classified as an AE as long as they are within the normal day-to-day fluctuation or expected progression of the disease.

It is the responsibility of the Investigator to document all AEs that occur during the study. AEs should be reported on the appropriate page of the eCRF.

10.2. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence at any dose (including after the ICF is signed and prior to dosing) that:

- Results in death
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires inpatient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Important medical events that may not result in death, are not immediately life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For SAE reporting purposes, hospitalization is defined as an inpatient hospital stay ≥ 24 hours. Hospitalizations for elective surgery or other medical procedures that are not related to a TEAE are not considered SAEs. Hospitalization, which in the opinion of the Investigator, is unrelated to the study drug, and due to purely non-medical circumstances (e.g., respite care, lack of a caretaker at home, lack of transportation home) are also not considered to be SAEs. PD under study (including signs and symptoms of progression) if documented by use of appropriate methods, should not be reported as an SAE unless the outcome is fatal during the study or within the safety reporting period (see Section 10.3, Reporting of Adverse Events and Serious Adverse Events). If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event should be reported using the term "disease progression" with a CTCAE severity of Grade 5.

Death is an outcome. The primary reason for patients' death should be reported as an SAE.

10.3. Reporting of Adverse Events and Serious Adverse Events

The AE reporting period begins from the time that the patient signs the ICF through and including 30 calendar days after the last study drug dose. All treatment-related AEs/SAEs should be followed until resolution or stabilization. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to the investigational drug is suspected. If the patient begins a new anticancer therapy, the safety reporting period ends at the time the new treatment is started, however, death must always be reported if it occurs during the AE reporting period irrespective of intervening treatment.

Elective or previously scheduled hospitalizations for pre-existing conditions that have not worsened after initiation of treatment should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE.

All AEs should be recorded individually unless, in the opinion of the Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be reported rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken with study drug and the outcome must also be recorded.

All SAEs, regardless of relationship to the study treatment, must be reported immediately to the Sponsor and Contract Research Organization (CRO) pharmacovigilance group, with the timeframe not to exceed 24 hours of the Investigator becoming aware of the event. Initial SAE

notification should be made by e-mailing or faxing the SAE report form to the e-mail or fax number provided on the SAE report form.

An initial SAE Report may be sent without the Investigator's signature but must be followed by a report signed by the Investigator within 48 hours of becoming aware of the event. Follow-up SAE reports must be submitted by the Investigator as new information becomes available.

The Medical Monitors for this study may be contacted in case of need for advice or assistance. Contact details will be provided in the Study Manual.

10.4. Severity of Adverse Events

The severity of the AE will be graded according to the NCI CTCAE, version 5.0 (see web page at http://ctep.cancer.gov for details). AEs not listed in the CTCAE should be graded as summarized in Table 11.

Table 11: CTCAE Grading

CTC Grade	Equivalent To:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk
Grade 4	Life-threatening/ disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival
Grade 5	Death	AE resulting in death

10.5. Relationship of Adverse Events to Study Drug

The Investigator will make a judgment regarding whether or not the AE was related to study drug, as outlined below:

- **Definitely related**: This category applies when, after careful medical consideration, there is almost no consideration of other causation.
- **Probably related**: There is a clinically plausible time sequence between onset of the AE and study drug administration. The AE is unlikely to be caused by a concurrent or underlying illness, other drugs, or procedures. If applicable, the AE follows a clinically consistent resolution pattern upon withdrawal of study drug.
- **Possibly related**: There is a clinically plausible time sequence between onset of the AE and study drug administration, but the AE could also have been caused by the concurrent or underlying illness, other drugs, or procedures. Information regarding study drug withdrawal may be lacking or unclear. "Possible" should be used when study drug administration is one of several biologically plausible causes of the AE.
- **Unlikely related**: The AE is most likely due to a cause not related to study drug administration. However, association with the study drug cannot be completely ruled out.
- **Unrelated**: Another cause of the AE is most plausible and a clinically plausible temporal sequence is inconsistent with the onset of the AE and study drug administration and/or a causal relationship is considered biologically implausible.

For the purpose of regulatory reporting requirements, causal relationships of definite, probable, and possible will be considered treatment-related, while unlikely and unrelated will be considered not treatment-related.

10.6. Clinical Laboratory Adverse Events

A clinical laboratory AE is any laboratory value that is deemed clinically significant by the Investigator, is greater than Grade 2 in severity, and is accompanied by one of the following:

- requires a medical intervention
- requires a change or suspension of study drug
- is accompanied by clinical symptoms

Laboratory abnormalities that have not required medical intervention should not be recorded as AEs and will be captured and reported in the Laboratory section of the clinical study report. If a medical intervention occurs, it should be recorded as a treatment with the abnormal laboratory finding as the AE (e.g., anemia with treatment required and blood transfusion recorded as a

procedure, hyperglycemia with treatment required and change in insulin dose recorded on concomitant medications).

The Investigator should decide, based upon the AE criteria and the clinical condition of the patient, whether a change in a laboratory parameter is clinically significant and therefore represents an AE.

If, at the end of the treatment phase with the study drug, there are pathological laboratory values which were not present at Baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (i.e., concomitant disease) is found for the pathological laboratory values.

10.7. Regulatory Aspects of Adverse Event Reporting

The Sponsor is responsible for submitting reports of SAEs associated with the use of the study drug to the appropriate Regulatory Authority (e.g., the US Food and Drug Administration), Investigators, and IRB/IEC/central ethics committee (CEC) in accordance with all applicable regulations and guidelines.

It is the responsibility of the Investigator to notify the IRB of all SAEs that occur at his or her site. Investigators will be notified of all suspected unexpected serious adverse reactions (SUSARs; 7 / 15 Day Safety Reports) that occur during any clinical studies that are using the investigative compound. Each site is responsible for notifying their IRB/IEC/CEC of these additional SUSARs in accordance with local regulations.

10.8. Overdose

In the case of overdose, clinic staff should be notified immediately, and supportive care is to be given as indicated. Patients should be informed to contact their doctor immediately if they have taken an overdose and should stop taking duvelisib.

For this study, overdose is defined as a daily dose of duvelisib higher than the prescribed daily dose. Overdoses will not be considered SAEs unless the outcome of the overdose meets seriousness criteria as defined in Section 10.2, Definition of a Serious Adverse Event. In the event of an overdose, the Sponsor should be immediately notified. The patient should be carefully monitored for potential adverse reactions and symptomatic treatment instituted as per institutional standards of care.

10.9. Pregnancy

Pregnancy per se is not considered an AE unless there is cause to believe that the study drug may have interfered with the effectiveness of a contraceptive medication or if the outcome of the pregnancy meets SAE criteria (miscarriage or congenital anomaly/birth defect, etc.), in which case it should be reported in the same manner and timelines as an SAE. In addition, any infant death or congenital anomaly occurring after 30 days that the Investigator suspects is related to

the in-utero exposure to the study drug should also be reported as an SAE. Hospitalization for normal delivery of a healthy newborn is not an SAE.

Since duvelisib has not been evaluated in pregnant or nursing women, the treatment of pregnant women or WCBP who are not using effective contraception is contraindicated (see Section 6.10.2 and Section 9.5.3 for instructions on pregnancy testing and birth control).

Pregnancies occurring in patients or partners of male patients during the study treatment period until 30 days after the patient's last dose of study treatment are considered immediately reportable events. If a pregnancy occurs in a patient, study treatment must be discontinued immediately. The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The pregnancy must be reported to the Sponsor or designee within 24 hours of the Investigator's knowledge of the pregnancy using a Pregnancy Report Form.

The Investigator will follow the pregnant woman until completion of the pregnancy and must notify the Sponsor of the outcome within 24 hours of the Investigator's knowledge of the pregnancy outcome using a Pregnancy Outcome Form. This notification includes pregnancies resulting in live, "normal" births.

11. STATISTICAL METHODS

11.1. Statistical Analysis Plan

A formal detailed Statistical Analysis Plan (SAP) will be used for the evaluation of the Dose Optimization Phase and Expansion Phase. The SAP will be finalized prior to database lock.

Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

11.2. Determination of Sample Size

Approximately 20 patients will be enrolled in the Dose Optimization Phase, with approximately 10 evaluable patients per cohort. However, enrollment may discontinue in either cohort if no CR/PR is noted in the first 5 evaluable patients per cohort. This stopping rule is based on the first stage decision rule of a Simon 2-stage design, with assumptions of a hypothesized ORR of 50% and a null rate of 15% with a one-sided alpha of 0.05 and a power of 85%.

Patients in the Dose Optimization Phase who discontinue before receiving at least 1 cycle of study drug may be replaced.

In the Expansion Phase, the target enrollment is approximately 100 patients with a centrally confirmed diagnosis of PTCL. It is anticipated up to 5% of patients may have a diagnosis that is not confirmed upon central pathology review. One-hundred patients will provide 99.2% power to distinguish between a null ORR of 20% and an alternative ORR of 40% with a two-sided alpha of 0.05. Further, with approximately 100 patients treated at the optimal duvelisib dose, the obtained ORR will have 95% confidence bounds of no greater than ± 10% when the normal approximation method is employed (assumes 50% ORR). If the observed ORR is greater or less than 50%, the confidence bounds will be less than ± 10%. These bounds around the obtained ORR are thought to adequately characterize the effect of the optimal dose of duvelisib in this PTCL population.

With protocol amendment 7.0, 20-30 additional patients will be enrolled in the expansion phase. Assuming a total of 120 or 130 patients the power to distinguish between a null hypothesis of ORR of 20% and an alternative ORR of 40% will be 99.4% or 99.6%, respectively. Table 12 has been updated with the 95% confidence bounds using the normal approximation method under the assumption of 120 and 130 total patients.

Table 12 below shows the 95% confidence bounds that would be observed under different ORRs by total number of patients:

Table 12: Confidence Bounds for Potential ORR Scenarios

ORR %	95% CI Bound	95% CI Bound	95% CI Bound
	(N=100)	(N=120)	(N=130)
30%	21%-39%	22%-38%	22%-38%
35%	26%-44%	26%-44%	27%-44%
40%	30%-50%	31%-49%	32%-48%
45%	35%-55%	36%-54%	37%-54%
50%	40%-60%	41%-59%	41%-59%

Abbreviations: CI = confidence interval; ORR = overall response rate

The primary analysis for the Expansion Phase will be performed once approximately 100 patients with a centrally confirmed diagnosis of PTCL have been enrolled and evaluated for the primary endpoint. In the event that enrollment in the expansion phase exceeds 110% of the planned sample size, a sensitivity analysis will be performed on the first 100 patients enrolled in the Expansion Phase.

The final analysis for the Expansion phase will be performed once all patients with a centrally confirmed diagnosis of PTCL have been enrolled and evaluated for the primary endpoint. The total number of patients (up to 130) will be determined by the Sponsor. An important driver of the final sample size may be the number of additional patients needed to add an additional 8-10 patients having PTCL subtype of either ALCL or NK cell.

11.3. Randomization and Stratification

In the Dose Optimization Phase only, patients will be randomly assigned on C1D1 to either Cohort 1 or 2 on a 1:1 basis via a computer-generated randomization scheme. No stratification methodology will be employed in this study.

11.4. Populations for Analysis

The populations used for analysis will include the following:

- Dose Optimization Efficacy Population, consisting of all patients who 1) receive at least one dose of study drug and 2) complete at least one cycle of treatment and 3) have at least one scan to assess disease response after completion of one cycle of treatment
- The Safety Population, consisting of all patients receiving at least 1 dose of duvelisib

- The mITT Population, consisting of all patients who receive at least one dose of duvelisib which will be used for the Expansion Phase primary and secondary analyses as well as all safety analyses

All patients enrolled into the study will be included in data listings. All primary and secondary analyses will be performed separately for patients in the Dose Optimization and Expansion phases. Additional analyses combining patients from the Dose Optimization and Expansion phases may be performed as applicable. Further details will be provided in the SAP. Summary statistics will be produced by dose level, for patients with dose changes and for the overall study population for both safety and biological effect parameters.

11.5. Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified.

11.6. Patient Disposition

The number of screened patients, screen failures, treated patients, patients who completed the study, and patients who discontinued the study will be summarized. Reasons for discontinuation will also be summarized.

11.7. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized in a descriptive fashion. Data to be tabulated will include gender, age, race, ethnicity, height, and weight, as well as disease-specific characteristics and other parameters as appropriate. These analyses will be conducted on the Safety Population.

11.8. Exposure

Treatment exposure will be summarized by cycle and overall.

11.9. Efficacy Analyses

For the Dose Optimization Phase, all primary and secondary efficacy analyses will be performed using the Dose Optimization Efficacy Population and will be based on the Investigator's determination of response, with the IRC's determination of response used for supportive efficacy analyses. Analysis of the Expansion Phase primary and secondary efficacy analyses will be performed using the mITT population and will be based on the IRC's determination of response, with the Investigator's determination of response used for supportive efficacy analyses. All time

to event analyses will present median times to event and 2-sided 95% confidence bounds. Censoring rules will be detailed in the SAP. Neither IRC or Investigator's determination will require confirmation by a second assessment.

Primary Efficacy Analysis:

- ORR will be tabulated using response determination by the Investigator (Dose Optimization) or IRC (Expansion). Best overall response and response assessments over time will be presented along with 2-sided confidence intervals

Secondary Efficacy Analyses:

- DOR will be calculated for those patients with a CR or PR from the time of first response to PD, using Kaplan-Meier methods
- The proportion of patients demonstrating DCR defined as CR + PR + SD ≥ 8 weeks, will also be presented along with 2-sided confidence intervals
- The proportion of patients receiving the optimal dose of duvelisib will be summarized
- PFS will be assessed using Kaplan-Meier methods from time of first treatment to PD, or death
- OS will be assessed using Kaplan-Meier methods from time of first treatment to death

11.10. Safety Analyses

Safety analyses will be performed on the Safety population, and safety endpoints will be tabulated and presented.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for purposes of summarization. All AEs occurring during the study will be included in by-patient data listings and tabulated by MedDRA system organ class and preferred term. Adverse events will be summarized overall, by relationship and by severity. Events leading to death, SAE, and events resulting in treatment discontinuation will be listed and, if warranted by the data, tabulated.

Exposure to study drug and study drug compliance will be tabulated.

A by-patient listing of ECOG performance status data will be prepared.

The actual value and change from Baseline to each on-study evaluation will be summarized for vital sign measurements, as warranted by the data. By-patient listings of vital sign measurements will be prepared.

Individual patient laboratory parameter values and summary statistics over time will be prepared using descriptive statistics. Severity of select clinical laboratory measures will be determined using NCI CTCAE criteria and Grade 3 or 4 laboratory values will be presented in a separate patient listing.

The use of concomitant medications, coded using World Health Organization Drug Dictionary, will be included in by-patient listing.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of duvelisib.

11.11. Pharmacodynamic and Biomarker Data

Pharmacodynamic and Biomarker analyses will be conducted on all or some of the Safety Population. Pharmacodynamic sample collection will only occur in the US.

Biomarkers such as gene mutation status, gene translocations, immunophenotype, functional immune assays, gene expression, and cytokines, will be evaluated with regard to baseline levels and change to baseline levels. Additional exploratory analyses identified by the Sponsor also may be performed. Listing of individual patient and summary statistics for duvelisib effects on biomarkers and graphs of changes versus time will be prepared. Biomarker effects will be summarized using descriptive statistics and associations with clinical efficacy and/or safety outcomes may be explored.

11.12. Pharmacokinetic Data

Pharmacokinetic analyses will be conducted on the Safety Population.

Blood samples will be taken for the analyses of duvelisib and possible metabolite(s) in plasma at the time points defined in the schedule of assessments. The relevant PK parameters will be determined using bioanalytical data. The PK data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form.

11.13. Interim Analyses

During the Dose Optimization Phase, the ORR will be evaluated in the first 5 evaluable patients for each cohort. Enrollment may discontinue in either cohort if no CR/PR is noted in the first 5 evaluable patients.

After a sufficient number of patients from the Dose Optimization Phase are evaluable, all available data will be reviewed and an optimal dose for the Expansion Phase will be selected (Note: the optimal dose for the Expansion Phase has been selected and documented in Protocol Amendment 2, V3, 14 March 2019 – see Expansion Phase Dose Selection below and Section 1.3). The interim results of the Optimization Phase may also drive changes to the Expansion Phase of the study such as modification to the study patient population, other aspects of entry

criteria, and the inclusion of patients from geographic regions outside the US; any such changes will be documented in an amendment to the protocol. The Secura Bio study team, in collaboration with the Investigators, will make the determination of duvelisib dose for the Expansion Phase of the study based on the safety and activity data.

During the Expansion Phase, an assessment of ORR will be conducted after 40 patients have been followed for a minimum 4 months from the last patient's first dose. Enrollment in the Expansion Phase may be held if ORR as assessed by IRC is less than 20%. At that time, the efficacy data (including durability of response) will be reviewed in combination with safety and PK and upon review, the study may be fully stopped for futility.

Interim analyses may be performed at various timepoints during the Expansion Phase. The additional interim analyses should have no impact on statistical power, as the study is an open label single arm design.

12. ADMINISTRATIVE REQUIREMENTS

12.1. Good Clinical Practice

The study will be conducted in accordance with ICH-GCP and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the IB.

12.2. Ethical Considerations

Before implementing this study, the protocol, the proposed patient informed consent forms and any other information provided to the patients, must be reviewed and approved by a properly constituted IRB/IEC/CEC.

Any substantive change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor, the IRB/IEC/CEC and the Regulatory Authority.

The study will be conducted only at sites where IRB/IEC/CEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator or the Sponsor, as required by local regulations.

12.3. Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with ICH-GCP and all applicable regulatory requirements. Patients who are detained by administrative or judicial order will be excluded from participating in the study.

12.4. Patient Confidentiality and Disclosure

The Investigator and Investigator's staff shall maintain the confidentiality of all patient records. To maintain patient privacy, all eCRFs, study drug records, reports and communications will identify the patient by initials where permitted and/or the assigned patient number. The patient's confidentiality will be maintained and will not be publicly available to the extent permitted by the applicable laws and regulations.

12.5. Data Collection

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each patient.

Secura Bio or designee will provide the study sites with secure access to and training on the electronic data capture system, sufficient to permit site personnel to enter or correct information in the eCRFs. eCRFs will be completed for each study patient. The Investigator is responsible for ensuring the accuracy, completeness, and timeliness of the data entered in the eCRF. The audit trail will indicate the user's identification information and date and time of entry and/or change.

eCRFs should be completed in a timely manner, and every effort should be made to have forms completed and up-to-date.

At the conclusion of the study, Secura Bio or a designee will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a CD or other electronic media will be placed in the Investigator's study file.

12.6. Patient Data Protection

Patients will be assigned a unique identifier during Screening. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information that would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC/CEC members, and by inspectors from regulatory authorities.

12.7. Data Quality Assurance and Monitoring

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., 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 and monitoring techniques [central, remote, or on-site monitoring]) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients 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.

Upon study completion, the monitor will arrange for a final review of the study files, after which the file should be secured by storage for the appropriate period as specified in Section 12.12 Retention of Documents.

12.8. Auditing Procedures

In addition to routine monitoring Secura Bio or designee, the IRB/IEC/CEC, or Regulatory Authority may inspect the study (during the study or after its completion) to evaluate compliance with the protocol and GCP.

The Investigator agrees that representatives of the Sponsor and Regulatory Authorities will have direct access, both during and after the course of this study, to audit and review all study-relevant records.

12.9. Investigator Compliance

The Investigator will conduct the study in compliance with the protocol provided by Secura Bio and approved by the IRB/IEC/CEC and the appropriate regulatory authority. Modifications to the protocol will not be made without agreement of Secura Bio, the IRB/IEC/CEC and the regulatory authority, except where modification is needed to eliminate an immediate hazard to the patient. In this event, the Investigator will contact Secura Bio or designee to discuss the planned course of action. Any deviation from the protocol must be documented.

12.10. Product Complaints

If a product complaint indicating dissatisfaction regarding the study drug is received, the Investigator should contact Secura Bio or designee. A product complaint in and of itself is not an AE. If a product complaint results in an SAE, an SAE form should be completed per the defined procedure.

12.11. Study Closure

Secura Bio or designee will notify the Regulatory Authorities and IRB/IEC/CECs that the study has ended.

Study participation by individual sites or the entire study may be prematurely terminated if in the opinion of the Investigator or Secura Bio there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the Investigator or Secura Bio by the terminating party.

Circumstances that may warrant termination include but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data
- Plans to modify, suspend or discontinue the development of the study drug

12.12. Retention of Documents

The Investigator must maintain source documents for each patient according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and Secura Bio notified.

12.13. Disclosure of Information

All information provided to the Investigator by Secura Bio, Inc. or its designee, will be kept strictly confidential. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Secura Bio. No information about this study or its progress will be provided to anyone not involved in the study other than to Secura Bio or its designees, or in confidence to the IRB, or similar committee, except if required by law.

Upon completion of the clinical study and evaluation of results by Secura Bio, the hospital or institution, and/or Investigator may publish or disclose the clinical study results pursuant to the terms contained in the applicable Clinical Study Agreement. Sponsor will comply with current regulatory requirements for disclosure and submission of study results.

The results of this study may be published or presented at scientific meetings with prior approval of the Sponsor. 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 multi-site studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement between the Sponsor and the Investigators.

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

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14. APPENDICES

APPENDIX 1: CONTRACEPTION GUIDANCE

The effects of duvelisib on conception, pregnancy, and lactation are unknown. Every woman of childbearing potential (WCBP) and male patients with a partner who is a WCBP must use contraception as described below. A woman is considered to be a WCBP after menarche and until becoming postmenopausal (i.e., > 55 years and postmenopausal for at least 1 year), unless permanently sterile.

At Screening, all male and female patients of reproductive potential (i.e., not surgically sterile or female patients who are not postmenopausal) must agree to use a highly effective method of contraception (see below) for the duration of study treatment, and for at least 3 months after the last dose of duvelisib. Male patients must also refrain from donating sperm during their participation in the study and for at least 3 months after the last dose of duvelisib.

The use of contraceptive methods is not required if the male patient or the male partner (of the female patient) has a documented history of a vasectomy or if the female patient or the female partner (of the male patient) has a documented history of bilateral oophorectomy, hysterectomy, or tubal ligation, or if she is > 55 years of age and postmenopausal for at least 1 year.

See Section 10.9 for requirements for pregnancy reporting.

Highly Effective Forms of Contraception

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. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a]:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[a]:
  - oral
  - injectable
  - implantable[b]
- intrauterine device (IUD)[b]
- intrauterine hormone-releasing system (IUS)[b]
- bilateral tubal occlusion[b]
- vasectomized partner[b,c]
- sexual abstinence[d]

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

[b]This method of contraception should preferably be used, in particular when contraception is introduced as a result of participation in the clinical study.

[c]Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.

[d] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

APPENDIX 2: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) SCALE FOR PERFORMANCE STATUS

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	In bed < 50% of the time. 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	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

APPENDIX 3: MEDICATIONS OR FOODS KNOWN TO INHIBIT OR INDUCE CYP3A

The following list provides medications known to induce or inhibit CYP3A activity. Note that this is not a comprehensive list of all medications which may modulate CYP3A activity. Additional information can be found at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

NOTE: Patients receiving duvelisib are prohibited from concomitant use of medications or foods that are known to be strong inhibitors or inducers of CYP3A.

Classification of In Vivo Inhibitors of CYP3A

Strong Inhibitors([1])	Moderate inhibitors([2])	Weak inhibitors([3])
Boceprevir, clarithromycin, conivaptan, grapefruit juice,([5]) indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, ([6]) nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, ([5]) imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, ([4]) goldenseal,([4]) isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

1. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the area under the curve (AUC) of a substrate for that CYP by equal or more than 5-fold or > 80% decrease in CL.
2. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold or 50-80% decrease in CL.
3. A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold or 20-50% decrease in CL.
4. Herbal product.
5. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength).
6. Withdrawn from the United States market because of safety reasons.

Classification of In Vivo Inducers of CYP3A

Strong Inducers **≥ 80% decrease in AUC**	**Moderate Inducers** **50-80% decrease in AUC**	**Weak Inducers** **20-50% decrease in AUC**
Avasimibe,([1]) carbamazepine, phenytoin, rifampin, St. John's Wort([2])	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, Echinacea,([3]) pioglitazone, prednisone, rufinamide

1. Not a marketed drug.
2. The effect of St. John's Wort varies widely and is preparation-dependent.
3. Herbal product.

APPENDIX 4: CYP3A OR CYP2C8 SUBSTRATES

The following lists provide known sensitive CYP3A substrates, CYP3A substrates with a narrow therapeutic range, and CYP2C8 substrates. Drugs or foods that are substrates of CYP3A should only be used if medically necessary and therapeutic alternatives do not exist. Medications that are metabolized via CYP2C8 may be used as medically indicated but with caution.

Additional information can be found at http://www.medicine.iupui.edu/clinpharm/ddis/ClinicalTable.asp and http://www.pharmacytimes.com/issue/pharmacy/2008/2008-09/2008-09-8687.

Sensitive CYP3A Substrates	
budesonide buspirone eplerenone eletriptan felodipine fluticasone lovastatin	midazolam saquinavir sildenafil simvastatin triazolam vardenafil
CYP3A Substrates with a Narrow Therapeutic Range	
alfentanil astemizole cisapride cyclosporine diergotamine ergotamine	fentanyl pimozide quinidine sirolimus tacrolimus terfenadine
CYP2C8 Substrates	
paclitaxel torsemide amodiaquine	cerivastatin repaglinide rosiglitazone pioglitazone

APPENDIX 5: P-GP SUBSTRATES AND MEDICATIONS THAT ARE INHIBITORS OF P-GP

The following list provides medications that are substrates or inhibitors of P-gp, which should be used with caution during treatment with duvelisib. Note that this is not a comprehensive list of all medications which may be substrates of P-gp or may modulate P-gp activity.

P-gp Substrates	
Amitriptyline	Loperamide
Amiodarone	Losartan
Atorvastatin	Lovastatin
Cefoperazone	Methadone
Chlorpromazine	Methotrexate
Cimetidine	Methylprednisolone
Ciprofloxacin	Morphine
Clarithromycin	Nadolol
Colchicine	Norfloxacin
Cyclosporine	Nortriptyline
Dexamethasone	Ondansetron
Digoxin	Omeprazole
Diltiazem	Pantoprazole
Erythromycin	Phenytoin
Estradiol	Pravastatin
Fentanyl	Propranolol
Fexofenadine	Quinidine
Hydrocortisone	Ranitidine
Itraconazole	Sirolimus
Lansoprazole	Tacrolimus
Levofloxacin	Timolol
Lidocaine	Trimethoprim
	Verapamil
P-gp Inhibitors	
Amiodarone	Lovastatin
Amitriptyline	Mefloquine
Carvedilol	Nicardipine
Chlorpromazine	Nifedipine
Clarithromycin	Ofloxacin

Cortisol	Omeprazole
Cyclosporine	Pantoprazole
Desipramine	Progesterone
Diltiazem	Propafenone
Dipyridamole	Propranolol
Doxepin	Quinidine
Erythromycin	Rifampicin (Rifampin)
Felodipine	Saquinavir
Fluphenazine	Simvastatin
Grapefruit juice	Sirolimus
Haloperidol	Tacrolimus
Itraconazole	Testosterone
Ketoconazole	Verapamil

Source: Atkinson AJ et al. Principles of Clinical Pharmacology, 2nd ed. Academic Press, Massachusetts, 2007.

APPENDIX 6: SUMMARY OF CHANGES

Protocol Version 7.1 (Amendment 7.1), 24 November 2021

AMENDMENT RATIONALE

Language was added to allow additional interim analyses which may occur at various times during the expansion phase of the study. This protocol amendment is considered administrative in nature as there is no impact on statistical powering of the study, due to the open label single arm design. Further, the additional interim analyses may be used to inform future health authority discussions.

The revised protocol, Version 7.1, dated 24 November 2021 may be submitted by the Investigator(s) to all applicable IRBs, IECs, or CECs, as required by their institution and by Secura Bio, Inc. to all applicable Regulatory Authorities.

Protocol Version 7.0 (Amendment 7), 20 July 2021

AMENDMENT RATIONALE

The protocol will be amended to allow for the addition of up to 30 Expansion Phase patients, with a target of approximately 24 additional patients. The statistical design has been updated to demonstrate the advantages and limitations of the increase in sample size.

The purpose of this amendment is to increase the Expansion Phase sample size from 100 patients to approximately 120-130. The key rationales for the increase in sample size are (1) to increase confidence in the efficacy results, with an expansion phase N analogous to those of other label enabling trials in relapsed/refractory PTCL; and (2) to include more patients that carry diagnoses of ALCL and NK cell subtypes, to more closely match the subtype percentage breakdowns noted in the epidemiologic literature regarding PTCL in Western populations.

As the amendment was not based on lack-of-efficacy or safety concerns, this amendment has been deemed not substantial.

The revised protocol, Version 7.0, dated 20 July 2021 will be submitted by the Investigator(s) to all applicable IRBs, IECs, or CECs, and by Secura Bio, Inc. to all applicable Regulatory Authorities.

Protocol Version 6.1 (Amendment 6), 08 December 2020

AMENDMENT RATIONALE

Secura Bio, Inc. acquired the global rights in Oncology for the Investigational Medicinal Product (IMP), duvelisib (also referred to as Copiktra®) from Verastem. Updates were made in this

document in all sections, as applicable, to reflect that Secura Bio is now the Sponsor for this study. This is an administrative change that does not affect the planned study.

In addition, minor language and format corrections were also done throughout the document.

The revised protocol, Version 6.1, dated 08 December 2020 will be submitted by the Investigator(s) to all applicable IRBs, IECs, or CECs, and by Secura Bio, Inc. to all applicable Regulatory Authorities.

Protocol Version 6.0 (Amendment 5), 16 September 2019

AMENDMENT RATIONALE

The primary purpose for this amendment was to clarify applicable protocol sections based on agency questions. The key updates included the following: clarifying selection of the optimal dose was completed based on interim data from the Dose Optimization Phase, to align pregnancy testing frequency with Clinical Trial Facilitation Group (CTFG) recommendations, to add an exclusion criterion for known hypersensitivity to duvelisib or its excipients, and to add prohibition on the use of live vaccines for 3 months after the last dose of study drug.

A summary of key changes that were made to protocol Version 5.0, including the rationales for these changes, is provided below.

Table 13 Summary of Changes for Version 6.0

Section(s)	Description of Change	Rationale for the Change
Global	Updated the version number and date of protocol from Version 5.0 dated 09 August 2019 to Version 6.0 dated 16 September 2019	Administrative change
Global	Updated missing abbreviations, grammar, editorial as necessary.	Administrative change
Synopsis, Section 5.2	Added exclusion criterion for patients with known hypersensitivity to duvelisib and/or its excipients	To exclude patients who may have an adverse hypersensitivity reaction to treatment
Synopsis, Section 1.3, Section 5.1	Modified the units on CD4 lymphocyte count	Correction of error
Synopsis, Section 4.1.2, Section 10.13	Modified text to indicate the optimal dose for the Expansion Phase has been selected and that the optimal dose was selected based on the interim results of the Dose Optimization Phase	To improve the clarity of the description of optimal dose selection
Table 2, Table 2 footnote #13, Section 6.10.2	Increased frequency of pregnancy testing to monthly for the Expansion Phase. This was added as Cycle 4 column in Table 2 with footnote and also to body text.	To align with CTFG (Final Version-2014- 09-15) recommendations on pregnancy testing in clinical studies
List of Abbreviations, Table 8	Added definition for the term “Gi”as 1 X 10^9 (1 billion cells or giga)	To clearly distinguish the “Gi” abbreviation from the “GI” abbreviation

Section(s)	Description of Change	Rationale for the Change
Section 8.4	Added new section: "End of Study Definition"	To provide definition for End of Study
Section 8.2	Removed sentence about observing patients during follow-up	Correction as after withdraw from study, no observation would occur
Section 9.6.1	Modified text to indicate that live vaccines are prohibited for 3 months after last dose of study drug	To clarify the guidance on use of live vaccines after last dose of study drug
Appendix 6	Added Summary of Changes made to version 5.0 and added Version History section and table.	Administrative change

Protocol Version 5.0 (Amendment 4), 09 August 2019

AMENDMENT RATIONALE

The primary purpose for this amendment was to align pregnancy guidance to Clinical Trial Facilitation Group (CTFG), add Study Design Figure to align to ICH, include ongoing cardiac function per Investigator discretion and update vital sign collection at each visit to be independent of Investigator discretion.

A summary of key changes that were made to protocol Version 4.0, including the rationales for these changes, is provided below.

Table 14: Summary of Changes for Version 5.0

Section(s)	Description of Change	Rationale for the Change
Global	Minor internal changes were made to syntax, grammar, and punctuation to improve clarity and eliminate inconsistencies among sections (e.g., changed subject to patient, Dose Escalation to Dose Optimization where applicable, aligned wording for Inclusion Criterion #3 in Section 5.1 and Exclusion Criterion #1 in Section 5.2 with wording in Synopsis, modification of CYP3A metabolism in Section 8.6.4)	Administrative change
Global	Updated the version number and date of protocol from Version 4.0 dated 16 April 2019 to Version 5.0 dated 09 August 2019	Administrative change
After Synopsis, Section 4.1	Added Figure 1 for Study Overview after the synopsis and removed text in Section 4.1 stating that the schematic diagram is contained in the training materials for the investigational sites	To align to ICH recommendations to include a schematic diagram of the study design in the protocol
Synopsis, Section 5.1, Section 8.5.3, Appendix 1	Updated Inclusion Criterion 11 and birth control/contraception guidance	To align to CTFG (Final Version-2014- 09-15) recommendations on contraception and pregnancy testing in clinical studies
Table 2, Section 6.7	Additional ECGs may be conducted on treatment and during follow-up per Investigator discretion	An ECG was required during screening (per the Schedule of Events) but was not repeated during on-treatment or follow-up periods. Since duvelisib has non-significant cardiac toxicity, the test was added for on-treatment and follow-up periods with language “at the Investigator’s discretion” to allow for evaluation of this health parameter if needed to ensure patients are not negatively influenced by their participation in the clinical study.

Section(s)	Description of Change	Rationale for the Change
Table 2, Section 6.8	Additional echocardiograms may be conducted on treatment and during follow-up per Investigator discretion	An echocardiogram during screening was required (per the Schedule of Events) but was not repeated during on-treatment or follow-up periods. Since duvelisib has non-significant cardiac toxicity, the test was added for on-treatment and follow-up periods with language "at the Investigator's discretion" to allow for evaluation of this health parameter if needed to ensure patients are not negatively influenced by their participation in the clinical study.
Table 2	Revised vital sign collection to occur at every visit, including C1D8, C1D15 and C2D15 visits; therefore, removed "if clinically indicated" from footnote 11	To allow for a thorough examination of the health status of study patients and rule out potential adverse events, vital signs are to be performed at each study visit.
Section 1.2	Inserted the following description of the differentiation capability of myeloid cells to the background on duvelisib: "tumor-associated macrophages that promote angiogenesis and augment tumor growth (Lewis et al, 2006)."	To correct inadvertent deletion in the prior version.
Section 6.13	Clarified that the following samples will only be collected in the US: • pharmacodynamic markers of target inhibition in PTCL and immune populations • immunophenotypes and functional tests of major immune populations in the blood	To indicate which samples will only be collected in the US
Section 11.3	Clarified that patients who are detained by administrative or judicial order will be excluded from participating in the study	To provide information regarding the eligibility of patients who are detained by administrative or judicial order, per regulatory request
Section 11.6, Section 11.7, Section 11.8	Added new sections with details related to patient data protection and quality assurance; and combined previous section for monitoring procedures (11.8) with the new Section 11.7	To provide more information on data protection and quality assurance, per regulatory request
Section 11.13	Expanded the disclosure of information to include details related to the publication policy	To clarify the publication policy

Version History

Table 15: Primary Reason for Each Version

Version	Primary Reason for Version
7.1	Addition of interim analyses language in the expansion phase of the study.
7.0	Increase sample size and updated statistics to match sample size increase.
6.1	To update Sponsor contact information
6.0	To clarify applicable protocol sections based on agency questions. The key updates included the following: clarifying selection of the optimal dose was completed based on interim data from the Dose Optimization Phase, to align pregnancy testing frequency with Clinical Trial Facilitation Group (CTFG) recommendations, to add an exclusion criterion for known hypersensitivity to duvelisib or its excipients, and to add prohibition on the use of live vaccines for 3 months after the last dose of study drug.
5.0	To align pregnancy guidance to Clinical Trial Facilitation Group (CTFG), add Study Design Figure to align to ICH, include ongoing cardiac function per Investigator discretion, and update vital sign collection at each visit to be independent of Investigator discretion
4.0	To add a requirement for central pathology review of FFPE slides to confirm PTCL diagnosis and update the toxicity management guidance to include febrile neutropenia
3.0	To update planned enrollment, number of clinical sites, some inclusion/exclusion criteria, objective/endpoint alignment, clarification of imaging scan information, population clarification, and Expansion Phase dose determination
2.0	To clarify that response to study treatment will be determined by IRC. The IRC's determination of response to study treatment will be used in primary and secondary efficacy analyses. The Investigator's determination of disease response will be used in supportive efficacy analyses
1.0	Original version