PROTOCOL NO. RP6530+Romidepsin-1805

An Open label, Phase I/II study to evaluate the safety and efficacy of Tenalisib (RP6530), a novel PI3K δ/γ dual inhibitor given in combination with a histone deacetylase (HDAC) inhibitor, Romidepsin in adult patients with relapsed/refractory T-cell Lymphoma

PROTOCOL NUMBER	RP6530+Romidepsin-1805
TRIAL DRUG	RP6530 (Tenalisib) and Romidepsin
IND NUMBER	[redacted]
SPONSOR	**Rhizen Pharmaceuticals S.A.** Fritz-Courvoisier 40, Ch-2300 La Chaux-de-Fonds, Switzerland
PRINCIPAL INVESTIGATOR AND STUDY CHAIR	[redacted]
SPONSOR'S MEDICAL EXPERT	[redacted]
DOCUMENT VERSION	**Amendment 1 to Version 1.0, Dated 16 August 2018** Amendment version dated 30 November 2018

Clinical Trial Protocol Statement of Compliance

This clinical trial shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **<Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the PI, I understand that my signature on the protocol constitutes my agreement and understanding of PI responsibilities to conduct the clinical trial in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

Protocol Approval Page

An Open label, Phase I/II study to evaluate the safety and efficacy of Tenalisib (RP6530), a novel PI3K δ/γ dual inhibitor given in combination with a histone deacetylase (HDAC) inhibitor, Romidepsin in adult patients with relapsed/refractory T-cell Lymphoma

PROTOCOL NUMBER	RP6530+Romidepsin-1805
TRIAL DRUG(S)	Tenalisib and Romidepsin
IND NUMBER	124584
DOCUMENT VERSION	**Amendment 1 to version 1.0, Dated 16 August 2018** Amendment Version dated 30 November 2018

[redacted]

[redacted]

[redacted]

Protocol Acceptance Page

An Open label, Phase I/II study to evaluate the safety and efficacy of Tenalisib (RP6530), a novel PI3K δ/γ dual inhibitor given in combination with a histone deacetylase (HDAC) inhibitor, Romidepsin in adult patients with relapsed/refractory T-cell Lymphoma

PROTOCOL NUMBER	RP6530+Romidepsin-1805
TRIAL DRUG(S)	Tenalisib and Romidepsin
[redacted]	[redacted]
DOCUMENT VERSION	**Amendment 1 to version 1.0, Dated 16 August 2018** Amendment Version dated 30 November 2018

Principal Investigator	**Signature**	**Date**

Amendment History

Amendment#/date	Reference to section	Summary	Rationale
Amendment 1 to version 1.0, Dated 16 August 2018 Amendment Version dated 30 November 2018	Section 4.1 Inclusion criteria	Inclusion criteria #9 is clarified	Protocol clarification
	Section 5.3 Concomitant medication	Concomitant medication section is updated as "Similarly, Dabigatran and Edoxaban, Direct-acting Oral Anti-Coagulants (DOAC) class of drugs are acceptable".	Protocol clarification. Dabigatran and Edoxaban are acceptable as they are not metabolized by CYP3A4/CYP2C9 enzymes.
	Section 5.4 Prohibited medication	Prohibited medication section is updated as "Apixaban and Rivaroxaban, DOAC class of drugs, are prohibited.	Protocol clarification. Apixaban and Rivaroxaban are prohibited as they are metabolized by CYP3A4 enzymes.
	Section 6: Trial assessment and procedure	The time points for vitals, ECGs and laboratory assessment and visits are clarified.	Protocol clarification
	Section 7.7 dose modifications	Dose modifications are clarified.	Protocol clarification
	Throughout the document	Minor protocol clarifications and administrative changes	

PROTOCOL SYNOPSIS

Study Title	An Open label, Phase I/II study to evaluate the safety and efficacy of Tenalisib (RP6530), a novel PI3K δ/γ dual inhibitor, given in combination with a histone deacetylase (HDAC) inhibitor, Romidepsin in adult patients with relapsed/refractory T-cell Lymphoma.
Phase	Phase I/II
Study Sponsor	Rhizen Pharmaceuticals S.A.
Study Centers	Approximately about 15 study centers
Study Objectives	**Primary Objectives** • To characterize safety, tolerability and to establish the maximum tolerated dose (MTD) of Tenalisib in combination with Romidepsin in patients with R/R T-cell lymphoma. **Secondary Objectives** • To assess the preliminary anti-tumor activity of various dose levels of Tenalisib in combination with Romidepsin, as determined by the objective response rate (ORR) and Duration of Response (DoR) • To characterize the Pharmacokinetics (PK) of Tenalisib and Romidepsin when given in combination. **Exploratory Objectives** • To correlate clinical efficacy with markers that include but are not limited to quantitative and qualitative measurements of malignant cells, cytokines, and chemokines in blood/serum.
Endpoints	**Safety:** • Adverse Event (AE), Grade 3/ 4 AEs, Serious and fatal Adverse Event (SAE), graded using NCI CTCAE Version 5.0. **Efficacy:** • **Objective response rate (ORR)**, defined as sum of CR and PR rates, assessed according to the Lugano Classification for initial evaluation, staging, and response assessment of Hodgkin/non-Hodgkin lymphoma in PTCL patients; and according to the modified Severity Weighted Assessment Tool (mSWAT) in CTCL patients. • **Duration of Response (DoR),** calculated as time from the initial response to documented disease progression. **Pharmacokinetics:** • PK Parameters [$AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, t_{max}, Kel, and $t_{½}$] of Tenalisib and Romidepsin.

<table>
<tr><td></td><td>Correlative/Exploratory:
Correlative markers include baseline and on-treatment serum levels of chemokines, cytokines, antibodies to tumor antigens, and other immune mediators (e.g. sIL2R and CTACK for PTCL; CD30, IL-31 and IL-32 for CTCL) as deemed relevant by the sponsor.</td></tr>
<tr><td>Study Design and Procedure</td><td>This is a multi-center, open label, non-randomized, two-part Phase I/II study of Tenalisib in combination with Romidepsin in adult patients with relapsed/refractory TCL. The first part is an open label, 3+3 design, Phase I dose escalation for MTD determination. The second part is a Phase II, dose expansion to delineate the safety and anti-tumor activity of the combination at the MTD/optimal dose.

In dose escalation, a minimum of 2 and maximum 18 patients will be enrolled in three dose levels unless additional dose levels are required to reach MTD/ optimal dose. In dose expansion, up to 24 TCL patients will be enrolled (Group 1 = 12 PTCL patients and Group 2 = 12 CTCL patients).

The study will end when all ongoing subjects have reached their third tumor assessment on Cycle 8/Day 1 (C8D1) or have discontinued from the study for any reason, whichever is earlier. At the end of the study, all ongoing patients with no evident disease progression will be given the opportunity to enroll in an open-label compassionate use study protocol and will be followed up.

<u>PHASE I (DOSE ESCALATION):</u>
Sequential dose escalation will begin with Cohort 1. A minimum of three patients will be enrolled at each dose level. Dose levels will be increased in successive increments according to the dose escalation cohorts mentioned in the table below. Escalation to the next cohort will occur if no patient within a three-patient cohort or one in six patients experiences a dose limiting toxicity (DLT). De-escalation to different lower doses in case DLT criteria is met, will be done as per the discretion of Safety Review Committee (SRC). The highest doses of the combination (Tenalisib at 800 mg BID plus Romidepsin IV 14 mg/m^2) will be considered as optimal in case there is no DLT at this dose level.

Dose escalation scheme:
<table>
<tr><th>Cohort</th><th>N</th><th>Tenalisib[1]</th><th>Romidepsin[2]</th></tr>
<tr><td>Cohort 1</td><td>3-6</td><td>Tab. 400 mg PO twice a day</td><td>IV 12 mg/m^2 on Day 1, 8 and 15</td></tr>
<tr><td>Cohort 2</td><td>3-6</td><td>Tab. 600 mg PO twice a day</td><td>IV 12 mg/m^2 on Day 1, 8 and 15</td></tr>
<tr><td>Cohort 3</td><td>3-6</td><td>Tab. 800 mg PO twice a day</td><td>IV 14 mg/m^2 on Day 1, 8 and 15</td></tr>
</table>
Note: Alternate dose levels/dosing schedules may be considered by the SRC if deemed essential based on emerging safety and PK data.
[1]In case the dose (e.g. 800 mg BID) is leading to DLT of the combination, the dose of Tenalisib will be reduced to lower dose (e.g. 600 mg BID) and will be evaluated for safety in a separate cohort.</td></tr>
</table>

	[2]In case the dose (e.g. 14 mg/m^2) is leading to DLT of the combination, the dose of Romidepsin will be reduced to lower dose (e.g.12 mg/m^2) and if required further to 10 mg/m^2 and will be evaluated for safety in a separate cohort. **DLT assessment:** The data of at least 3 patients will be required for DLT assessment. DLT assessment period will be **28-days** (inclusive) (will begin on C1D1 and end on C2D1), unless extended by the medical monitor. In the first cycle, patients must have been treated with at least 2 doses of Romidepsin and minimum 14 days with Tenalisib to be considered eligible for safety analysis unless identified to have a DLT. Patients who experience a DLT will be considered evaluable regardless of the number of doses received. Individual patients will be considered for ***Intra-subject dose*** escalation at the discretion of investigator after discussion with medical monitor. **PHASE II (DOSE EXPANSION):** After establishing the MTD/optimal dose, the Phase II (expansion part) will be opened as approved by the SRC to enroll two groups of patients.

Group	N	Patient population	Tenalisib	Romidepsin
Group 1	12	Patients with R/R PTCL	MTD/Optimal dose	MTD/Optimal dose on Day 1, 8 and 15
Group 2	12	Patients with R/R CTCL	MTD/Optimal dose	MTD/Optimal dose on Day 1, 8 and 15

The details of the study procedures are given in the schedule of events.

No. of Patients	**Phase I**: Total 2-18 patients will be enrolled in 3 escalating cohorts unless additional dose levels are required to reach MTD/ optimal dose. **Phase II**: Total 24 patients with relapsed/refractory TCL will be enrolled.
Inclusion Criteria	**Inclusion criteria** 1. Age ≥18 years on the day of signing informed consent. 2. Pathologically confirmed T-cell lymphoma at the enrolling institution*. 3. Disease status as defined as relapsed after or refractory to at least one systemic therapy. 4. The patients should have received NOT more than three prior systemic combination chemotherapies. 5. Must have ECOG performance status ≤ 2 6. PTCL patients must have measurable disease defined as at least one bi-dimensional measurable lesion with minimum measurement of > 1.5 cm in the longest diameter. 7. Life expectancy of at least 3 months 8. Toxicities related to prior therapy must have returned to Grade 1 or less, except for alopecia.

	9. Adequate bone marrow, liver and renal function in line with below mentioned laboratory requirements. Hemoglobin and platelet requirements should not be met by use of recent transfusion or growth factor support (GCSF or erythropoietin) within 3 weeks prior to treatment initiation. • Hemoglobin ≥8.0 g/dL • Absolute neutrophil count (ANC) ≥1,000/μL • Platelet count ≥75,000/μL • Total bilirubin ≤1.5 times the ULN (or ≤3 x ULN, if patient has Gilbert syndrome) • AST (SGOT) and ALT (SGPT) ≤ 3 x ULN; ≤ 5 ULN in case of liver involvement • Calculated creatinine clearance (CrCl) > 50 ml/min by Cockcroft-Gault formula. 10. Use of an effective means of contraception for women of childbearing potential and men with partners of childbearing potential. 11. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. 12. Provide written informed consent prior to any study-specific screening procedures. 13. Willingness and capability to comply with the requirements of the study. *Note: The EORTC classification of CTCLs will be used to classify patients. CTCL includes other variants other than MF (e.g. Gamma delta cutaneous T-cell lymphoma or subcutaneous or panniculitic like T-cell lymphoma and CD8 positive T-cell lymphoma). PTCL includes patients with predominantly nodal disease (systemic involvement) but some patients (e.g. AITCL or ATCL) may have skin lesions. Patient having both skin and node lesions will be placed into one of the group (CTCL or PTCL) as approved by investigator.
Exclusion Criteria	1. Patient receiving anticancer therapy including any investigational therapy (e.g. chemotherapy, biologic therapy, hormonal therapy, radiotherapy (except limited field palliative radiation), surgery and/or tumor embolization) ≤3 weeks or 5 half-lives (whichever is shorter) prior to C1D1. 2. Patient who discontinued prior therapy with PI3K inhibitors or HDAC inhibitors due to drug toxicity. 3. PTCL patients with Allo-SCT on active GVHD or immunosuppression therapy within 3 months prior to C1D1. CTCL patients with the history of Allo-SCT will be excluded. 4. Patient with medical conditions requiring the use of systemic immunosuppressive medications (> 20 mg/day of prednisone or equivalent). 5. Severe bacterial, viral or mycotic infection requiring systemic treatment. 6. Pregnancy or lactation. 7. History of chronic liver disease, hepatic veno-occlusive disease, or current alcohol abuse.

	8. Known clinically active central nervous system (CNS) or meningeal involvement. (Note: In the absence of symptoms, investigation into CNS involvement is not required. Patients are eligible if metastases have been treated and patients are neurologically returned to baseline or neurologically stable for at least 4 weeks prior to C1D1). 9. Known seropositive requiring anti-viral therapy for human immunodeficiency virus (HIV) infection. 10. Known seropositive requiring anti-viral therapy for hepatitis B virus (HBV) infection OR evidence of active hepatitis B infection as defined by detectable viral load if the antibody tests are positive. [Note: A positive HBcAb subject with an undetectable/negative hepatitis B DNA test (e.g., polymerase chain reaction [PCR] test) can be enrolled]. 11. Known seropositive requiring anti-viral therapy for hepatitis c virus (HCV) infection OR patients with positive hepatitis C virus Ab. 12. Subjects with active EBV unrelated to underlying lymphoma (positive serology for anti-EBV VCA IgM antibody and negative for anti-EBV EBNA IgG antibody, or clinical manifestations and positive EBV PCR consistent with active EBV infection. 13. Subject with active CMV (positive serology for anti-CMV IgM antibody and negative for anti-CMV IgG antibody and positive CMV PCR with clinical manifestations consistent with active CMV infection) and requiring therapy. [Note: Carriers will be monitored per institutional guidelines.] 14. Subjects with concomitant second malignancies (except adequately treated non-melanomatous skin cancers, ductal carcinoma in situ, superficial bladder cancer, prostate cancer or in situ cervical cancers) are excluded unless a complete remission is achieved at least 2 years prior to study entry and no additional therapy (except adjuvant or maintenance therapy to reduce the risk of recurrence) is required or anticipated to be required during the study period. 15. Administration of any of the following within 1 week prior to C1D1: • Strong inhibitors or inducers of CYP3A4 including but not limited to grapefruit products, herbal supplements and drugs • Strong inhibitors or inducers of CYP2C9 including but not limited to herbal supplements and drugs • Substrates of CYP3A4 enzyme with a narrow therapeutic range. 16. History of Grade 4 anaphylactic reaction. 17. Administration of live vaccines within 6 weeks of C1D1. 18. History of prior surgery or gastrointestinal dysfunction that may affect drug absorption (e.g., gastric bypass surgery, gastrectomy) 19. Current history of a serious uncontrolled medical disorder, metabolic dysfunction, physical examination findings, or clinical laboratory findings giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drugs or render the subject at high risk from treatment complications.

	20. Uncontrolled or significant cardiovascular disease including, but not limited to: • Congenital long QT syndrome. • QTcF interval > 450 msec • Myocardial infarction or stroke/TIA within the past 6 months • Uncontrolled angina within the past 3 months • Significant ECG abnormalities including 2nd degree atrio- ventricular (AV) block (AV) block type II, 3rd degree AV block. • History of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation or torsades de pointes), • History of other clinically significant heart disease (ie, cardiomyopathy, congestive heart failure with NYHA functional classification III-IV, pericarditis, significant pericardial effusion) • Requirement for daily supplemental oxygen therapy.
Estimated Study Participation	**Dose Escalation:** Approximately 10 months for accrual and follow up **Dose Expansion:** Approximately 18 months for accrual plus patient follow up.
Assessment of Response	Initial disease assessment will be performed at screening. The response to treatment will be done at C3D1 (± 7 days), C5D1 (± 7 days), C8D1 (± 7 days) and/ or at the EOT and or as clinically indicated (if clinical progression is suspected or for confirmation of complete response/disease progression). The following assessments will be done. **PTCL:** The response assessment will be done using CT scan as per the Lugano classification. PET-CT will be preferred for FDG-avid lymphomas. PET-CT will be performed at C3D1 (± 7 days) and to confirm the CR. Bone marrow biopsy will be performed to confirm complete response. **CTCL:** Response assessment in CTCL will be done as per the modified Severity Weighted Assessment Tool (mSWAT). Additionally, CT scan will be done in the CTCL patients with lymph node and visceral involvement. CTCL patients with subcutaneous lesions which cannot be measured by mSWAT will be assessed by change in PET-CT avid lesions. Bone marrow biopsy will be performed in patients with B_2 blood involvement. In these patients, Sezary cell count will be quantified by flow cytometry or morphology in blood/bone marrow.
Study Treatment	For purposes of this study, each cycle of therapy consists of 4 weeks. **Tenalisib:** Tenalisib will be administered from Day 1-28 in 28-days of cycle up to C8D1 in absence of disease progression and unacceptable toxicity. However, in Cycle 1 of Dose Escalation, Tenalisib will be started from Day 3 to permit pharmacokinetic analysis of Romidepsin alone prior to combination treatment.

	Tenalisib tablets will be self-administered orally twice daily one hour before a major meal (e.g. breakfast and dinner). Patients should not consume food during this one-hour period. On the day of Romidepsin therapy, the morning dose of Tenalisib will be given in clinic one hour prior to Romidepsin infusion. **Romidepsin:** Romidepsin will be administered intravenously (IV) over a 4-hour period on days 1, 8 and 15 in a 28-day cycle.
Statistical Analysis	**Part 1:** In Dose Escalation, three patients per cohort are considered appropriate for the assessment of overall safety and tolerability and for providing adequate confidence for dose escalation. No formal sample size and power analysis is done. Accordingly, total 2-18 patients will be enrolled in 3 escalating cohorts unless additional dose levels are required to reach MTD/ optimal dose. Optimal dose will be determined by the SRC. **Part 2:** Total 24 patients with relapsed/refractory TCL will be enrolled in two groups (12 patients in each group). The SRC may modify the sample size due to unforeseen clinical situations.

GENERAL INFORMATION	
SPONSOR	[redacted]
PRINCIPAL INVESTIGATOR AND STUDY CHAIR	
CO- PRINCIPAL INVESTIGATOR	
SPONSOR'S REPRESENTATIVE	
SPONSOR'S MEDICAL EXPERT	
STATISTICIAN	
CLINICAL PK, BIOMARKER LABORATORY	

List of Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT (SGOT)	Alanine aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
Allo-SCT	Allogeneic Hematopoietic Stem Cell Transplantation
AST (SGPT)	Aspartate aminotransferase
AUC_{0-t}	Area Under the plasma-concentration time curve from zero up to the last measurable concentration
BID	Twice Daily
β-HCG	β-human chorionic gonadotropin
BSA	Body Surface Area
C_{max}	Peak Drug Concentration
CBC	Complete Blood Count
CMV	Cytomegalovirus
CNS	Central Nervous System
CR	Complete Response
CrCl	Creatinine Clearance
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T cell Lymphoma
DLT	Dose Limiting Toxicity
DoR	Duration of Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
FSH	Follicular Stimulating Hormone
GCP	Good Clinical Practices
GGT	Gamma Glutamyl Transpeptidase
G-CSF	Granulocyte Colony-Stimulating Factor
GVHD	Graft Versus Host Disease
Hb	Hemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HDPE	High-density Polyethylene
HEENT	Head, Eyes, Ears, Nose and Throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immune Deficiency Virus
HPV	Human Papilloma Virus
IB	Investigator's brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
INR	International Normalized Ratio
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRR	Infusion related reactions
ISCL	International Society of Cutaneous Lymphoma
IUD	Intrauterine Device
IUS	Intrauterine System
Kel	Elimination Constant
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LLN	Lower Limit of Normal
LMWH	Low Molecular Weight Heparin
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mycosis fungoides
mITT	Modified Intent-to-Treat
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mSWAT	Modified Severity Weighted Assessment tool
NCI	National Cancer Institute
NOAEL	No-Observed-Adverse Effect Level
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
ORR	Objective Response Rate
pAKT	Phospho AKT
PCP	Pneumocystis Carinii
PD	Progressive Disease
PD-1	Programmed Death-1
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PI	Principle Investigator
PI3K	Phosphoinositide-3-Kinase
PK	Pharmacokinetics
PP	Per-Protocol
PR	Partial Response
PTCL	Peripheral T-Cell Lymphoma
QA	Quality Assurance
QTcF	Frederica's (QTcf)
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Stable Disease
SDV	Source Document Verification
SLL	Small Lymphocytic Lymphoma
SOP	Standard Operating Procedures
SRC	Safety Review Committee
SS	Sezary Syndrome

SUV	Standardized Uptake Value
$t_{1/2}$	Plasma Half Life
t_{max}	Time to maximum plasma concentration
TAM	Tumor Associated Macrophages
TEAE	Treatment-Emergent Adverse Event
TG	Triglyceride
TIA	Transient Ischemic Attack
TID	Thrice Daily
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
USP	United States Pharmacopeia
UV	Ultra-violet
WBC	White Blood Cells
WHO	World Health Organization

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1 BACKGROUND INFORMATION

1.1 Tenalisib (RP6530)

The phosphoinositide-3-kinases (PI3Ks) are a family of enzymes involved in various cellular functions, including cell proliferation and survival, cell differentiation, intracellular trafficking and immunity.[1-3] Tenalisib is a highly specific and orally available dual PI3K δ/γ inhibitor with nano-molar inhibitory potency and several fold selectivity over α and β PI3K isoforms. The specificity of Tenalisib towards PI3K δ and γ is evidenced by >1000 and >100-fold selectivity over α and β isoforms in an enzyme-based assay. Chemically, Tenalisib is an iso-flavone substituted adenine.

1.1.1 Summary of Pre-Clinical Evaluation

Tenalisib has equimolar potency against both PI3K δ/γ isoforms in enzyme, cell, and blood-based assays. Additionally, the compound inhibited antigen-induced superoxide or cytokine release from primary human neutrophils or monocytes at nano-molar concentration indicating a potential in modulation of the tumor microenvironment. Studies using immortalized B and T lymphoma cell lines demonstrated the anti-proliferative effect of Tenalisib coupled with induction of apoptosis and a concomitant inhibition of the downstream biomarker, pAKT. Similarly, cytokine induced pAKT was inhibited in malignant primary CTCL cells isolated from patient donors. Tenalisib induced apoptosis of patient derived primary CTCL cells following 48 hr incubation.

In vivo efficacy of Tenalisib was confirmed in a subcutaneous mouse MOLT-4 xenograft model representative of human T-cell acute lymphoblastic leukemia. Oral administration of 50 mg/kg/BID over an 18-day period resulted in a significant delay in tumor growth.[4] In 28-days toxicity studies in rat and dog, once daily oral administration of Tenalisib was well tolerated. Target organ effects were observed in thyroid and liver. The no-observed-adverse-effect level (NOAEL) was 20 mg/kg/day in rat and 10 mg/kg/day in dog.

Refer to the Investigator's Brochure (IB) for detailed background information on Tenalisib.[5]

1.1.2 Summary of Clinical Evaluation

To date, Tenalisib has been evaluated in four clinical trials:

1. A Phase I Dose Escalation Study Evaluating the Safety and Efficacy of RP6530, a dual PI3K δ/γ inhibitor, in Patients with Relapsed or Refractory Hematologic Malignancies (European study: Protocol Number RP6530-1301) Status: Completed
2. A Phase I/Ib, Dose Escalation Study to Evaluate Safety and Efficacy of RP6530, a dual PI3K δ/γ inhibitor, in Patients with Relapsed or Refractory T-cell Lymphoma (US study: Protocol number RP6530-1401). Status: Recruitment completed. Study Ongoing
3. An open label, randomized, single dose, crossover study to evaluate food effects on relative bioavailability of RP6530 administered in fasting and fed conditions in healthy volunteers (Food effect study, Protocol no: RP6530-1501). Status: Completed
4. An Open label, Phase I/II study to evaluate the safety and efficacy of RP6530, a novel PI3K δ/γ dual inhibitor given in combination with an anti-PD-1 therapy, Pembrolizumab in adult patients with relapsed or refractory Classical Hodgkin's lymphoma (cHL). Status: Ongoing and currently recruiting.

- **Safety:**

In RP6530-1401 study, a total of 58 patients were treated at 200 mg BID (n=4), 400 mg BID (n=4), 800 mg BID (Fasting) (n=44) and 800 mg BID (Fed) (n=6) in both dose escalation and dose expansion cohorts. Tenalisib demonstrated acceptable safety and tolerability profile up to 800 mg BID (fasting). Tenalisib 800 mg BID (Fasting) was considered as MTD dose in patients with T-cell lymphoma. Majority of AEs include transaminitis, skin rash. Treatment related Grade ≥ 3 includes AST/ALT elevation (n=12), rash (n=4), hypophosphatemia (n=2), neutropenia (n=1), INR Increase (n=1), sepsis (n=1), pyrexia (n=1), diplopia secondary to neuropathy (n=1), drug reaction (n=1), and bacteremia (n=1). Treatment related SAE reported were pyrexia (n=1), raised INR (n=1), sepsis (n=1), diplopia secondary to neuropathy (n=1), drug reaction (n=1) and bacteremia (n=1).

- **Pharmacokinetics:**

In RP6530-1401 study, at the 200 mg dose, AUC_{0-t} and C_{max} were 3713.94 h*ng/mL and 1463.57 ng/mL at C1D1 respectively; corresponding levels at C2D1 were 3985.52 h*ng/mL and 1781.24 ng/mL. Similarly, at the 800 mg dose (fed), AUC_{0-t} and C_{max} were 13204.17 h*ng/mL and 2988.66 ng/mL at C1D1 respectively; corresponding levels at C2D1 were 12737.21 h*ng/mL and 3234.50 ng/mL. At the 800 mg dose (fasting), AUC_{0-t} and C_{max} were 14033.67 h*ng/mL and 4174.71 ng/mL at C1D1 respectively; corresponding levels at C2D1 were 13210.24 h*ng/mL and 3395.28 ng/mL. Based on C_{max} and AUC, dose proportionality was observed up to the 800 mg dose. Upon increasing doses, no changes in T_{max} were observed and while changes in $T_{1/2}$ were observed, steady state PK parameters of Tenalisib as determined on C2D1 revealed no accumulation.

- **Efficacy:**

In RP6530-1401 study, response assessments of the thirty-five evaluable patients receiving at least two cycles of Tenalisib showed an ORR of 46% (16/35 patients) out of which 3 (9%) were CR and 13 (37%) were PR. Eleven patients showed stable disease (31%). Indication specific analysis showed an ORR of 47% (7/15, 3 CR, 4 PR) in PTCL and 45% (9/20, 9 PR) in CTCL. Effect of RP6530 on associated correlative markers in PTCL (sIL-2R and CD30) and CTCL (IL-31, IL-32α, and CTACK) patients that were either a CR, PR, or SD on C3D1 showed decreased plasma concentrations of markers with the reductions being most pronounced for CD30 (57%) and IL-31 (33%) in the respective patient populations.[6]

1.2 Romidepsin

Romidepsin is a histone deacetylases (HDAC) inhibitor and was approved by FDA for the treatment of CTCL and PTCL in 2009 and 2011 respectively for the patients who have received at least one prior systemic therapy. A pivotal phase II study on Romidepsin in 131 patients with relapsed or refractory PTCL showed an ORR of 26 % (CR rate of 15 %), progression free survival (PFS): 4 months and DoR of 13 months.[7] Similarly, Romidepsin was evaluated in 2 multicenter, single-arm clinical studies in patients with CTCL. Cumulative, response rate (ORR) in 167 patients was 35 % (CR rate of 6%) and DoR of 13 months.[7]

1.3 Study Rationale

1.3.1 Rationale for Study Population

T-cell lymphomas (TCL) comprise a heterogeneous group of lymphoid malignancies arising from mature T-cells. Peripheral T cell lymphoma (PTCL) constitute 10–12 % of non-Hodgkin's lymphomas (NHL) in Western countries but are relatively common in Eastern Asian, constituting about 20 % of mature NHL.[8] There is no consensus regarding optimal treatment for PTCL, especially in relapsed or refractory cases, which have very poor prognosis. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) has been accepted as a salvage treatment for eligible patients, although the evidence is unclear.[9] Moreover, the overall prognosis remains dismal in patients unsuitable for ASCT.

Cutaneous T-cell lymphomas (CTCLs) represent a group of rare, clinically and pathologically heterogeneous diseases. The incidence of CTCL has been increasing and is currently 6.4 per million persons, with the highest incidence rates being reported among males and African-Americans. Mycosis fungoides (MF) is the most common primary CTCL variant and is closely related to a rare leukemic variant, Sézary syndrome (SS). Skin-directed therapies, such as psoralen plus ultraviolet A in combination with retinoids or interferon, are used in the early stage disease and generally produce good, long-term responses. Patients with advanced-stage disease require a multidisciplinary approach that includes combinations of skin-directed therapies, biologic-response modifiers and systemic chemotherapeutic agents. Although patients with early stages of disease have an excellent prognosis, ∼25% develop progressive disease.[10-12] The prognosis for patients presenting with advanced-stage disease is poor.[10, 11, 13, 14]

Over recent years, several single-agent therapies have proven to be effective in relapsed/refractory PTCL. Pralatrexate, romidepsin, and belinostat are all approved broadly for PTCL with ORR's in phase II studies of 29, 25, and 26 %, respectively. Brentuximab vedotin is also approved in relapsed ALCL with an ORR of 86 % in a small phase II trial.

Despite recent progress, there are hurdles to overcome in managing patients with PTCL as responses with these therapies are not optimal (all approved therapies except brentuximab has response rate <30%). Given the aggressive nature of PTCL, which has a poor prognosis, this patient population represents an unmet medical need.

CTCL patients are responsive to treatment in the early stages; patients have a long duration of survival but are rarely cured of the disease. For refractory early-stage and advanced-stage disease (IIB-IV), a multidisciplinary approach is used that include bexarotene, interferon α, extracorporeal photopheresis, histone deacetylase inhibitors (vorinostat and romidepsin), and antibody therapies such as alemtuzumab, systemic chemotherapy, and allogeneic transplantation. Though, these agents, alone or in combinations, are associated with high response rates, unfortunately response is often of limited duration (frequently measured in months) and especially in advanced cases, characterized by frequent recurrences, probably due to treatment resistance. Therefore, the prognosis for patients presenting with advanced-stage disease generally poor[10, 11, 13, 14]. Hence, novel therapeutic agents, either alone or in combination, are needed to achieve better disease control in these patients.

1.3.2 Rationale for Combination of Tenalisib and Romidepsin

Modification of histones by acetylation plays a key role in epigenetic regulation of gene expression and is controlled by the balance between histone deacetylases (HDAC) and histone acetyltransferases (HAT). HDAC inhibitors induce cancer cell cycle arrest, differentiation and cell death, reduce angiogenesis and modulate immune response.

Recently it is recognized that TCL may be a disease characterized by epigenetic dysregulation, partly explained by TCL sensitivity to histone deacetylase (HDAC) inhibitors. Early phase clinical studies have demonstrated that combination therapy with epigenetic therapies such as HDAC inhibitors plus other agents known to have activity in T cell lymphoma have enhanced clinical benefit for this group of diseases. Therefore, HDAC inhibitors have been increasingly used as a platform to which other novel therapies or chemotherapy can be added.

Pre-clinical experiments demonstrated the synergistic anti-tumor activity achieved by combining PI3K inhibitor with HDAC inhibitor in B-cell lymphoma cell lines and primary NHL/ CLL cells. These experiments indicated that interference with PI3K signalling dramatically increases HDAC inhibitor-mediated apoptosis in malignant haematopoietic cells - this might be through either AKT-dependent or AKT-independent mechanisms. Moreover, the dramatic increase in HDAC inhibitor-related apoptosis observed in PI3K inhibitor-treated cells appears to be related to the disruption of the ERK signalling pathway.[15]

Synergistic potential of the combination of Tenalisib and Romidepsin in attenuating T-cell lymphoma cell proliferation was determined using HuT-78, HuT-102, MOLT-4, and Jurkat. Cells were incubated with desired concentrations of DMSO (Vehicle), Tenalisib (RP6530), or a combination of Tenalisib (RP6530) and Romidepsin for 72 hours cell viability estimated in the MTT-based assay. Combination effect was determined by calculating the Bliss score where *scores >10* indicate synergism. Among the cell lines evaluated, synergism between RP6530 and Romidepsin was most evident in the CTCL cell lines, Hut-78 and HuT-102.

Figure 1. Inhibition of Cell Growth in T-Cell Lymphoma Cell Lines

A. HuT-78

Excess over Bliss Score		RP6530 (nM)					
	Conc (nM)	0	500	1000	3000	5000	10000
Romidepsin (nM)	0						
	3		4.60	1.57	16.83	8.64	14.28
	4		10.37	2.63	27.00	28.29	33.47
	5		13.50	15.53	30.11	12.29	29.05
	6		-1.95	12.46	10.93	27.21	36.13
	8		7.61	23.33	22.34	23.91	32.42

B. Hut-102

Excess over Bliss Score		RP6530 (nM)					
	Conc (nM)	0	500	1000	3000	5000	10000
Romidepsin (nM)	0						
	3		-2.08	14.34	0.39	6.95	20.15
	4		2.55	12.95	9.15	8.35	26.22
	5		-13.32	-6.69	-7.72	-2.29	25.95
	6		-8.39	-7.28	-1.32	2.90	11.33
	8		-13.51	-6.08	-12.95	-9.42	11.03

In the clinical setting, individually, both Tenalisib and Romidepsin has shown good response rate of > 25 % (ORR) and durable response for >4 months in TCL patients in relapsed/refractory setting. It is therefore hypothesized that a Tenalisib/Romidepsin combination has the potential to synergize and improve depth and durability of responses in these patients.

1.3.3 Rationale for Dose Selection

The safety and tolerability of Tenalisib has been established at 800 mg BID in an ongoing study in patients with relapsed/refractory T-cell lymphoma. Given the fact that both Romidepsin and Tenalisib have non-overlapping toxicity profiles, half of the optimal dose of Tenalisib (400 mg BID) and one dose below the approved dose of Romidepsin (12 mg/m^2) are considered reasonable as starting doses of the combination from safety point of view. In line with the approved prescribing information, Romidepsin will be administered at Day 1, 8 and 15 in a 28-day cycle. The lower doses may be selected on the basis of emerging toxicities of each of the agents given the distinctive nature of toxicities.

1.4 Benefit and Risk

It is expected that proposed combination of Tenalisib with Romidepsin has the potential to improve response rates and increase the durability of response. However, all the patients in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine. Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and Informed Consent documents.

2 TRIAL OBJECTIVES

2.1 Primary Objectives

- To characterize safety, tolerability and to establish the maximum tolerated dose (MTD) of Tenalisib in combination with Romidepsin in patients with R/R T-cell lymphoma.

2.2 Secondary Objectives

- To assess the preliminary anti-tumor activity of various dose levels of Tenalisib in combination with Romidepsin as determined by the Objective Response Rate (ORR) and Duration of Response (DoR).
- To characterize the Pharmacokinetics (PK) of Tenalisib and Romidepsin when given in combination.

2.3 Exploratory Objectives

- To correlate clinical efficacy with markers that include but are not limited to quantitative and qualitative measurements of malignant cells, cytokines, and chemokines in blood/serum.

3 TRIAL DESIGN

3.1 Trial End Points

3.1.1 Primary Endpoint

- **Safety:**
  Adverse Event (AE), Grade 3/ 4 AEs, Serious and fatal Adverse Event (SAE), graded using NCI CTCAE Version 5.0.

3.1.2 Secondary Endpoints

- **Efficacy:**

1. **Objective Response Rate (ORR)**, defined as sum of CR and PR rates, assessed according to the Lugano Classification for initial evaluation, staging, and response assessment of Hodgkin/non-Hodgkin lymphoma in PTCL patients; and according to the modified Severity Weighted Assessment Tool (mSWAT) in CTCL patients.
2. **Duration of Response (DoR),** calculated as time from the initial response to documented disease progression.

- **Pharmacokinetics:**
  PK Parameters [$AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, t_{max}, Kel, and $t_{½}$] of Tenalisib and Romidepsin.

3.1.3 Correlative/Exploratory End Points

Correlative markers include baseline and on-treatment serum levels of chemokines, cytokines, antibodies to tumor antigens, and other immune mediators (e.g. sIL2R and CTACK for PTCL; CD30, IL-31 and IL-32 for CTCL) as deemed relevant by the sponsor.

3.2 Design of Trial

This is a multi-center, open label, non-randomized, two-part Phase I/II study of Tenalisib in

combination with Romidepsin in adult patients with relapsed/refractory TCL. The first part is an open-label, 3+3 dose escalation, Phase I study for MTD determination. The second part is a Phase II, dose expansion to delineate the safety and anti-tumor activity of the combination at the MTD/optimal dose.

In dose escalation, a minimum of 2 and maximum 18 patients will be enrolled in three dose levels unless additional dose levels are required to reach MTD/ optimal dose. In dose expansion, up to 24 TCL patients will be enrolled (Group 1= 12 PTCL patients and Group 2= 12 CTCL patients).

The study will end when all ongoing subjects have reached their third tumor assessment on Cycle 8/Day 1 (C8D1) or have discontinued from the study for any reason, whichever is earlier. At the end of the study, all ongoing patients with no evident disease progression will be given the opportunity to enroll in an open-label compassionate use study protocol and will be followed up.

3.2.1 Phase I: Dose Escalation

3.2.1.1 Dose Escalation Cohorts

Sequential dose escalation will begin with Cohort 1. A minimum of three patients will be enrolled at each dose level. Dose levels will be increased in successive increments according to the dose escalation cohorts mentioned in Table 1. Escalation to the next cohort will occur if no patient within a three-patient cohort or one in six patients experiences a dose limiting toxicity (DLT). De-escalation to different lower doses in case of DLT criteria met will be done as per the discretion of the Safety Review Committee (SRC). The highest doses of the combination (Tenalisib at 800 mg BID plus Romidepsin IV 14 mg/m^2) will be considered as optimal in case there is no DLT at this dose level.

Table 1: Dose Escalation Scheme

Cohort	N	Tenalisib[1]	Romidepsin[2]
Cohort 1	3-6	Tab. 400 mg PO twice a day	IV 12 mg/m^2 on Day 1, 8 and 15
Cohort 2	3-6	Tab. 600 mg PO twice a day	IV 12 mg/m^2 on Day 1, 8 and 15
Cohort 3	3-6	Tab. 800 mg PO twice a day	IV 14 mg/m^2 on Day 1, 8 and 15

Note: Alternate dose levels/dosing schedules may be considered by the SRC if deemed essential based on emerging safety and PK data.

[1]In case the dose (e.g. 800 mg BID) is leading to DLT of the combination, the dose of Tenalisib will be reduced to lower dose (e.g. 600 mg BID) and will be evaluated for safety in a separate cohort.

[2]In case the dose (e.g. 14 mg/m^2) is leading to DLT of the combination, the dose of Romidepsin will be reduced to lower dose (e.g.12 mg/m^2) and if required further to 10 mg/m^2 and will be evaluated for safety in a separate cohort.

Notes:

- For dose escalation decision, safety data of the first 28-days follow up and PK data of C1D1 and C1D8 is essential.
- The dose escalation may occur if no patient within a three-patient cohort experiences a DLT as defined in *Section* 7.6 If one of three patients within a 3-patient cohort experiences

a DLT, an additional three patients will be treated at the same dose level. If one of six patients within a dose level experiences a DLT, dose escalation will continue. If two or more of six patients within a dose level experience a DLT, that dose level will be defined as exceeding MTD, no further dose escalation will occur. The previous dose level will be considered the MTD or de-escalation to lower dose level will be done as per the discretion of the Safety Review Committee (SRC). Once the MTD/optimal dose of the combination is established; the same doses will be expanded to further elucidate safety and efficacy. Multiple expansion cohorts will be opened at different dose levels, if deemed necessary.

- If two of the first 3 patients in a cohort experience a DLT, that dose level will be defined as exceeding MTD, no further dose escalation will occur. The previous dose level will be considered the MTD and will be expanded to further elucidate safety and to evaluate efficacy.
- The actual number of dose cohorts explored will depend upon the MTD and the safety profile observed during the conduct of the trial. Intermediate dose levels and dosing schedules may be explored if deemed appropriate.
- An optimal dose of combination is defined as the threshold doses of individual drugs at which Tenalisib/Romidepsin combination shows clinical activity/efficacy (shows complete response or partial response) in the disease population and is at or below the maximum tolerated dose.

3.2.1.1 Intra-subject Dose Escalation

During dose escalation, individual patients may be considered for treatment at a dose level of Tenalisib/Romidepsin higher than the dose to which they are initially assigned at investigator's discretion after discussion with Medical Monitor. For a patient to be treated at a higher dose level of Tenalisib/Romidepsin, the patient must not have experienced a DLT at the assigned dose and tolerated the lower dose for at least one cycle of therapy. The patient must have undergone a disease evaluation and been found appropriate to continue on study. (e.g. A patient on Tenalisib 400 mg can be escalated to 600 mg dose once the safety of 600 mg dose is established. For a patient to be treated at 600 mg dose level, the patient must not have experienced a DLT at 400 mg dose and tolerated the dose for at least one cycle of therapy. Similar is the case for Romidepsin)

The new higher dose must be a dose that has completed evaluation and has not exceeded the MTD. The dose escalation can occur at the start of a new cycle. At the discretion of investigator, dose escalation may be done in patient who received lower doses (de-escalation) due to safety reasons.

3.2.1.2 Alternative Dosing Cohorts

Depending on nature and timing of the toxicities, pharmacokinetic data of Tenalisib/Romidepsin, alternative dosing regimens and schedules may be examined. If in the opinion of the SRC, observed toxicities (DLTs and/or non-dose limiting adverse events of concern) are likely to have resulted from a continuous exposure to the study drug or cumulative effect, alternative dosing regimens or schedules may be explored. The SRC will determine an alternative schedule, based on PK data, nature and timing of toxicities, and the

recovery periods of the observed toxicities. Dose escalation will be continued with an alternative schedule till determination of the MTD/optimal dose of the combination.

3.2.2 Phase II: Dose Expansion

After establishing the MTD/optimal dose, the Phase II (Dose Expansion) will be opened as approved by the SRC to enroll two groups of patients.

Table 2: Dose Expansion

Group	N	Patient population	Tenalisib	Romidepsin
Group 1	12	R/R PTCL	MTD/Optimal dose	MTD/Optimal dose on Day 1, 8 and 15
Group 2	12	R/R CTCL	MTD/Optimal dose	MTD/Optimal dose on Day 1, 8 and 15

3.3 Randomization and Blinding

This is a non-randomized, open label study.

3.4 Investigational Medicinal Product

3.4.1 Dosage Form and Strengths

Investigational Product(s)	Dosage form, strength	Manufacturer
Tenalisib	Tablets; 200 mg and 400 mg.	STA Pharma Co., Ltd
Romidepsin	10 mg single-dose vial	*For Romidepsin, please refer to prescribing information.*

Note: *Please refer Investigator's Brochure for additional information of Tenalisib. For Romidepsin, please refer to prescribing information.*

3.4.2 Labeling, Packaging and Supply

- **Tenalisib**

Tenalisib will be supplied through Rhizen Pharmaceuticals SA. Tenalisib will be available in 30 tablets per High-density Polyethylene (HDPE) bottle. All trial drugs must be kept in a secure place at below 25°C (77°F), protected from moisture".

- **Romidepsin**

Commercially available Romidepsin will be used. Please refer to ***Appendix H*** for storage conditions and handling of Romidepsin.

3.4.3 Preparation and Administration of Investigational Products

3.4.3.1 Tenalisib

At the start of each cycle, sufficient quantity of Tenalisib will be dispensed. Study drug compliance should be reviewed with the patient at the beginning of each new treatment cycle. Study drug compliance must be documented, including missed doses and subject re-education and dose administration.

Guideline for Administration of Tenalisib:

- Method of Administration: Tenalisib will be administered orally twice daily in a 28-day cycle (Day 1-28). Only during Cycle 1 of Dose Escalation, Tenalisib will be given starting from Day 3 (i.e. C1D3) to permit PK assessment of Romidepsin alone. Patients will be, therefore, instructed to start Tenalisib treatment on C1D3 and will be informed that they will receive Tenalisib for only 25 days in the first cycle.
- Pre-medications: None for Tenalisib. However, routine prophylactic anti-emetics or pre-medications may be required for Romidepsin.
- Tenalisib tablets will be self-administered orally twice daily one hour before a major meal (e.g. breakfast and dinner). Patients should not consume food during this one-hour period.
- Tenalisib tablets should be taken at approximately same time each day. Tablets should be swallowed; and should NOT be crushed or chewed.
- If a dose of Tenalisib is missed, it should be taken as soon as possible on same day with an interval of 8 hours between two doses. If it is missed for the entire day, it should not be repeated. If vomiting occurs, no attempt should be made to replace the vomited dose.
- Study drug compliance should be reviewed with the patient at the beginning of each new treatment cycle. Missed doses should be documented.
- On the day of Romidepsin administration, the morning dose of Tenalisib should be given in clinic one hour prior to Romidepsin infusion.

3.4.3.2 Romidepsin

Romidepsin will be supplied as a standard kit. Below is the general outline of preparation and administration of Romidepsin. However, please refer the Prescribing information for these instructions.

- **Preparation of Romidepsin**
  - Romidepsin must be reconstituted with the supplied diluent and further diluted with 0.9% Sodium Chloride Injection, USP before intravenous infusion.
  - Romidepsin and diluent vials contain an overfill to ensure the recommended volume can be withdrawn at a concentration of 5 mg/mL

- **Preparation for Intravenous Administration**
  - Each 10 mg single-dose vial of Romidepsin must be reconstituted with 2.2 mL of the supplied diluent.
  - With a suitable syringe, aseptically withdraw 2.2 mL from the supplied diluent vial, and slowly inject it into the Romidepsin for injection vial. Swirl the contents of the vial until there are no visible particles in the resulting solution.
  - The reconstituted solution will contain Romidepsin 5 mg/mL. The reconstituted Romidepsin vial will contain 2 mL of deliverable volume of drug product. The

reconstituted Romidepsin solution is chemically stable for up to 8 hours at room temperature.
- Extract the appropriate amount of Romidepsin from the vials to deliver the desired dose, using proper aseptic technique. 0Before intravenous infusion, further dilute Romidepsin in 500 mL 0.9% Sodium Chloride Injection, USP.
- Infuse over 4 hours.

Guideline for Administration of Romidepsin:
- Method of administration: Romidepsin will be administered as an intravenous infusion in outpatient basis/ hospital setting.
- **Pre-medications:**
  - Nausea and vomiting are common following treatment with Romidepsin, therefore **prophylactic antiemetics** are recommended for all patients. Advise patients to report these symptoms so that appropriate treatment can be instituted the earliest. Due to potential for CYP3A4 interaction, administration of a neurokinin-1 receptor inhibitor antiemetics (e.g. aprepitant, fosaprepitant) is not permitted.
  - Patients with advanced stage disease and/or high tumor burden are at the risk of tumor lysis syndrome, therefore these patients are advised to maintain **high fluid intake** for at least 72 hours after each dose.
- Serum potassium and magnesium should be ≤ ULN before Romidepsin treatment.
- Trial treatment should be administered on Day 1, Day 8 and Day 15 of each cycle of 28 days. Interruptions from the treatment plan may be allowed for toxicity management, but require consultation between the investigator and Sponsor, and written documentation of the collaborative decision on subject management.
- All trial treatments will be administered on an outpatient basis.
- Romidepsin should be infused over 4 hours. Sites should make every effort to target infusion timing to be as close to 4 hours as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted.
- Romidepsin must be stored as per prescribing information. .
- Prescribing information should be referred for specific instructions for Romidepsin reconstitution, preparation of the infusion fluid, and administration.

3.4.4 Accountability of Investigational Products

The PI/ designee are responsible for accountability of all trial drug supplies (used/unused) at the site. During on-site monitoring visit, the study monitor/CRA will verify receipt of investigational product, returned and empty vials/cartons, batch numbers of used vials, and will conduct an inventory of remaining clinical trial supplies at the site close-out visit. All trial drug inventories must be made available for inspection by the monitor, sponsor representatives and regulatory agency inspectors/monitor upon request.

Following monitor/CRA verification and instruction, expired or unused trial drugs can be return to the sponsor or destroyed according to local institutional policy with sponsor pre-approval of a site-specific destruction policy. Certificate(s) of destruction or documentation of destruction must be filed at the site and in Trial Master File. Used, returned trial drugs can be destroyed according to local institutional policy with sponsor pre-approval of a site-

specific destruction policy. Certificate(s) of destruction or documentation of destruction must be filed at the site and in the Trial Master File.

3.4.5 Precautions and Risks Associated with Investigational Products

3.4.5.1 Tenalisib

Monitoring of liver enzymes and levels of TSH, T3, and T4 in subjects receiving Tenalisib is recommended based on target organ toxicity. Patients will be monitored for increased ALT/AST, skin rash, neutropenia as these are reported with Tenalisib. In addition, enteritis (colitis), pneumonia/pneumonitis as these events are reported with other PI3K inhibitors.

Tenalisib elicits no photo instability upon exposure to ultraviolet (UV) radiations. However, in absence of in vitro data, possibility of photo-toxicity with Tenalisib cannot be ruled out.

Tenalisib shows inhibition of CYP3A4 enzyme. Therefore, concomitant administration of Tenalisib with predominant CYP3A4 substrates (e.g. calcium channel blockers, warfarin, carbamazepine, macrolide antibiotics, lovastatin, simvastatin, terfenadine) may reduce clearance of these drugs increasing the risk of adverse events. Similarly, as Tenalisib is inhibited by CYP3A4/5 and CYP2C9, there is possibility of drug interaction with inhibitors or inducers of CYP3A4 and CYP2C9. If concomitant treatment of these drugs are clinically warranted, careful observation of the patient is advised. Strong inhibitor or inducers should be avoided as directed in Section on prohibited medication. Please refer to the recent Investigator Brochure for additional safety information.

3.4.5.2 Romidepsin

The following adverse events have been reported in patients receiving Romidepsin:

- Myelosuppression: Romidepsin can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia; monitor blood counts during treatment with Romidepsin; interrupt and/or modify the dose as necessary.
- Fatal and serious infections, including pneumonia, sepsis, and viral reactivation, including Epstein Barr and Hepatitis B viruses, have been reported in clinical trials with Romidepsin. These can occur during treatment and within 30 days after treatment. The risk of life-threatening infections may be greater in patients with a history of prior treatment with monoclonal antibodies directed against lymphocyte antigens and in patients with disease involvement of the bone marrow.
- Several treatment-emergent morphological changes in ECGs (including T-wave and ST-segment changes) have been reported in clinical studies. The clinical significance of these changes is unknown.
- Tumor lysis syndrome (TLS) has been reported to occur in 1% of patients with tumor stage CTCL and 2% of patients with Stage III/IV PTCL. Patients with advanced stage disease and/or high tumor burden are at greater risk, should be closely monitored, and managed as appropriate.
- Since Romidepsin is a substrate of CYP3A4 enzymes, concomitant administration of CYP3A4 inhibitor or inducer may interact with Romidepsin. If concomitant treatment of these drugs is clinically warranted, careful observation of the patient is advised.

Strong inhibitor or inducers should be avoided as directed in Section on prohibited medication.

Please refer to the full prescribing information of Romidepsin for additional safety information.

3.5 The Expected Duration of Subject Participation and Follow-up

The expected duration of subject participation in the study will be about 8 months. Post C8D1, patients with no evident disease progression will be given the opportunity to enroll in an open-label compassionate use study protocol and will be followed up.

3.6 Study Stopping Rules

3.6.1 Stopping Rule for Dose Escalation

The SRC will be in charge of reviewing safety data following the final treatment dose (Day 28 of Cycle 1) of the last patient in each cohort and will decide whether or not it is possible to proceed to the next cohort according to the dose escalation procedure described in *Section 3.2.1.1.* In order to ensure safety and limit toxicity for enrolled patients, dose modifications will be performed according to the procedure described in *Section* 7.7.

3.6.2 Suspension of Patient Enrollment

In the event of one (1) death attributed to the study drug, study accrual will be suspended pending further investigation, and will only be resumed at the recommendation of the SRC. The SRC will have discretion to terminate the trial if an additional death occurs that can be attributed to the study drug.

3.6.3 Stopping Rule for Dose Expansion

After establishing the MTD/optimal dose, the Phase II expansion part will be opened as approved by the SRC. The SRC will continue to monitor safety of the combination (or toxicity trends that may be of concern) at interval of 3 months from initiation of expansion cohort till the completion of the study. Safety/toxicity will be monitored across cohorts combined together. The SRC will have discretion to terminate the trial if there are major safety concerns.

3.6.4 Study Stopping

Sponsor reserves the right to terminate the study in the interest of patient safety, for non-compliance with the protocol, lack of recruitment or any other administrative reasons. The sponsor and PIs will notify the regulatory authority and respective IRB(s) respectively if the trial terminates early with a justification for the early termination.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

1. Age ≥18 years on the day of signing informed consent.
2. Pathologically confirmed T-cell lymphoma at the enrolling institution*.
3. Disease status as defined as relapsed after or refractory to at least one systemic therapy.

4. The patients should have received NOT more than three prior systemic combination chemotherapies.
5. Must have ECOG performance status ≤ 2.
6. PTCL patients must have measurable disease as defined at least one bi-dimensional measurable lesion with minimum measurement of > 1.5 cm in the longest diameter.
7. Life expectancy of at least 3 months.
8. Toxicities related to prior therapy must have returned to **Grade 1 or less**, except for alopecia.
9. Adequate bone marrow, liver and renal function in line with below mentioned laboratory requirements. Hemoglobin and platelet requirements should not be met by use of recent transfusion or growth factor support (GCSF or erythropoietin) within 3 weeks prior to treatment initiation.
   - Hemoglobin ≥8.0 g/dL
   - Absolute neutrophil count (ANC) ≥1,000/μL
   - Platelet count ≥75,000/μL
   - Total bilirubin ≤1.5 times the ULN (or ≤3 x ULN, if patient has Gilbert syndrome)
   - AST (SGOT) and ALT (SGPT) ≤ 3 x ULN; ≤ 5 ULN in case of liver involvement
   - Calculated creatinine clearance (CrCl) > 50 ml/min by Cockcroft-Gault formula.
10. Use of an effective means of contraception for women of childbearing potential and men with partners of childbearing potential.
11. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
12. Provide written informed consent prior to any study-specific screening procedures.
13. Willingness and capability to comply with the requirements of the study.

*Note: The EORTC classification of CTCLs will be used to classify patients. CTCL includes other variants other than MF (e.g. Gamma delta cutaneous T-cell lymphoma or subcutaneous or panniculitis like T-cell lymphoma and CD8 positive T-cell lymphoma). PTCL includes patients with predominantly nodal disease (systemic involvement) but some patients (e.g. AITCL or ATCL) may have skin lesions. Patient having both skin and node lesions will be placed into one of the group (CTCL or PTCL) as approved by investigator.

4.2 Exclusion Criteria

1. Patient receiving anticancer therapy including any investigational therapy (e.g. chemotherapy, biologic therapy, hormonal therapy, surgery, radiotherapy (except limited field palliative radiation) and/or tumor embolization) ≤3 weeks or 5 half-lives (whichever is shorter) prior to C1D1.
2. Patient who discontinued prior therapy with PI3K inhibitors or HDAC inhibitors due to drug toxicity.
3. PTCL patients with Allo-SCT on active GVHD or immunosuppression therapy within 3 months prior to C1D1. CTCL patients with the history of Allo-SCT will be excluded.
4. Patient with any medical conditions requiring the use of systemic immunosuppressive medications (> 20 mg/day of prednisone or equivalent).

5. Severe bacterial, viral or mycotic infection requiring systemic treatment.
6. Pregnancy or lactation.
7. History of chronic liver disease, hepatic veno-occlusive disease, or current alcohol abuse.
8. Known clinically active central nervous system (CNS) or meningeal involvement. (Note: In the absence of symptoms, investigation into CNS involvement is not required. Patients are eligible if metastases have been treated and patients are neurologically returned to baseline or neurologically stable for at least 4 weeks prior to C1D1).
9. Known seropositive requiring anti-viral therapy for human immunodeficiency virus **(HIV) infection.**
10. Known seropositive requiring anti-viral therapy for hepatitis B virus (HBV) infection **OR** evidence of **active hepatitis B infection** as defined by detectable viral load if the antibody tests are positive. [Note: A positive HBcAb subject with an undetectable/negative hepatitis B DNA test (e.g., polymerase chain reaction [PCR] test) can be enrolled]
11. Known seropositive requiring anti-viral therapy for hepatitis c virus (HCV) infection **OR** patients with positive hepatitis C virus Ab.
12. Subjects with active EBV unrelated to underlying lymphoma (positive serology for anti-EBV VCA IgM antibody and negative for anti-EBV EBNA IgG antibody), or clinical manifestations and positive EBV PCR consistent with active EBV infection.
13. Subject with active CMV (positive serology for anti-CMV IgM antibody and negative for anti-CMV IgG antibody and positive CMV PCR with clinical manifestations consistent with active CMV infection) and requiring therapy. [Note: Carriers will be monitored per institutional guidelines.]
14. Subjects with concomitant second malignancies (except adequately treated non-melanomatous skin cancers, ductal carcinoma in situ, superficial bladder cancer, prostate cancer or in situ cervical cancers) are excluded unless a complete remission is achieved at least 2 years prior to study entry and no additional therapy (except adjuvant or maintenance therapy to reduce the risk of recurrence) is required or anticipated to be required during the study period.
15. Administration of any of the following within 1 week prior to C1D1:
    - Strong inhibitors or inducers of CYP3A4 including but not limited to grapefruit products, herbal supplements and drugs
    - Strong inhibitors or inducers of CYP2C9 including but not limited to herbal supplements and drugs
    - Substrates of CYP3A4 enzyme with a narrow therapeutic range.
16. History of Grade 4 anaphylactic reaction.
17. Administration of live vaccines within 6 weeks of C1D1.
18. History of prior surgery or gastrointestinal dysfunction that may affect drug absorption (e.g., gastric bypass surgery, gastrectomy)
19. Current history of a serious uncontrolled medical disorder, metabolic dysfunction, physical examination findings, or clinical laboratory findings giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drugs or render the subject at high risk from treatment complications.
20. Uncontrolled or significant cardiovascular disease including, but not limited to:

- Congenital long QT syndrome.
- QTcF interval > 450 msec
- Myocardial infarction or stroke/TIA within the past 6 months
- Uncontrolled angina within the past 3 months
- Significant ECG abnormalities including 2nd degree atrio- ventricular (AV) block (AV) block type II, 3rd degree AV block
- History of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation or torsades de pointes)
- History of other clinically significant heart disease (ie, cardiomyopathy, congestive heart failure with NYHA functional classification III-IV, pericarditis, significant pericardial effusion)
- Requirement for daily supplemental oxygen therapy.

4.3 Discontinuation from Trial Treatment

The following events may be considered sufficient reason for discontinuing treatment with the study medication:

- NCI CTCAE v5.0 Grade 3/4 non-hematological toxicity related to study drug that necessitate withdrawal in the opinion of investigator
- Development of an intercurrent illness, condition or procedural complication, which could interfere with the patient's continued participation.
- Voluntary patient withdrawal from study treatment (all patients are free to withdraw from participation in this study at any time, for any reasons, specified or unspecified, and without prejudice).
- Any other situation where, in the opinion of the investigator, continued participation in the study would not be in the best interest of the patient
- Disease progression during therapy
- Study completion

5 TREATMENT OF SUBJECTS

5.1 Administration of Tenalisib

Tenalisib will be administered orally twice daily in 28-days cycle (Day 1-28) up to C8D1 unless progression of disease or toxicity warranting discontinuation of therapy. Only during Cycle 1 of Dose Escalation, Tenalisib will be given starting from Day 3. Thus, patients will receive Tenalisib for 25 days in the first cycle of Dose Escalation. Please refer to Section 3.4.3 for administration of Tenalisib.

5.2 Administration of Romidepsin

Romidepsin will be administered intravenously (IV) over a 4-hour period on days 1, 8 and 15 of a 28-day cycle. Please refer to Section 3.4.3 for administration of Romidepsin.

5.3 Concomitant Medications

- Antimicrobial and anti-viral prophylaxis should be used according to local standard practice; PCP and Zoster prophylaxis is strongly recommended.
- G-CSF and other hematopoietic growth factors may be used for the management of acute

toxicity such as febrile neutropenia when clinically indicated or at the discretion of the investigator.

- Transfusions may be given, based on standard criteria and clinical judgment.
- No prophylaxis will be given for Tenalisib. However, patient may receive prophylactic anti-emetics for Romidepsin at the discretion of the investigator.
- Patient may receive prophylactic allopurinol, in case risk of tumor lysis syndrome.
- Low doses of steroids are allowed if it stabilized at < 20 mg per day of prednisone or equivalent and started at least 7 days prior to first dose.
- Patients are permitted to use of topical, ocular, intra-articular, intranasal, and inhaled corticosteroids (with minimal systemic absorption). A brief (less than 4 weeks) course of corticosteroids for treatment related AE is permitted.
- Inactivated seasonal influenza vaccine can be given to subjects before treatment and while on therapy without restriction.
- If concomitant treatment of drugs metabolized by CYP3A4 enzymes are clinically warranted, careful observation of the patient is advised. Use of heparin or warfarin for prophylaxis and treatment of venous thrombosis is prohibited. Low molecular weight heparin (LMWH) is acceptable. Similarly, Dabigatran and Edoxaban, Direct-acting Oral Anti-Coagulants (DOAC) class of drugs, are acceptable as they are not metabolized by CYP3A4/CYP2C9 enzymes.
- Patients should be warned about the possible photosensitivity and advised to be careful with the UV exposure while on Tenalisib treatment. Patients should be recommended to wear loose-fitting clothes that protect skin from sun exposure, in case they need to be outdoors. If sunburn like reaction or skin eruption occurs, patients should contact study physician.

5.4 Prohibited Medications

The following treatments are prohibited while on the clinical trial:

- Any other anti-lymphoma therapy (e.g. radiation therapy, hormonal therapy for cancer, cancer immunotherapy or other biologic therapy).
- Herbal preparations/medications are not allowed throughout the trial. Patients should stop using these herbal medications at least 7 days prior to C1D1.
- Strong inhibitors or inducers of CYP3A4, including grapefruit products, herbal supplements and drugs (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and rifampicin). Patients should stop using these medications at least 7 days prior to C1D1.
- Strong inhibitors or inducers of CYP2C9, including herbal supplements and drugs (e.g. fluconazole and rifampicin). Patients should stop using these medications at least 7 days prior to C1D1.
- Substrates of CYP3A4 enzyme with a narrow therapeutic range (e.g. Warfarin and phenytoin, alfentanil, astemizole, cisapride, cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine). Patients should stop using these medications at least 7 days prior to C1D1.
- Use of heparin or warfarin for prophylaxis and treatment of venous thrombosis is prohibited. Similarly, Apixaban and Rivaroxaban, DOAC class of drugs, are also prohibited they are metabolized by CYP3A4 enzymes. These drugs should be stopped at

least 7 days prior to C1D1.
- Live attenuated vaccine (e.g. Flu vaccine, pneumovax, varicella)
- Steroids > 20 mg unless for management of toxicity.

Discontinuation of patient who received concomitant/prohibited medication will be taken by the PI in consultation with Medical Monitor on case to case basis, after reviewing ongoing clinical benefit and risk. The decision to allow a patient to continue will be documented and archived at the site and at Rhizen.

5.5 Procedures for Monitoring Subject Compliance.
The following measures will be employed to ensure treatment compliance.

5.5.1 Tenalisib
Subjects will be instructed to bring any unused study drug to the site at each visit. Research personnel will count and record the number of used and unused study drug tablets at each visit. The study coordinator will question the patient regarding adherence to the dosing regimen, record the number of tablets and strengths returned, the date returned and determine treatment compliance before dispensing new medication to the study patient. Compliance below 80% will require counseling of the patient by study site personnel.

5.5.2 Romidepsin
Administration of trial medication will be documented by the investigator and/or trial staff as per institutional practice. The total volume of treatment infused will be compared to the total volume prepared to determine compliance with each dose administered. Compliance with trial treatment will be measured by number of Romidepsin infusion.

6 TRIAL ASSESSMENT AND PROCEDURE
6.1 Overview
The Schedule of Event (Table 5 and Table 6) summarizes the trial procedures to be performed at each visit and is divided into following.
1. Screening (Day -28 to Day 0)
2. On treatment procedures (C1D1 to C7D28)
3. End of Treatment (C8D1 or within 7 days from the last dose)
4. End of Study (Day +30 from the last dose)

Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Multiple procedures may be scheduled at the same time point relative to Tenalisib. Priority should be given to PK collection at the time specified and vital signs should be performed prior to blood collections.

6.2 Informed Consent
The investigator or qualified designee must obtain documented written consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial. Consent must be documented by the subject's dated signature or by the

subject's legally acceptable representative's dated signature on an IRB-approved consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature. Specifics about a trial and the trial population will be added to the consent form template at the protocol level. The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

6.3 Screening

Written informed consent must be obtained ≤30 days prior to the initiation of trial treatment and before any protocol-specific procedures are performed. (The first day of trial treatment will be considered as C1D1.) Patients should be re-consented in the case that informed consent is obtained >30 days prior to the initiation of trial treatment. Screening vitals, laboratory tests, as described in the Schedule of Events, will be performed as per institutional practice and will be reviewed by the site PI/designee. The laboratory tests should be done ≤7 calendar days prior to the initiation of trial treatment. Re-screening can be done at the discretion of PI. Scans and other investigations to document measurable disease should be performed within 28 days prior to C1D1.

Lymphoma diagnosis should be made on the basis of morphology, immunohistochemistry, and flow cytometry reviewed by an experienced lymphoma pathologist. Appropriate, molecular studies should be considered to accurately categorize the lymphoma. For CTCL, the histopathologic diagnosis should be confirmed in a skin biopsy representative of current disease by a pathologist with expertise in cutaneous lymphoma. For Sezary patients, the diagnosis should be based on skin and blood criteria (defined as meeting T4 plus B_2 criteria) ***(Appendix D)***.

Clinical assessments of patients will include ECOG performance status (***Appendix A),*** lymph nodes, organomegaly, and "B" symptoms. The staging of NHL/HL and CTCL patients will be done according to Ann Arbor ***(Appendix G)*** and ISCL/EORTC criteria ***(Appendix E)*** respectively [10]. CTCL patients will have half body global and up to 5 selected representative index lesions photographed at baseline.

Table 3: Summary of Key Assessments at Screening

Procedures	PTCL	CTCL
Lab investigation	√	√
ECG	√	√
Bone marrow biopsy	√ [1]	In case of patients with blood involvement (B_2)[2]
Radiological assessment[3]	√	In case of nodal/visceral involvement
Skin assessment (mSWAT)	-	√
Skin biopsy	-	√
Skin photograph	-	√
Biomarker	√	√

1. A bone marrow biopsy and/or aspirate should be collected ≤3 months prior to C1D1.
2. A bone marrow biopsy will be done unless it has been shown to be negative within the last 6 months.
3. The scan and other investigations to document measurable disease should be performed within 28 days prior to C1D1.

During screening, active infection with HBV, HCV, CMV, EBV or HIV should be ruled out. To be considered negative for active infection, following algorithm will be used:

- HBV: HBc antibody should be negative or if HBc antibody is positive, HBVDNA should be undetectable
- HCV: HCV antibody should be negative or if HCV antibody is positive, HCVDNA should be undetectable
- HIV: HIV antibody should be negative. (HIV 1/ 2 antibody should be negative unless positive result is considered false positive by PI)
- EBV: Negative for anti-EBV VCA IgM antibody or if anti-EBV VCA IgG antibody is positive, EBV DNA should be negative.
- CMV: Negative for anti-CMV IgM antibody or if positive anti-CMV IgG antibody is positive, CMV DNA should be negative. [Note: Carriers will be monitored per institutional guidelines.]

Note: *Patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), need to be evaluated for initiation of HBV antiviral prophylaxis and should be closely monitored for HBV reactivation.*

6.3.1 Assignment of Subject Number

All consented subjects who undergo at least one post-consent procedure will be given a unique subject number that will be used to identify the subject for all procedures that occur prior to enrollment. Each subject will be assigned only one subject number. Subject numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain their original subject number assigned at the initial screening visit.

6.3.2 Medical history

Medical history will be obtained by the investigator or qualified designee. A comprehensive history includes but is not limited to age; sex; absence/presence of fevers to more than 101°F (38.3°C), chills, drenching night sweats, or unexplained weight loss more than 10% of body mass over 6 months; and history of malignancy. Fatigue, pruritus, and alcohol-induced pain should also be noted.

6.3.3 Prior and Concomitant Medication Review

Prior medication: The investigator/qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial (i.e. C1D1). Treatment for the disease for which the subject has enrolled in the study will be recorded separately and not listed as a prior medication.

Concomitant medication: The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

6.3.4 Prior Therapies Details

The investigator or qualified designee will record all prior cancer treatments including systemic treatments, prior transplantation, radiation, and surgeries received for the treatment of TCL.

6.3.5 Physical Examination

Full physical examination: The investigator/qualified designee will perform a complete physical exam during the screening period and as defined in Schedule of Events. Physical examination will include lymph node and systemic examination (General Appearance, HEENT, neck, cardiovascular, lungs, abdomen, lymph nodes, genitourinary, extremities, neurological, skin, and musculoskeletal). Physical examination also includes measurement of accessible nodal groups and the size of the spleen and liver. Clinically significant abnormal findings should be recorded as medical history.

Abbreviated (Directed) physical examination: For cycles that do not require a full physical exam per the Schedule of Events, the investigator or qualified designee will perform a directed physical exam as clinically indicated depending on assessment of tumor, prior to trial treatment administration. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

6.3.6 Vital Signs

Vital signs include temperature (oral/axillary), pulse, respiratory rate, weight and blood pressure and should be recorded as per institutional practice. Historical data can be used for height. Vitals will be done prior to the administration of study treatments (Pre-dose and Pre-infusion), during infusion and post-infusion as applicable, at the time points specified below.

- In the first cycle, vitals will be taken prior to the administration of study treatments (15 min before Tenalisib dose and 5 min prior to infusion). During the infusion, vitals should be done at every 15 min (± 5 min) during first hour and at every 30 min (± 10 min) for next 3 hours and 1 hr (± 15 min) post infusion. All time points will be recorded in the CRF.

- In subsequent cycles, vitals will be done as per the institutional practice. Pre-dose; and Pre- and Post-infusion vitals will be recorded in the CRF.
- When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored at every 15 minutes or as directed by the investigator until the infusion is completed and 15, 30 and 60 min post-infusion and longer if necessary until the subject is stabilized. In such case, the event of infusion reaction should be recorded as an adverse event.
- The window periods for vitals will be ±5 min for 15 min interval time points during first hour of infusion; ±10 minutes for 30 min interval time points during the next three hours and ± 15 min for 1 hr post infusion time point.

6.4 Laboratory Investigations

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 4**.**

Table 4: Laboratory Tests for Hematology, Chemistry and Urinalysis

Hematology	Chemistry Panel I	Chemistry Panel II	Urinalysis	Other
Hematocrit	Total bilirubin	Blood glucose	Blood	Serum β-hCG
Hemoglobin	Alkaline phosphatase (ALP)	Urea or blood urea nitrogen [a]	Glucose	Urine pregnancy test
CBC with differentials	Alanine aminotransferase (ALT)	Creatinine	Protein	PT/INR
Platelet count	Aspartate aminotransferase (AST)	Albumin	Specific gravity	Serology (Only at Screening) (Hepatitis B, Hepatitis C, HIV, EBV and CMV)
WBC (Total and differentials)	Lactate dehydrogenase (LDH)	Total protein	Microscopic exam[b]	
Red blood cell count	Gamma-glutamyl transferase (GGT)	Total Cholesterol		
Absolute neutrophil count	Sodium	Triglyceride (TG)		
Absolute lymphocyte count	Potassium	LDL		
	Calcium	HDL		
	Phosphorous	TSH		
	Bicarbonate or Carbon dioxide (CO2)	T3 (Total or Free)		
	Chloride	T4 (free)		
	Magnesium			

[a] Blood Urea Nitrogen is preferred; if not available Urea may be tested.
[b] Microscopic exam, if abnormal results are noted

Blood drawn for these tests will be specified in informed consent form (ICF). The investigations will be performed at each local laboratory. Additional details will be provided in the study-specific Laboratory Manual.

Screening labs will be done within 7 calendar days prior to the initiation of trial treatment. If these initial examinations are obtained within 72 hours of Cycle 1 Day 1, the labs need not be repeated. Re-screening can be done at the discretion of PI. Scans and other investigations

to document measurable disease should be performed ≤28 weeks prior to initiation of treatment.

6.5 12-Lead Electrocardiograms

An ECG will be performed at the time points mentioned below table. Additional ECGs will be obtained if clinically indicated. A single ECG will be performed at all-time points unless specified. Triplicate ECGs only need to be performed at other time points to confirm the significant changes of single ECG (e.g. If QTcF > 450msec on single EKG at screening or >500 msec during treatment). All ECGs will be performed on local equipment. Window period of ± 5 minutes will be applicable to 30 min time point. For all time 1 hr time points, ± 15 minutes window period will be applicable.

Dose Escalation		
Days	Time points	Note
Screening	Within last 28 days	-
C1D1	All PK matched time points (Pre-infusion (0), 1, 2, 3, 5, 7, 9, 10 hrs).	Time points are with respect to Romidepsin infusion.
C1D8	All PK matched time points (Pre-dose (0), 0.5, 1 (pre-infusion of Romidepsin), 2, 3, 4, 6, 8, 10, 11 hrs post-dose).	Time points are with respect to Tenalisib dosing
C1D15	Before-infusion and immediately after infusion.	Time points are with respect to Romidepsin infusion.
Rest of the cycles (Day 1 of each cycle)	Before-infusion and immediately after infusion.	Time points are with respect to Romidepsin infusion.

Dose Expansion		
Days	Time points	Note
Screening	Within last 28 days	-
Day 1 of each cycle	Before Romidepsin infusion.	

6.6 Bone Marrow Biopsy

- **PTCL:**

A bone marrow biopsy and/or aspirate should be collected ≤3 months prior to C1D1 and/or to confirm a complete response to the study drug. If patient has negative bone marrow at baseline, there is no need to have it repeated to confirm CR. Additional biopsy will be obtained if clinically indicated.

- **CTCL patients with predominantly blood involvement (B_2):**

Patients with predominantly blood involvement (B_2) will have a bone marrow biopsy at screening (unless it has been shown to be negative within the last 6 months) and as indicated to confirm a complete response.

6.7 Radiological Evaluations

Initial disease assessment by tumor imaging (baseline scan) must be performed within 28 days prior to C1D1. The site investigator/designee must review radiological images to confirm the subject has measurable disease as defined in the inclusion criteria. Disease assessments or scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment.

- **PTCL and CTCL patients with lymph node/visceral involvement:**

Computed tomography (CT) scan (chest/abdomen/pelvis/neck as appropriate) will be performed at screening for disease assessment. PET-CT is preferred for FDG-avid lymphomas. Other radiological evaluations (e.g. X-ray/MRI/USG) will be performed if warranted.

- **CTCL patients with skin and blood involvement:**

CT scan will be performed at screening for disease assessment.

- In patients with clinically early disease (maximum/current $T_{1-2}N_0M_0B_{0-1}$), repeat scans should not be performed except in cases of an objective response (OR) in the skin.
- In those patients with more advanced disease at baseline (TNMB > $T_{1-2}N_0M_0B_{0-1}$), CT scan should be performed at the time of PR and CR in the skin; any time there is a question of new or PD in the lymph nodes or viscera; and at end of study.

6.8 Skin Biopsy

In CTCL patients, skin biopsy should be taken at screening, and to confirm a complete response. Biopsy should be performed at the most indurated area if only one biopsy. Skin biopsy will not be done in other patients.

6.9 Skin Photograph

CTCL patients will have half body global and up to 5 selected representative index lesions photographed at screening (baseline), at the time of response (PR/CR/PD) and at other time points as required by the PI.

6.10 Pharmacokinetic (PK) Assessments

Blood samples will be collected for PK analysis of Tenalisib and its metabolites/Romidepsin in the Dose Escalation part of the study at the timepoints indicated in the below table. PK will not be performed in Dose Expansion. Blood will be collected, processed and stored at -70 °C at the site and shipped to the sponsor's central bioanalytical laboratory: ***NorthEast Bioanalytical Laboratories***, 925 Sherman Avenue, Hamden, CT 06514, USA. See laboratory manual for PK processing instructions.

The window periods for PK blood collection will ±5 min for 30 min time points; ±10 minutes for one-hour time points up to 3 hrs (1-3 hrs); and ±15 minutes for subsequent one-hour time points (4-11 hrs).

C1D1	C1D8		C2D1, C3D1, C4D1
Romidepsin	**Tenalisib**	**Romidepsin**	**Tenalisib**
-	0 (Pre-dose)	-	0 (Pre-dose)
-	0.5	-	-
Pre-infusion	1	Pre-infusion	-
1	2	1	-
2	3	2	-
3	4	3	-
5	6	5	-
7	8	7	-
9	10	9	-
10	11	10	-

All time points are in hours.

Patient may be hospitalized on C1D1 and C1D8 at the discretion of the PI and site staff in order to facilitate multiple procedures (e.g. PK blood draws, ECGs) that required to be performed on C1D1 and C1D8.

On C2D1, C3D1, C4D1, patients should consume their morning dose at the clinic after the pre-dose sample.

6.11 Correlative /Exploratory Markers

The analyses of correlative markers (e.g. CTACK, sILR2 (PTCL) and IL-30, IL-31 (CTCL) in plasma or blood are exploratory and will not be used to guide treatment decisions. During treatment, blood samples may be taken for correlative/exploratory marker evaluation in the dose escalation and expanded cohort of the study. Plasma aliquots will be prepared and shall be stored at below -70^0C until analysis of correlative markers. The decision to analyze the plasma samples will be taken at a later stage at the discretion of sponsor.

6.12 End of Trial Treatment (EOT) Visit

Post C8D1, patients experiencing clinical benefit with no evident disease progression will be given the opportunity to enroll in an open-label compassionate use study protocol and will be followed up. Excluding patients who participate in the compassionate use study protocol, all other patients will undergo the end-of-treatment (EOT) assessments within 7 days after the last dose of study drug or discontinuation from the study. Radiological assessment and bone marrow biopsy will not be performed if done earlier within 28 days.

6.13 End of Study (EOS) Visit

All patients must be followed up telephonically for adverse events for 30 calendar days after the last dose of study drug. In case of drug related SAE/AE or treatment discontinuation due to adverse event, the subjects will be followed till the resolution/stabilization of the AE or 30 days after the last study dose whichever is the earlier

Table 5: Schedule of Events for Dose Escalation

	Screening	Cycle 1					Cycle 2				Cycle 3			Cycle 4-7			EOT[24] /C8D1	EOS[25]
Day	**D-28 to 0**	D1	D3	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D1	D8	D15	D1	-
Window period	**-28**	0	-	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	+7	+30
Study Days	**D-28 to 0**	1	3	8	15	22	29	36	43	50	57	64	71	-	-	-	197	227
Informed Consent[1]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics[2]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical history[3]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Vitals[4]	X	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Height and weight[5]	X	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Complete Physical exam[6]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-
Abbreviated Physical exam[6]	-	X	-	X	X	-	X	X	X	-	X	X	X	X	X	X	-	-
ECOG Performance Status	X	X	-	-	-	-	-	-	-	-	X	-	-	-	-	-	X	-
Tumor staging	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Laboratory assessment																		
Complete blood count[7]	X	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Chemistry panel I[8]	X	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Chemistry panel II[9]	X	X	-	-	-	-	-	-	-	-	X	-	-	X	-	-	X	-
Serology[10]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PT and INR[11]	X	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Urinalysis (routine)	X	X	-		X	-	X	-	X	-	X	-	X	X	-	X	X	-
Pregnancy test[12]	X	X	-	-	-	-	X	-	-	-	X	-	-	X	-	-	X	-
12-lead ECGs[13]	X	X	-	X	X	-	X	-	-	-	X	-	-	X	-	-	X	-
Pharmacokinetic samples[14]	-	X	-	X	-	-	X	-	-	-	X	-	-	X	-	-	-	-
Bone marrow biopsy[15]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Skin biopsy[16]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Disease assessment																		
Radiological scan/imaging[17]	X	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	X	-
mSWAT[18]	X	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	X	-
Skin photographs[19]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Correlative markers[20]	X	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-
Treatment administration																		
Tenalisib[21]	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Romidepsin infusion[22]	-	X	-	X	X	-	X	X	X	-	X	X	X	X	X	X	-	-
Drug compliance	-	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Safety evaluation																		
AE evaluation[23]	X	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAE evaluation	X	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Foot notes:

1. Patient should be re-consented, if informed consent is obtained >30 days prior to the initiation of trial treatment. The first day of Romidepsin administration will be considered the initiation of treatment (C1D1).
2. Demographic profile will include age, sex and race.
3. Detailed history will be taken at screening that includes history of cancer, past history, no of prior therapies and prior medication (in last 4 weeks); and other medical history. Any medical significant history at subsequent visit will be captured as adverse event.
4. Vitals will be done prior to the administration of study treatments (Pre-dose and Pre-infusion), during infusion and post-infusion as applicable, at the time points specified above.
   - In the first cycle, vitals will be taken prior to the administration of study treatments (15 min before Tenalisib dose and 5 min prior to infusion). During the infusion, vitals should be done at every 15 min (± 5 min) during first hour and at every 30 min (± 10 min) for next 3 hours and 1 hr (± 15 min) post infusion. All time points will be recorded in the CRF.
   - In subsequent cycles, vitals will be done as per the institutional practice. Pre-dose; and Pre- and Post-infusion vitals will be recorded in the CRF.
   - When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored at every 15 minutes or as directed by the investigator until the infusion is completed and 15, 30 and 60 min post-infusion and longer if necessary until the subject is stabilized. In such case, the event of infusion reaction should be recorded as an adverse event.
5. Weight will be measured at all visits. Height to be recorded at screening only; historical data is acceptable.
6. Physical examination will include lymph node and systemic examination. Complete physical examination will be done at screening and EOT visits. At other visits, abbreviated examination (directed physical examination) will be done depending on the assessment of tumor.

7. Complete blood count: Hb, complete blood count, total leucocyte and differential count and platelet count. Additional investigations will be performed if clinically indicated. Hematology must be done ≤7 days prior to C1D1. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated.
8. Chemistry Panel I must be done ≤7 days prior to C1D1. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated. These tests will be performed at supplementary (unscheduled) visits if clinically indicated.
9. Chemistry Panel II must be done ≤7 days prior to C1D1. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated. During treatment, the labs will be performed at C3D1 (± 1 days), C5D1 (± 1 days) and C8D1 (± 7 days) and/ or at the EOT. These tests will be performed at supplementary (unscheduled) visits if clinically indicated.
10. Serology includes HIV, HBV, HCV and CMV. Historical evidence in last 12 weeks is acceptable.
11. PT/INR: PT and INR test must be done ≤7 days prior to C1D1. However, if initial examination is obtained within 72 hours of C1D1; this do not have to be repeated. In case of abnormality, additional tests including aPTT to be done as per investigator discretion. This test will be performed at supplementary visits if clinically indicated.
12. Pregnancy test is required for women of child bearing potential. A serum/urine pregnancy test will be performed at screening and C1D1 (within 72 hours) of dosing. Urine pregnancy test will be performed at other visits as indicated.
13. 12-lead ECG: PK matching ECG will be done on C1D1 and C1D8. Please refer ECG table for detailed time points. Additional ECGs will be obtained if clinically indicated. Triplicate ECGs will be performed to confirm the significant changes of single ECG. Refer Section 6.5.
14. PK: The blood will be collected for PK on following time points: C1D1: Pre-infusion (0), 1, 2, 3, 5, 7, 9, 10 hrs post-infusion. C1D8: Sampling with respect to Tenalisib dosing. Pre-dose (0), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 11 post-dose. Pre-dose sample will be taken on C2D1, C3D1 and C4D1. Patient will be hospitalized on C1D1 and C1D8 at the discretion of the site in order to facilitate multiple procedures (e.g. PK blood draws, ECGs) that required to be performed on C1D1 and C1D8. On C2D1, C3D1, C4D1, patients should consume their morning dose at the clinic after the pre-dose sample. Refer Section 6.10.
15. A bone marrow biopsy: PTCL: Bone marrow biopsy should be collected ≤12 weeks prior to C1D1 and/or to confirm a complete response to the study drug. If patient has negative bone marrow at baseline, there is no need to have it repeated to confirm CR. Additional biopsy will be obtained if clinically indicated. CTCL patients with predominantly blood involvement (B_2) will have a bone marrow biopsy at screening (unless it has been shown to be negative within the last 6 months) and as indicated to confirm a complete response.
16. Skin biopsy: In CTCL patients, skin biopsy should be performed at screening, and to confirm a complete response. Historical data of 12 weeks is acceptable.
17. Radiological scan: In PTCL and CTCL patients with nodal and visceral involvement, PET and "diagnostic quality" CT scan will be performed at the time of screening within 28 days of screening. Following screening, CT scans should be repeated at C3D1 (± 7 days), C5D1 (± 7 days) and C8D1 (± 7 days). PET should be done at C3D1 (± 7 days) and to confirm CR.
18. Skin assessment: In all CTCL patients, mSWAT will be performed at the time of screening within 28 days of screening and at C3D1 (± 7 days), C5D1 (± 7 days) and C8D1 (± 7 days). Disease response assessment will be performed at C3D1 (± 7 days), C5D1 (± 7 days) and C8D1 (± 7 days) and/ or at the EOT or as clinically indicated using mSWAT.
19. Skin photograph: In CTCL patients, skin lesion photograph will be taken at screening, at the time of response (PR/CR/PD) and at other time points as required by the PI.
20. Blood will be collected for biomarkers (e.g. sIL2R and CTACK for PTCL; CD30, IL-31 and IL-32 for CTCL).
21. Tenalisib will be administered orally twice a day from Day 3 (C1D3) onward in 28-days of cycle for 7 cycles in absence of disease progression or toxicity warranting discontinuation of therapy. On the day of Romidepsin administration, the morning dose of Tenalisib should be given in clinic one hour prior to Romidepsin infusion. Tenalisib will be dispensed at the start of each cycle (C1D1, C2D1, C3D1 …). Only in Cycle 1, Tenalisib will be

given starting from Day 3 (i.e. C1D3). Patients will be, therefore, be instructed to start the treatment on C1D3 and will be informed that they will receive Tenalisib for 25 days in the first cycle.

22. Romidepsin will be administered as an intravenous infusion over 4 hours unless progression of disease or toxicity warranting discontinuation of therapy.
23. All AEs regardless of seriousness or relationship to study drug should be recorded spanning from the informed consent drug until 30 calendar days after the last dose of study drug.
24. Post C8D1, *patient experiencing clinical benefit* with no evident disease progression will be given the opportunity to enroll in an open-label compassionate use study protocol and will be followed up. Excluding patients who participate in compassionate use study protocol, all other patients will undergo the end-of-treatment (EOT) assessments within 7days after the last dose of study drug or discontinuation from the study.
25. Patients should be followed for AEs for 30 calendar days after the last dose of study treatment. Telephonic follow up during this period is acceptable. All new AEs occurring during this period should be reported and followed until resolution unless, in the opinion of the investigator, the adverse event or laboratory abnormality/ies are not likely to improve because of the underlying disease.

Table 6: Schedule of Events for Dose Expansion																	
	Screening	**C1**				**C2**				**C3**			**C4-C7**			**EOT[22] /C8D1**	**EOS[23]**
Day	**D-28 to 0**	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D1	D8	D15	D1	
Window period	**-28**	0	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	+7	+30
Study Days	**D-28 to 0**	1	8	15	22	29	36	43	50	57	64	71	-	-	-	197	227
Informed Consent[1]	X	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-
Demographics[2]	X	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-
Medical history[3]	X	-	-	-		-	-	-	-	-	-	-	-	-	-	-	
Vitals[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Height and weight[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Complete Physical exam[6]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-
Abbreviated Physical exam[6]	-	X	X	X		X	X	X		X	X	X	X	X	X	-	-
ECOG Performance Status	X	X	-	-	-	-	-	-	-	X	-	-	-	-	-	X	-
Tumor staging	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Laboratory assessment																	
Complete blood count[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Chemistry panel I[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Chemistry panel II[9]	X	X	-	-	-	-	-	-	-	X	-	-	X	-	-	X	-
Serology[10]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PT and INR[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Urinalysis (routine)	X	X		X		X	-	X		X		X	X		X	X	-
Pregnancy test[12]	X	X	-	-	-	X	-	-	-	X	-	-	X	-	-	X	-
12-lead ECGs[13]	X	X	-	-	-	X	-	-	-	X	-	-	**X**	-	-	**X**	-
Bone marrow biopsy[14]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Skin biopsy[15]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Disease assessment																	
Radiological scan/imaging[16]	X	-	-	-	-	-	-	-	-	X	-	-	-	-	-	X	-
mSWAT[17]	X	-	-	-	-	-	-	-	-	X	-	-	-	-	-	X	-
Skin photographs[18]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Treatment administration																	
Tenalisib[19]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
Romidepsin infusion[20]	-	X	X	X	-	X	X	X	-	X	X	X	X	X	X	-	-
Drug compliance	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Safety evaluation																	
AE evaluation [21]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAE evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Foot notes:

1. Patient should be re-consented, if informed consent is obtained >30 days prior to the initiation of trial treatment. The first day of Romidepsin administration will be considered as C1D1.
2. Demographic profile will include age, sex and race.
3. Detailed history will be taken at screening that includes history of cancer, past history, no of prior therapies and prior medication (in last 4 weeks); and other medical history. Any medical significant history at subsequent visit will be captured as adverse event.
4. Vitals will be done prior to the administration of study treatments (Pre-dose and Pre-infusion), during infusion and post-infusion as applicable, at the time points specified above.
   - In the first cycle, vitals will be taken prior to the administration of study treatments (15 min before Tenalisib dose and 5 min prior to infusion). During the infusion, vitals should be done at every 15 min (± 5 min) during first hour and at every 30 min (± 10 min) for next 3 hours and 1 hr (± 15 min) post infusion. All time points will be recorded in the CRF.
   - In subsequent cycles, vitals will be done as per the institutional practice. Pre-dose; and Pre- and Post-infusion vitals will be recorded in the CRF.
   - When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored at every 15 minutes or as directed by the investigator until the infusion is completed and 15, 30 and 60 min post-infusion and longer if necessary until the subject is stabilized. In such case, the event of infusion reaction should be recorded as an adverse event.
5. Weight will be measured at all visits. Height to be measured at screening only; historical data is acceptable.
6. Physical examination will include lymph node and systemic examination. Complete physical examination will be done at screening and EOT visits. At other visits, abbreviated examination (directed physical examination) will be done depending on the assessment of tumor.

7. Complete blood count: Hb, complete blood count, total leucocyte and differential count and platelet count. Additional investigations will be performed if clinically indicated. Hematology must be done ≤7 days prior to C1D1. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated.
8. Chemistry Panel I: These tests must be done ≤7 days prior to C1D1. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated. These tests will be performed at supplementary (unscheduled) visits if clinically indicated.
9. Chemistry Panel II: These tests must be done ≤7 days prior to C1D1. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated. During treatment, the labs will be performed at C3D1 (± 1 days), C5D1 (± 1 days) and C8D1 (± 7 days) and/ or at the EOT. These tests will be performed at supplementary visits if clinically indicated.
10. Serology includes HIV, HBV, HCV and CMV. Historical evidence in last 12 weeks is acceptable.
11. PT/INR: PT and INR test must be done ≤7 days prior to C1D1. However, if initial examination is obtained within 72 hours of C1D1; this do not have to be repeated. In case of abnormality, additional tests including aPTT to be done as per investigator discretion. This test will be performed at supplementary visits if clinically indicated.
12. Pregnancy test is required for women of child bearing potential. A serum/urine pregnancy test will be performed at screening and C1D1 (within 72 hours) of dosing. Urine pregnancy test will be performed at other visits as indicated.
13. 12-lead ECG: Please refer ECG table for detailed time points. Additional ECGs will be obtained if clinically indicated. Triplicate ECGs will be performed to confirm the significant changes of single ECG.
14. **A bone marrow biopsy:** PTCL: Bone marrow biopsy should be collected ≤12 weeks prior to C1D1 and/or to confirm a complete response to the study drug. If patient has negative bone marrow at baseline, there is no need to have it repeated to confirm CR. Additional biopsy will be obtained if clinically indicated. The CTCL patients with predominantly blood involvement (B_2) will have a bone marrow biopsy at screening (unless it has been shown to be negative within the last 6 months) and as indicated to confirm a complete response.
15. **Skin biopsy:** In CTCL patients, skin biopsy should be performed at screening, and to confirm a complete response. Historical data of 12 weeks is acceptable.
16. **Radiological scan:** In PTCL and CTCL patients with nodal and visceral involvement, PET and "diagnostic quality" CT scan will be performed at the time of screening within 28 days of screening. Following screening, CT scans should be repeated at C3D1 (± 7 days), C5D1 (± 7 days) and C8D1 (± 7 days). PET should be done at C3D1 (± 7 days) and to confirm CR. Tumor imaging should remain consistent throughout study and should include those thought by investigator to best capture status of disease. Baseline scans, if already available as SOC within 28-days of screening is accepted as part of study protocol.
17. **Skin assessment:** In all CTCL patients, mSWAT will be performed at the time of screening within 28 days of screening and at C3D1 (± 7 days), C5D1 (± 7 days) and C8D1 (± 7 days). Disease response assessment will be performed at C3D1 (± 7 days), C5D1 (± 7 days) and C8D1 (± 7 days) and/ or at the EOT or as clinically indicated using mSWAT.
18. **Skin photograph:** In CTCL patients, skin lesion photograph will be taken at screening, at the time of response (PR/CR/PD) and at other time points as required by the PI.
19. Tenalisib will be administered orally twice a day in 28-days of cycle for 7 Cycles in absence of disease progression or toxicity warranting discontinuation of therapy. On the day of Romidepsin administration, the morning dose of Tenalisib should be given in clinic one hour prior to Romidepsin infusion. Patient will receive Tenalisib at the start of each cycle (C1D1, C2D1, C3D1 …).
20. Romidepsin will be administered as an intravenous infusion over 4 hours unless progression of disease or toxicity warranting discontinuation of therapy.
21. All AEs regardless of seriousness or relationship to study drug should be recorded spanning from the informed consent drug until 30 calendar days after the last dose of study drug.

22. Post C8D1, *patient experiencing clinical benefit* with no evident disease progression will be given the opportunity to enroll in an open-label compassionate use study protocol and will be followed up. Excluding patients who participate in compassionate use study protocol, all other patients will undergo the end-of-treatment (EOT) assessments within 7 days after last dose of study drug or discontinuation from the study.
23. Patients should be followed for AEs for 30 calendar days after the last dose of study treatment. Telephonic follow up during this period is acceptable. All new AEs occurring during this period should be reported and followed until resolution unless, in the opinion of the investigator, the adverse event or laboratory abnormality/ies are not likely to improve because of the underlying disease.

7 ASSESSMENT OF SAFETY

7.1 Adverse Events

The PI is responsible for collecting and reporting adverse events (see *Section 7.1.2*). It is Sponsor responsibility to report relevant SAEs to the applicable regulatory body.

7.1.1 Definitions of Adverse Events

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

7.1.2 Recording of Adverse Events

All adverse events of any patient during the course of the trial will be reported in the case report form, and the investigator will give his or her opinion as to the relationship of the adverse event to trial drug treatment (i.e., whether the event is related or unrelated to trial drug administration). If the adverse event is serious, it should be reported immediately to Sponsor. Other untoward events occurring in the framework of a clinical trial are also to be recorded as AEs (i.e., AEs that occur prior to assignment of trial treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

All AEs regardless of seriousness or relationship to Tenalisib/Romidepsin, spanning from the informed consent drug until 30 calendar days after the last dose of study drug, discontinuation or completion of protocol-specific treatment as defined by the protocol for that patient, are to be recorded in the electronic Case Record Form (eCRF).

7.1.3 Handling of Adverse Events

All adverse events resulting in discontinuation from the trial should be followed until resolution or stabilization. Patients must be followed for AEs for 30 calendar days after the last dose of study treatment. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, the adverse event or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the eCRF. After 30 days of completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

7.2 Adverse Event/Serious Adverse Event Causality Assessment

Causality is assessing the relationship of the trial treatment to the adverse event. For this study, the causality assessment will be categorized as related and not related.

- **Related:** All toxicities should be considered to be related to Tenalisib/Romidepsin unless there is a clear alternative explanation.
- **Not related:** If there is no temporal association, or another etiology has been identified as the cause, or the trial treatment cannot be implicated based upon the current information.

7.3 Serious Adverse Events

7.3.1 Definitions of Serious Adverse Events

The definitions of serious adverse events (SAEs) are given below. The principal investigator is responsible for ensuring that all staff involved in the trial is familiar with the content of this section.

An SAE or reaction is defined as any untoward medical occurrence that: results in death, is immediately life-threatening, requires at least a 24-hour in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

The definition of SAE also includes any important medical event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. ***Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per Lugano classification 2014), should not be reported as a serious adverse event.***

Treatment within or admission to the following facilities is not considered to meet the criteria of "in-patient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay in unit or short stay to facilitate PK blood draws
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the trial for a pre-planned surgical or medical procedure (one which is planned prior to entry in the trial or planned in advance and not related to the study procedure/ drug), does not require reporting as a serious adverse event to the Sponsor.

7.3.2 SAE Reporting by Investigators

It is important to distinguish between "serious" and "severe" adverse events, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

Adverse events classified by the treating investigator as **serious** require expeditious handling and reporting to sponsor in order to comply with regulatory requirements. Serious adverse events may

occur at any time from the signing of the informed consent form through the 30-day follow-up period after the last trial treatment. Sponsor/sponsor representative must be notified of all SAEs, regardless of causality, within 1 day of the first knowledge of the event by the investigator.

To report an SAE, the SAE Report Form should be completed with the necessary information. All SAEs occurring from the signing of consent until 30 calendar days of last trial treatment must be reported to the Sponsor as SAEs on the SAE Report and followed until resolution (with autopsy report if applicable).

Deaths and other SAEs occurring >30 calendar days after last trial treatment that are deemed related to Tenalisib/Romidepsin must be reported as SAEs on the SAE Report within 1 day of first knowledge of the event by the treating physician or research personnel (with an autopsy report if available). Deaths occurring >30 calendar days after last trial treatment and not attributed to trial treatment (e.g., disease progression) need not be reported as SAEs, but simply captured on the appropriate eCRF.

The SAE Report Form should be sent to the sponsor/sponsor representative via fax or e-mail within 24 hours of becoming aware of the event. The detailed SAE reporting process will be reviewed with sites during the site initiation visit as well as provided on the SAE report itself. Transmission of the SAE report should be confirmed by the site personnel submitting the report. Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to Sponsor as soon as it is available; these reports should be submitted using the SAE Report Form.

Investigators must report SAEs and follow-up information to their responsible IRB/IEC according to the policies of the responsible IRB/IEC.

7.3.3 Sponsor's SAE Reporting Requirements

Sponsor/Sponsor representative is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, and/or local regulatory requirements.

Sponsor/sponsor representative is responsible for reporting unexpected fatal or life-threatening events associated with the use of the trial drugs to the regulatory agencies and competent authorities via telephone or fax within 7 calendar days after being notified of the event.

The Sponsor will report all related, unexpected SAEs, including non-death/non-life-threatening related unexpected SAEs associated with the use of the trial medications to the FDA by a written safety report within 15 calendar days of notification. Reporting to the IRB/IEC will be done according to institutional policy.

7.4 Recording of AE and SAE

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the SAE Report Forms and AE eCRF. Avoid colloquialisms and abbreviations. All AEs, including those that meet SAE reporting criteria, should be recorded on the AE eCRF; AEs that meet the

definition of an SAE should additionally be reported following the procedures noted in above sections.

7.4.1 Diagnosis vs. Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Coordinating 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 named 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.

7.4.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF, irrespective of severity. (E.g. If a persistent AE becomes more severe or lessens in severity, it should be recorded once with highest grade of severity on a SAE Report Form and/or AE eCRF).

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent events should be recorded separately on an SAE Report Form and/or AE eCRF.

7.4.3 Abnormal Laboratory Values

Any grade 3 or 4 laboratory abnormalities or any clinically significant grade 1 or 2 hematology or biochemistry laboratory value(s) should be recorded as an AE. Isolated laboratory abnormality without clinical significance should not be captured as AE if confirmed by the investigator. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF.

7.4.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of disease will be recorded on the "Trial Discontinuation" eCRF and should not be reported as a SAE. All other on- trial deaths, regardless of attribution, will be recorded on an SAE Report and expeditiously reported to the Sponsor.

When recording a serious adverse event with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE report and Adverse Event page of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the CRF Adverse Event page.

7.4.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. (See *section 7.3)*

7.4.6 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the trial. Such conditions should be recorded on the General Medical History eCRF. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the trial. When recording such events on an SAE Report Form and/or AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable description.

7.4.7 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

Pregnancy, abortion, birth defects, and congenital anomalies are events of special interest. Please refer to pregnancy *Section 7.5.1* for specific instructions.

7.4.8 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include new lesions of the original cancer. Symptoms of metastasis or the new lesions itself should not be reported as an AE/SAE, as they are considered to be disease progression.

7.4.9 Lack of Efficacy

When there is deterioration in the condition for which the study treatment is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the sponsor or reporting physician considers the study treatment contributed to the deterioration of the condition, the deterioration should be considered lack of efficacy and not an AE.

7.5 Protocol-Defined Events of Special Interest

The following are events of special interest, and will need to be reported expeditiously.

7.5.1 Pregnancy, Abortion, Birth defects/Congenital anomalies

Female patients who are not of child-bearing potential (see ***Appendix B***) and female patients of child-bearing potential who have a negative pregnancy test within 72 hours prior to C1D1 are eligible for the study. Female patients of child-bearing potential (see ***Appendix B***)), and all male partners must consent to use a medically acceptable method of contraception throughout the study period and for 4 weeks after the last dose of Tenalisib. An approved barrier method of contraception must be discussed with the investigator and documented in source note.

During the course of the trial, all female patients of childbearing potential and pregnant partner of male subjects must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating investigator).

If an investigator suspects that a patient may be pregnant prior to administration of trial drug(s), the trial drug(s) must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the patient must not receive any trial drug(s), and must be discontinued from the trial. The outcome of the pregnancy will be monitored as outlined in ***Appendix B.***

If an investigator suspects that a patient may be pregnant after the patient has been receiving trial drug(s), the trial drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the trial drug(s) must be immediately and permanently stopped, the patient must be discontinued from the trial, and the investigator must notify the Medical Monitor and Sponsor Representative as soon as possible. If a patient becomes pregnant while enrolled in the trial, a Pregnancy Form should be completed and faxed to the Sponsor. The outcome of the pregnancy will be monitored as outlined in ***Appendix B***.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

7.5.2 Overdose

An overdose is defined as accidental or intentional administration of any dose of product that is considered both excessive and medically important. For purposes of this trial, an overdose will be defined as any dose exceeding the proposed dose of Tenalisib (e.g. > 400 mg in first cohort) and/or prescribed dose for Romidepsin.

Symptomatic and non-symptomatic overdose must be reported in the CRF. Any accidental or intentional overdose with the trial treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Sponsor immediately as an AE. All symptomatic overdose, fulfilling a seriousness criterion, is to be reported as an SAE as per the SAE reporting procedure. For patients who experience overdose, treatment should consist of supportive therapy. A decision to interrupt treatment or dose reduction to be taken depending on the symptoms.

7.6 Dose-Limiting Toxicity

All toxicities should be considered to be related to either Tenalisib/ Romidepsin combination or to either Tenalisib or Romidepsin individually unless there is a clear alternative explanation. Toxicity will be considered dose-limiting if it occurs during the first cycle (28 days) treatment and is considered related to the combination. Toxicity will be assessed utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. ***Dose-limiting toxicities are defined as the following:***

7.6.1 Hematological DLTs

- Grade 4 neutropenia that does not resolve to ≤ Grade 3 within 14 days with supportive treatment (e.g. growth factors) **OR** Grade ≥3 Febrile neutropenia (ANC <1000/μL with fever >38.5ºC [101ºF] that does not resolve to ≤ Grade 2 within 14 days with supportive treatment.

- Grade 4 thrombocytopenia that does not resolve to ≤ Grade 3 within 14 days with supportive treatment **OR** Grade ≥3 thrombocytopenia associated with Grade >2 bleeding that does not resolve to ≤ Grade 2 within 14 days with supportive treatment.

7.6.2 Non-Hematological DLTs

- Grade ≥3 non-hematologic toxicity that could not be controlled or prevented by supportive care including corticosteroids **with exception of:**
  - Grade ≥3 ALT/AST elevation that resolves to ≤ Grade 2 within 14 days;
  - Grade ≥3 diarrhea that improves ≤ Grade 2 within 48 hours **or** Grade ≥3 diarrhea in patients who have not received optimal treatment with anti-diarrhoeal drug**s**.
  - Grade ≥3 vomiting in patients who have not received the highest therapeutic dose of antiemetics (e.g. steroids, 5HT3 antagonists, prochlorperazine, lorazepam)
  - Single episode of Grade ≥3 infusion reaction.
  - Grade 3 nausea, Grade 3 asthenia or Grade 2 alopecia.
- Treatment delay of ≥14 days due to unresolved toxicity.

Adverse events meeting the above definitions but unrelated to study drug will not be considered DLTs. In some instances (e.g. in case of pre-existent Grade 2 toxicity), an event may fall within the protocol definition of a DLT but will not be considered a DLT (i.e., not clinically meaningful/significant or relevant to the combination). In such cases, the SRC will thoroughly review the event, supporting data, and the reasons for not considering the event a DLT will be clearly documented with supporting rationale. Conversely, other events which do not meet the definition of a DLT but are concerning to the SRC may be considered as DLTs.

7.6.3 Determination of Dose-limiting toxicity

The patient population used for determination of MTD will consist of patients who have met the minimum safety evaluation requirements of the study, and/or who have experienced a DLT. The data of at least 3 patients will be required for DLT assessment.

- DLT assessment period will be 28-days (inclusive) (will begin on C1D1 and end on C2D1), unless extended by the medical monitor.
- Patients must have been treated with at least 2 doses of Romidepsin and minimum 14 days with Tenalisib in the first cycle to be considered eligible for safety assessment unless identified to have a DLT.
- *Patients experiencing DLT after initiating combination will be considered evaluable regardless of the number of doses received (Please note Romidepsin alone will be administered on Day 1, therefore patient will not be considered for MTD assessment if patient develops DLT on these days).*

If a patient withdraws from the study during Cycle 1 due to any reason other than DLT (e.g. disease progression or consent withdrawal) and does not meet the minimum requirements for inclusion in the MTD-determining population described above will be replaced.

7.6.4 Maximum Tolerated Dose (MTD)

The MTD is the highest dose of the combination at which 0 of 3 patients or 1 of 6 patients experience a DLT during 1 cycle (28 days) of therapy. If 2 or more patients in a dosing group experience a DLT, the MTD has been exceeded.

7.7 Dose Modifications

All dose modifications are graded by the CTCAE v5.0.

Note: ***If cytopenia events are deemed related to the underlying disease rather than either Tenalisib or Romidepsin, dose reduction will be done as per the investigator's discretion.***

Patients who experience either a DLT or an adverse event meeting DLT criteria (that occurs after the DLT assessment window) will be allowed to delay dosing in order to recover from the toxicity. Patients may resume Tenalisib, provided that the toxicity has resolved to Grade ≤2 or baseline. If study drug is delayed >2 weeks due to drug toxicity, treatment initiation should be discussed and agreed with the Medical Monitor.

Dose reductions will be permanent. A dose re-escalation are not permitted for patients who previously had a dose reduction. Holidays from study drug are discouraged. Any patient in whom similar toxicity recurs at the reduced dose should be discontinued from further Tenalisib treatment. Note: In exceptional case, a patient may be allowed following a careful assessment of benefit and risk by the investigator and with approval from the Medical Monitor.

7.7.1 Criteria for Re-Starting Tenalisib after Drug toxicity

Treatment continuation in the study is at the discretion of the treating Investigator. In the absence of unacceptable toxicities or disease progression, patients may continue treatment with Tenalisib as long as:

- Absolute neutrophil count has returned to baseline, or >750/μL. Platelet count is >50,000/μL.
- Recovered from grade 3-4 non-hematologic toxicity to grade 2 or baseline (excluding alopecia). Treatment may be delayed for up to 2 weeks to recover from toxicity.
- No clinical or radiographic evidence of disease progression.
- If treatment is delayed > 2 weeks due to toxicity, because of an adverse event, treatment initiation should be discussed and agreed with the Medical Monitor.

7.7.2 Dose modifications

The dose modification guidelines are intended to be applied when the investigator determines the events to be related to either one of the investigational product.

- ***In case the investigator determines the events to be related to Romidepsin, Tenalisib can be continued depending on toxicity at discretion of investigator.***
- ***Similarly, in case the investigator determines the events to be related to Tenalisib, Romidepsin can be continued depending on toxicity at discretion of investigator.***
- ***In case the event is possibly related to Romidepsin as well as Tenalisib, the most conservative approach of dose modification should be used.***

7.7.2.1 Tenalisib Dose Modifications for Hematologic Toxicity

The dose modification guidelines are intended to be applied when the investigator determines the events related to Tenalisib.

Table 7: Dose Modifications for Hematologic Toxicity

Worst CTCAE Grade Toxicity	Action to be Taken
HEMATOLOGIC	
Neutropenia (ANC)	
Grade 3 1.0 X 10^9/L<ANC ≥ 0.5 X 10^9 /L	Maintain dose level. Monitor ANC at least weekly. Restart Tenalisib when the event resolved to ≤ Grade 2 or baseline.
Grade 4 0.5 x 10^9 /L<ANC	**First incidence**: Hold* dose until resolved to ≤ Grade 2 or baseline, Restart Tenalisib at one dose lower . **Subsequent occurrence**: Hold dose until resolved to ≤ Grade 2 or baseline, consider growth factor support. Discontinue if further dose modification required.
Grade 3 Febrile neutropenia ANC <1000/mm3 with a single temperature of > 38.3 0C (101 0F) or a sustained temperature of ≥ 38 0C (100.4 0F) for more than one hour.	Hold* dose until resolved to ≤ Grade 2 or baseline, consider growth factor support, then restart Tenalisib at one dose lower .
Thrombocytopenia	
Grade 3 (50.0 X 10^9 /L< PLT ≥ 25.0 X 10^9 /L)	Maintain dose level. Monitor ANC at least weekly. Restart Tenalisib when the event resolved to ≤ Grade 2 or baseline.
Grade 4 25.0 X 10^9/L< PLT **Or** thrombocytopenia that requires platelet transfusion	**1st occurrence**: Hold** dose until to ≤ Grade 2 or baseline, Restart Tenalisib at one dose lower. **Subsequent Occurrences**: Hold dose until to ≤ Grade 2 or baseline, consider platelet transfusion as necessary. Discontinue if further dose modification required.

*If study drug is delayed >2 weeks because of an adverse event, treatment strategy should be discussed with medical monitor.

** Patient receiving concomitant medication (e.g. anticoagulants, anti-platelets, aspirin, or low molecular weight heparin) must be discussed with the medical monitor for continued management.

Table 8: Dose Modifications for Non-Hematologic Toxicities

NON-HEMATOLOGIC	Action to be Taken
Renal*	If serum creatinine is Grade 3 (>3 x baseline or >3 x ULN), hold dose until ≤ grade 2. Monitor serum creatinine at least twice a week until resolution to ≤ grade 2, and then at least one week until it resolves to ≤ grade 1.
Hepatic*	**Transaminitis** **Grade ≥ 1 Transaminitis (**ALT/AST > 1-3 X ULN)**:** • Maintain Tenalisib dose and initiate **prednisone 40 mg daily**.

	• Monitor AST/ALT weekly until resolved and then taper steroid. • Withhold Tenalisib in case of development of grade 2 transaminitis or worsening of Grade 1 transaminitis while on steroids. **Grade ≥ 3 Transaminitis (**ALT/AST >5–20 X ULN**):** • Withhold Tenalisib and monitor ALT/AST twice a weekly until Grade ≤1; restart Tenalisib at one dose lower. . • Initiate **prednisone 1 mg/kg** in case no improvement with discontinuation of Tenalisib in 1 week. • Monitor ALT/AST twice a weekly until Grade ≤1; restart Tenalisib at one dose lower. and taper steroid. • If no immediate response to steroids within 7 days, initiate mycophenolate mofetil. • In case of recurrence of transaminitis at reduced doses, discontinue Tenalisib permanently after assessing risk versus benefit. **Grade ≥ 4 Transaminitis (**ALT/AST >20 X ULN**):** • Tenalisib should be permanently discontinued. **Bilirubin:** • **Grade ≥ 2** (> 1.5-3 X ULN): Maintain Tenalisib dose. Monitor at least weekly until ≤ 1X ULN • **Grade ≥ 3** (> 3-10 X ULN): Withhold Tenalisib. Monitor at least weekly until bilirubin is≤ 1X ULN; restart Tenalisib at one dose lower. • **Grade ≥ 4** (> 10 X ULN): Discontinue Tenalisib permanently
Infection	**Grade 3 or higher sepsis or pneumonia** • Interrupt Tenalisib until infection has resolved.
Diarrhea	**Moderate:** • Maintain Tenalisib dose. Monitor at least weekly until resolved. **Severe diarrhoea or hospitalization** • Withhold Tenalisib dose. Monitor at least weekly until resolved. • Restart Tenalisib at one dose lower . **Life threatening diarrhoea** • Discontinue Tenalisib permanently.
Cardiac	If a QTcF >500 msec has been demonstrated, hold dose. The patient will be monitored hourly with ECGs until the QTcF <500 msec and the QTcF has returned to "<30 msec from baseline". Immediate attention to potassium and magnesium and other clinical factors such as oxygenation and ischemia should be addressed. All cardiac events should be treated as per the local standard of care and referral to a specialist if clinically indicated. Any final decisions concerning dose modifications or permanently discontinuing the patient from study drug due to QTcF prolongation will occur after discussion with medical monitor.
OTHER NON-HEMATOLOGIC	**Action to be Taken**
Grade 3/4 CTCAE	**First occurrence:** Hold* dose until toxicity Grade ≤2; restart Tenalisib at one dose lower. **Subsequent Occurrences**: Hold dose until to ≤ Grade 2 or baseline. Discontinue if further dose modification required.

* If study drug is delayed >2 weeks because of an adverse event, treatment strategy should be discussed with medical monitor.

7.7.3 Romidepsin Dose Modifications

If toxicity, in the opinion of the investigator, is attributable to Romidepsin, the guideline for Romidepsin dose modification should be followed. Final discretion is with the treating investigator in regards to aggressive dose reductions, as well as the number of dose reductions.

7.7.3.1 Hematologic Toxicity

- Grade 3 or 4 neutropenia or thrombocytopenia: Treatment with romidepsin should be delayed until the specific cytopenia returns to ANC $\geq 1.5\times10^9$/L and platelet count $\geq 75\times10^9$/L or baseline, then therapy may be restarted at same dose.
- Grade 4 febrile (≥ 38.5ºC) neutropenia or thrombocytopenia that requires platelet transfusion: Treatment with romidepsin should be delayed until the specific cytopenia returns to ≤ Grade 1 or baseline, and then the dose should be permanently reduced to 10 mg/m^2 or lower dose.

7.7.3.2 Non-Hematologic Toxicities

Nonhematologic toxicities except alopecia

- Grade 2 or 3 toxicity: Treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline, then therapy may be restarted at same dose. If Grade 3 toxicity recurs, treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline and the dose should be permanently reduced to 10 mg/m^2 or lower.
- Grade 4 toxicity: Treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline, then the dose should be permanently reduced to 10 mg/m^2 or lower dose.
- Romidepsin should be discontinued if Grade 3 or 4 toxicities recur after dose reduction.

8 ASSESSMENT OF EFFICACY

8.1 Specification of the Efficacy Parameters

Evaluable for objective response: Patients who have had a pre-treatment baseline efficacy evaluation and at least one post-treatment efficacy evaluation will be considered evaluable for response. **"Investigator assessed response"** will be used in the study. These patients will have their response classified according to the definitions stated below.

Disease parameters:

- **Measurable disease:** Measurable lesions are defined as those that can be accurately measured in at least two dimensions with conventional techniques (PET/CT, MRI, x-ray) or as >1.5 cm with spiral CT scan. All tumor measurements should be recorded in centimeters.

- **Non-measurable disease (evaluable disease):** All other lesions (or sites of disease) including small lesions, (<1 cm using spiral CT scan) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis, and cystic lesions are all non-measurable.

- **Target lesions:** All measurable lesions up to a maximum of 6 lesions total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest SPD diameter), and the highest SUV avidity (high SUV lesions may be prioritized even if not the largest lesions, and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A baseline sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- **Non-target lesions:** All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Evaluation of best objective response: The best objective response is the best response recorded from the start of the treatment until disease progression/recurrence.

8.2 Response Evaluations and Measurements

In all patients (PTCL and CTCL), the response will be assessed approximately at 8 weeks interval for the first two assessments [(e.g. C3D1 (± 7 days), C5D1 (± 7 days)] and then at C8D1 (± 7 days) and/ or at the EOT or as clinically indicated (if clinical progression is suspected).

- **PTCL**

PTCL patients will be evaluated according to Lugano classification Cheson 2014)[16] ***(Appendix C)*** using the CT scan. PET-CT will be preferred for FDG-avid lymphomas. The modality chosen should be the same throughout the duration of the study. In addition, PET-CT will be performed at C3D1 (± 7 days) and to confirm CR. If PET and CT scan at Screening are negative for disease involvement in the neck, subsequent CT scans may not include neck. If PET and CT scans at Screening are positive for disease involvement of the neck, subsequent CT scans must include neck. Disease assessments and imaging should not be delayed for delays in cycle starts. Disease assessments and imaging should be continued until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

Each participating site will be responsible for radiological review and confirmation of response as per standard efficacy guidelines. The frequency outlined is the minimum required for study participation. Patients who progress according to the corresponding criteria will receive no further treatment. Patients who respond to the treatment (i.e., CR, PR or SD) may remain on trial. All disease specific assessments are to be completed as applicable to disease type.

- **CTCL:**

CTCL patients will be evaluated as per modified Severity Weighted Assessment Tool (mSWAT) ***(Appendix F)***. [17] Additionally, CT scan will be done in the CTCL patients with lymph node and visceral involvement. CTCL patients with subcutaneous lesions which cannot be measured by mSWAT will be assessed by change in PET-CT avid lesions. Bone marrow biopsy will be performed in patients with B_2 blood involvement. In these patients, Sezary cell count will be quantified by flow cytometry or morphology in blood/bone marrow.

In CTCL patients with other than presumed stage IA disease, or selected patients with limited T2 disease and the absence of adenopathy or blood involvement, CT scans of chest, abdomen, and pelvis alone ± FDG-PET scan will be done to further evaluate any potential lymphadenopathy, visceral involvement, or abnormal laboratory tests. MRI may be substituted if clinically indicated.

9 STATISTICAL METHOD AND CONSIDERATIONS

This section describes the statistical methods to be used to analyze efficacy and safety. These methods may be revised and updated due to reasons such as regulatory requirements or need for further clarifications. The final analysis plan will be documented in a formal statistical analysis plan (SAP) that must be finalized before database lock. The SAP will include details on how variables will be derived, how missing data will be handled, and how data will be presented as well as the details on statistical methods to be used for safety and efficacy analyses. The final clinical study report will discuss deviations from the SAP, if any.

9.1 General Considerations

Unless otherwise stated, all statistical analyses will be performed using a two-sided hypothesis test at the overall 5% level of significance. The primary efficacy endpoint for the Phase II trial will be evaluated at a one-sided 5% level. No adjustment for Type I error rate will be required because the study has only one primary endpoint with one comparison. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001".

Continuous data will be described using the following descriptive statistics: n, mean, median, minimum and maximum. Data will be displayed in all listings sorted by phase, group and patient number. When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where necessary to account for dropouts and missing values. Unless otherwise specified, the denominator for percentages will be the number of patients with a non-missing assessment in a given treatment group within the analysis population of interest.
All statistical analyses will be performed using SAS 9.1 or higher.

9.2 Determination of Sample Size

Part 1: In Dose Escalation, three patients per cohort are considered appropriate for the assessment of overall safety and tolerability and for providing adequate confidence for dose escalation. No formal sample size and power analysis is done. Accordingly, total 2-18 patients will be enrolled in 3 escalating cohorts unless additional dose levels are required to reach MTD/ optimal dose. Optimal dose will be determined by the SRC.

Part 2: Total 24 patients with relapsed/refractory TCL will be enrolled in two groups (12 patients in each group). Twelve patients per group is considered appropriate for assessment of preliminary anti-tumor activity of the combination. However, the SRC may modify the sample size due to unforeseen clinical situations.

9.3 Study Population

The following 3 analysis populations are planned for this study:

- Modified Intent-to-Treat Population (mITT): the mITT is the primary efficacy analysis population and will include data from all patients who received at least 1 dose of study medication and provide at least 1 post-baseline efficacy assessment.
- Per-Protocol (PP) Population: the PP Population is a subset of the modified Intent-to-Treat Population and will include patients without major protocol deviations.
- Safety Population: The Safety Population will include all subjects who receive at least 1 dose of the study drug.

Membership in the analysis populations will be determined before database lock.

9.4 Statistical Analysis

9.4.1 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics for continuous variables, and frequencies and percentages for categorical variables.

9.4.2 Safety Analyses

The safety endpoints will include:

- Incidence of DLTs
- Incidence of AEs and related AEs
- Incidence of grade 3 and grade 4 AEs
- Incidence of SAEs and death
- Laboratory values
- ECG/vital signs

The safety endpoints will be listed and/or summarized by dose cohort. No inferential statistical analyses will be performed.

The analyses of safety will be based on the frequency of adverse events and their severity for patients in each portion who received at least one dose of study treatment. Worst toxicity grades per patient will be tabulated for select adverse events and laboratory measurements by using NCI CTCAE criteria v5.0.

9.4.3 Efficacy analyses

The efficacy endpoints will include:

- ORR: The percentages of CR, CR+PR, and CR+PR+SD as well as Conversion Rate for Group 2 will be presented, as will the median duration of response. The 95% confidence intervals of these percentages may also be presented.
- DOR: DOR is defined as time from the initial response to documented disease progression. This variable will be analyzed via Kaplan-Meier methodology.

Additional analyses may also be performed as appropriate.
These analyses will be performed from time to time for presentation/publication purposes.

9.4.4 Pharmacokinetic Analyses

The PK parameters (e.g. $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, t_{max}, λ_z, and $t_{½}$) will be assessed by analysis of Tenalisib and its metabolite; and Romidepsin plasma concentrations during the dose escalation phase of the study. These variables will be summarized by n, mean (both arithmetic and geometric if applicable), standard deviation, median, minimum, and maximum by dose.

9.4.5 Exploratory Analysis

The analyses of correlative markers are exploratory and will not be used to guide treatment decisions.

10 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This trial will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline, and CFR Title 21 part 312, World Medical Association's Declaration of Helsinki, applicable government regulations, institutional research policies and procedures and local applicable regulatory requirement(s).

All potential serious breaches must be reported to Rhizen Pharmaceuticals SA immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

10.1 IRB/IEC Approval

The study protocol, ICF, IB, available safety information, patient documents, patient recruitment procedures (e.g., advertisements), information about compensation available to the patients and documentation evidencing the PI's qualifications should be submitted to the IRB/IEC for ethical review and approval if required by local regulations, prior to study start.

The PI/Rhizen and/or designee will follow all necessary regulations to ensure appropriate, initial, and ongoing, IRB/IEC trial review. The PI/Rhizen (as appropriate) must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by Rhizen or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB/IEC.

Safety updates for Tenalisib will be prepared by Rhizen or its representative as required, for submission to the relevant IRB/IEC.

10.2 Regulatory Approval

As required by local regulations, Rhizen will ensure that all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to trial initiation. If required, Rhizen will also ensure that the implementation of substantial amendment to the protocol and other relevant trial documents happen only after approval by the relevant regulatory authorities. Safety updates will be prepared by the Rhizen or its representative as required, for submission to the relevant regulatory authority.

10.3 Insurance and Indemnity

Details of insurance and/or indemnity will be contained within the written agreement between the PI/site and Rhizen. Rhizen will reimburse the subject for all study-related injuries provided that the injury does not arise from the subject's misuse of the study drug or failure to follow the Investigator's instructions.

10.4 Financial Disclosure and Obligations

Principal Investigators and Sub-Investigators are required to provide financial disclosure information to allow Rhizen to submit the complete and accurate certification or disclosure statements required under Part 54 of Title 21 of the CFR. In addition, the Principal Investigator or Sub- Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

10.5 Informed Consent

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

The informed consent form will be submitted for approval to the IRB/IEC that is responsible for review and approval of the trial. Each consent form must include all of the relevant elements currently required by the regulatory authorities or state regulations and national requirements. Translation of the informed consent form is allowed if necessary.

Before recruitment and enrollment into the trial, each prospective candidate will be given a full explanation of the trial. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this trial, the candidate will be asked to give consent to participate in the trial by signing an informed consent form. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the signed informed consent form will be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the trial design or the potential risks to the patients, the patient's re-consent to continue participation in the trial should be obtained.

10.6 Confidentiality

10.6.1 Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and national data protection laws or specific country requirements, as applicable. HIPAA regulations require that, in order to participate in the trial, a patient must sign an authorization from the trial that he or she has been informed of following:

a. What protected health information (PHI) will be collected from patients in this trial;
b. Who will have access to that information and why;
c. Who will use or disclose that information;
d. The information collected about the research trial will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the trial;
e. Whether the authorization contains an expiration date;
f. The rights of a research patient to revoke his or her authorization.

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled trial period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR, it is a requirement that the investigator and institution permit authorized representatives of Sponsor, the regulatory authorities and the IRB/IEC direct access to review the patient's original medical records at the site for verification of trial-related procedures and data.

Measures to protect confidentiality include mentioning of only a unique trial number and initials will identify patients on the CRF or other documents that will be submitted to Rhizen. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the CRF or database. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

10.6.2 Investigator's Responsibilities

Medical supervision is the responsibility of the Principal Investigator named on the FDA Form 1572/country specific forms. The Investigator may delegate day-to-day activities to a sub-investigator listed on these forms but retains overall responsibility for ensuring that the study is conducted properly and in accordance with the study protocol. The Investigator is required to provide the Sponsor with his/her own CV and applicable licensure, as well as those of the personnel assuming significant responsibility in the study (e.g., sub-investigators). The Investigator is responsible for ensuring that the study is conducted according to applicable health authorities (e.g. FDA), sound medical practices, and in compliance with applicable regulations (e.g. 21 CFR, ICH).

10.6.3 Investigator and Staff training and Information

Personal data of the investigators and sub-investigators may be included in the site database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub-investigator, the site shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

All Investigators and their study personnel will receive training regarding the study procedures and GCP/regulations specific to the conduct of clinical trials. This training will be documented and will take place prior to enrollment and throughout the study as necessary.

11 RECORD RETENTION AND DOCUMENTATION OF THE TRIAL

11.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented and signature authorized prior to implementation. If an amendment to the protocol is required, the amendment will be originated and documented by Rhizen. All amendments require review and approval of Rhizen and the Principal Investigator supporting the trial. The written amendment must be reviewed and submitted to the IRB/IEC at the investigator's facility for the board's approval.

11.2 Protocol Deviations

The Principal Investigator is required to follow the protocol. The Investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the Sponsor and the IRB/IEC and agreed to by the Principal Investigator. Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal Investigator will be notified of deviations in writing by the monitor. The IRB/IEC should be notified of all protocol deviations according to IRB/IEC reporting requirements.

11.3 Documentation Required to Initiate Trial

Before the trial may begin, documentation required by the health authorities will be provided by the Sponsor. Documents at a minimum required to begin a trial include, but are not limited to: a signature-authorized protocol and contract; a copy of the official IRB/IEC approval of the trial and the IRB/IEC members list; current Curricula Vita for the principal investigator and any associate investigator(s) who will be involved in the trial; indication of appropriate accreditation for any laboratories to be used in the trial and a copy of the normal ranges for tests to be performed by that laboratory; appropriately completed and signed Form FDA 1572 (Statement of Investigator); a copy of the IRB-approved consent form containing permission for audit by representatives of Sponsor, the IRB, and the FDA/health authorities; financial disclosure forms for all investigators listed on Form FDA 1572; site qualification reports, where applicable; verification of Principal Investigator acceptability from local and/or national debarment list(s).

12 DATA HANDLING AND RECORD KEEPING

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated trial duties and should ensure that all persons assisting in the conduct of the trial are informed of their obligations. All persons authorized to make entries and/or corrections on the CRFs are to be included on this document. All entries in the patient's CRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the patient's CRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The PI and study staff are responsible for maintaining a comprehensive and centralized filing system (Investigator Site File/ISF or Regulatory Binder) of all trial-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the trial and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP section E6 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed CRFs, IEC approval

documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the trial drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition.

Each form of drug accountability record, at a minimum, should contain PI name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the CRF must be maintained and be readily available.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents

The Investigator shall maintain adequate records of drug disposition, case histories and any other trial-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA/health authority; or, in the event that the marketing application has not been approved by FDA/health authority, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA/health authority has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., eCRFs and medical records), all original, signed informed consent forms, and copies of all eCRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor will notify the investigator(s)/institutions(s) when the trial-related records are no longer required.

If the investigator relocates, retires, or for any reason withdraws from the trial, both site and sponsor should be prospectively notified. The trial records must be transferred to an acceptable designee, such as another investigator, another institution, or to sponsor. The investigator must obtain the sponsor written permission before disposing of any records, even if retention requirements have been met. All trial files will be maintained by the Sponsor/Sponsor Representative/CRO throughout the trial, and will be transferred to the Sponsor at the conclusion of the trial.

12.1 Data Collection

The data will be captured in electronic Case Record Form (eCRF) via an Electronic Data Capture (EDC) system. The eCRF is clinical trials data management tool that provides investigational sites a standardized and validated, remote, electronic data capture system for the collection of clinical trial data. All data requested on the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF,

a note should be created verifying that the field is “Not Done” or “Unknown”. For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The Principal Investigator will sign and date each eCRF casebook attesting to his/her responsibility for the quality of all data included therein, and that the data represent a complete and accurate record of each subject's participation in the study.

Clinical data management will be performed in accordance with applicable standards. Data cleaning procedures will be performed with the objective of removing errors and inconsistencies in the data which would otherwise impact on the analysis and reporting objectives, or the credibility of the Clinical Study Report. Adverse events, medical history and concomitant medications will be coded using industry standard dictionaries (MedDRA and WHO Drug).

12.2 Trial Monitoring, Auditing, and Inspecting

The study will be monitored by the Sponsor and/or Sponsor's representatives at all stages of study conduct from inception to completion in accordance with current GCPs. This monitoring will be in the form of site visits and other communication and will include review of original source documents and eCRFs. The Sponsor's monitor or representative will notify the Principal Investigator prior to conducting any investigational site visit. The frequency of these visits will depend upon the progress of the study, and will include monitoring to assess facilities and equipment, recruiting, record-keeping, protocol adherence, data collection, AE reporting and other factors.

The investigator will permit trial-related monitoring, quality audits, and inspections by the sponsor, government regulatory authorities, the Sponsor or its representative(s) of all trial-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable trial-related facilities. The investigator will ensure that the trial monitor or any other compliance or QA reviewer is given access to all trial-related documents and trial-related facilities.

Participation as an investigator in this trial implies the acceptance of potential inspection by government regulatory authorities, the sponsor or its representative(s). At the Sponsor’s discretion Source Document Verification (SDV) may be performed on all data items or a percentage thereof.

The Investigator is responsible for notifying Rhizen in advance of an impending regulatory inspection. He/she may request that Rhizen provide support for preparation, if necessary, and is required to provide updates on the ongoing activities during the inspection and submit any citations/objectionable findings (i.e., FDA 483) and is required to share any follow up responses to the outcome.

12.3 Medical Monitoring

The sponsor will provide a Medical Monitor, a medical expert who advises the study investigators and monitors participant safety. The role of the Medical Monitor is to review all AEs/SAEs on a regular basis throughout the study, to advise the investigators on study-related medical questions

or problems as needed, and to evaluate cumulative participant safety data and make recommendations regarding the safe continuation of the study.

12.4 Quality Assurance and Quality Control

Each trial site shall be required to have Standard Operating Procedures (SOP's) to define and ensure quality assurance/control processes for trial conduct, data generation & collection, recording of data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

13 DISCLOSURE AND PUBLICATION POLICY

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the trial. Results from the trial will be published/presented as per the Sponsor's publication strategy.

Inclusion of the investigator in the authorship of any multi-center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the trial. The investigator acknowledges that the trial is part of a multi-center trial and agrees that any publication by the investigator of the results of the trial conducted at research site shall not be made before the first multi-center publication. In the event there is no multi-center publication within fifteen (15) months after the trial has been completed or terminated at all trial sites, and all data has been received, the investigator shall have the right to publish its results from the trial, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. Investigator shall provide the Sponsor thirty days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the trial for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any site Confidential Information from all publications.

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15 APPENDICES

Appendix A: ECOG Performance Status Scale

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease 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

Appendix B: Contraceptive Guidelines and Pregnancy

Women Not of Childbearing Potential are defined as Follows

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Contraceptive Guidelines for Women of Child-Bearing Potential

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 5 T1/2 (48 hrs) plus an additional 4 weeks after stopping treatment. The highly effective contraception is defined as either:

1. True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
2. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomised male partner should be the sole partner for that patient.
4. Use of a combination of any two of the following (a+b):
   a. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
   b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

The following are **unacceptable** forms of contraception for women of childbearing potential:

- Oral contraception, injected or implanted hormonal methods are not allowed as Tenalisib may potentially decrease the effectiveness of hormonal contraceptives.
- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Women of child-bearing potential must have a negative serum or urine pregnancy test ≤ 72 hours prior to initiating treatment.

Fertile Males
Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment, plus additional 12 weeks after stopping treatment and should not father a child in this period.
Pregnancies
To ensure patient safety, each pregnancy in a patient on study treatment must be reported to Rhizen Pharmaceuticals SA within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Consent to report information regarding these pregnancy outcomes should be obtained from the mother. Pregnancy is not considered a SAE. Initial and follow up information should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to Rhizen Pharmaceuticals SA. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational drugs to any pregnancy outcome will also be captured on the pregnancy form. Any SAE experienced during pregnancy must be reported on the SAE Report Form. Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Appendix C: Response Criteria for NHL-The Lugano classification

Response and Site	PET-CT–Based Response	CT-Based Response
COMPLETE	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extra lymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extra-nodal 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	No extra lymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
PARTIAL	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extra lymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extra-nodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	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 further evaluation with MRI or biopsy or an interval scan	Not applicable

NO RESPONSE OR STABLE DISEASE	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	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
Nonmeasured 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	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 (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of pre-existing Nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, 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 extra nodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
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 trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate responses (to avoid under treatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two 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 (eg, liver, spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non measured 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 (eg, 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 (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

† PET 5PS: 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.

Appendix D: Recommended evaluation for MF/SS patients

Recommended evaluation/initial staging of the patient with MF/Sézary syndrome

Complete physical examination including

- Determination of type(s) of skin lesions
  - If only patch/plaque disease or erythroderma, then estimate percentage of body surface area involved and note any ulceration of lesions
  - If tumors are present, determine total number of lesions, aggregate volume, largest size lesion, and regions of the body involved
- Identification of any palpable lymph node, especially those >1.5 cm in largest diameter or firm, irregular, clustered, or fixed
- Identification of any organomegaly

Skin biopsy

- Most indurated area if only one biopsy
- Immunophenotyping to include at least the following markers: CD2, CD3, CD4, CD5, CD7, CD8, and a B-cell marker such as CD20. CD30 may also be indicated in cases where lymphomatoid papulosis, anaplastic lymphoma, or large-cell transformation is considered.
- Evaluation for clonality of TCR gene rearrangement

Blood tests

- CBC with manual differential, liver function tests, LDH, comprehensive chemistries
- TCR gene rearrangement and relatedness to any clone in skin
- Analysis for abnormal lymphocytes by either Sézary cell count with determination absolute number of Sézary cells and/or flow cytometry (including CD4+/CD7- or CD4+/CD26-)

Radiologic tests

- In patients with T1N0B0stage disease who are otherwise healthy and without complaints directed to a specific organ system, and in selected patients with T2N0B0disease
- with limited skin involvement, radiologic studies may be limited to a chest X-ray or ultrasound of the peripheral nodal groups to corroborate absence of adenopathy
- In all patients with other than presumed stage IA disease, or selected patients with limited T2 disease and the absence of adenopathy or blood involvement, CT scans of chest, abdomen, and pelvis alone±FDG-PET scan are recommended to further evaluate any potential lymphadenopathy, visceral involvement, or abnormal laboratory tests. In patients unable to safely undergo CT scans, MRI may be substituted.

Lymph node biopsy

- Excisional biopsy is indicated in those patients with a node that is either ≥1.5 cm in diameter and/or is firm, irregular, clustered, or fixed
- Site of biopsy
  - Preference is given to the largest lymph node draining an involved area of the skin or if FDG-PET scan data are available, the node with highest standardized uptake value (SUV).
  - If there is no additional imaging information and multiple nodes are enlarged and otherwise equal in size or consistency, the order of preference is cervical, axillary, and inguinal areas.
- Analysis: pathologic assessment by light microscopy, flow cytometry, and TCR gene rearrangement.

Appendix E: ISCL/EORTC staging of MF and SS patients

TNMB Stages	Description of TNMB
Skin[*]	
T_1	Limited patches, papules, and/or plaques covering < 10% of the skin surface; may further stratify into T_{1a} (patch only) *v* T_{1b}(plaque ± patch)
T_2	Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T_{2a} (patch only) *v* T_{2b} (plaque ± patch)
T_3	One or more tumors (≥ 1 cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area
Node[†]	
N_0	No clinically abnormal lymph nodes; biopsy not required
N_1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative
N_{1b}	Clone positive
N_2	Clinically abnormal lymph nodes; histopathology Dutch Grade 2 or NCI LN_3
N_{2a}	Clone negative
N_{2b}	Clone positive
N_3	Clinically abnormal lymph nodes; histopathology Dutch grade 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize the histologic subcategories
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B_0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells
B_{0a}	Clone negative
B_{0b}	Clone positive
B_1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	High blood tumor burden: ≥ 1,000/µL Sézary cells with positive clone[‡]; one of the following can be substituted for Sézary cells: CD4/CD8 ≥ 10, CD4+CD7- cells ≥ 40% or CD4+CD26- cells ≥ 30%

- Abbreviations: ISCL, International Society for Cutaneous Lymphomas; EORTC, European Organisation for Research and Treatment of Cancer; MF, mycosis fungoides; SS, Sézary syndrome; NCI, National Cancer Institute.

- ↵* Patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: pokiloderma may be present. Plaque = any size lesion that is elevated or indurated: crusting or poikiloderma may be present. Tumor = any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.
- ↵† Lymph node classification has been modified from 2007 ISCL/EORTC consensus revisions1 to include central nodes. Lymph nodes are qualified as abnormal if > 1.5 cm in diameter.
- ↵‡ The clone in the blood should match that of the skin. The relevance of an isolated clone in the blood or a clone in the blood that does not match the clone in the skin remains to be determined.

Modified ISCL/EORTC Revisions to the Staging of MF/SS

Stage	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
IIA	1.2	1,2X	0	0,1
IIb	3	0-2X	0	0,1
IIIA	4	0-2X	0	0
IIIB	4	0-2X	0	1
IVA1	1-4	0-2X	0	2
IVA2	1-4	3	0	0-2
IVB	1-4	0-3X	1	0-2

X clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize histologic subcategories.

Appendix F: Modified Severity Weighted Assessment Tool (mSWAT)

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch*	Plaque†	Tumor‡
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		×1	×2	×4
Subtotal lesion BSA × weighting factor				

- NOTE. mSWAT score equals summation of each column line.
- Abbreviations: BSA, body surface area; mSWAT, modified Severity Weighted Assessment Tool.
- ↵* Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.
- ↵† Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.
- ↵‡ Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

Appendix G : Ann Arbor Staging System

Stage I

Either of the following means the disease is stage I:

- The lymphoma is in only 1 lymph node area or lymphoid organ such as the thymus (I).
- The cancer is found only in 1 area of a single organ outside of the lymph system (IE).

Stage II

Either of the following means the disease is stage II:

- The lymphoma is in 2 or more groups of lymph nodes on the same side of (above or below) the diaphragm (the thin band of muscle that separates the chest and abdomen). For example, this might include nodes in the underarm and neck area but not the combination of underarm and groin nodes (II).
- The lymphoma extends from a single group of lymph node(s) into a nearby organ (IIE). It may also affect other groups of lymph nodes on the same side of the diaphragm.

Stage III

Either of the following means the disease is stage III:

- The lymphoma is found in lymph node areas on both sides of (above and below) the diaphragm.
- The cancer may also have spread into an area or organ next to the lymph nodes (IIIE), into the spleen (IIIS), or both (IIISE).

Stage IV

Either of the following means the disease is stage IV:

- The lymphoma has spread outside of the lymph system into an organ that is not right next to an involved node.
- The lymphoma has spread to the bone marrow, liver, brain or spinal cord, or the pleura (thin lining of the lungs).

Other modifiers may also be used to describe the lymphoma stage:

Appendix H: Romidepsin Prescribing Information