

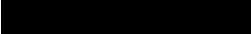


**An Open label, Phase II study to evaluate the efficacy and safety of Tenalisib (RP6530), a novel PI3K  $\delta/\gamma$  dual inhibitor in adult patients with relapsed/refractory indolent Non-Hodgkin's Lymphoma (iNHL)**

**PROTOCOL NUMBER**



**TRIAL DRUG**



**IND NUMBER**



**SPONSOR**



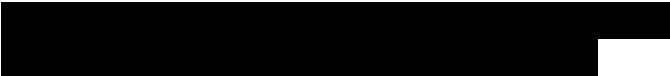
**PRINCIPAL INVESTIGATOR AND STUDY CHAIR**



**SPONSOR'S MEDICAL EXPERT**



**DOCUMENT VERSION**



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### **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 II study to evaluate the efficacy and safety of  
Tenalisib (RP6530), a novel PI3K  $\delta/\gamma$  dual inhibitor in adult patients with  
relapsed/refractory indolent Non-Hodgkin's Lymphoma (iNHL)**

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**PROTOCOL NUMBER**

[REDACTED]

**TRIAL DRUG(S)**

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**IND NUMBER**

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**DOCUMENT VERSION**

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**Protocol Acceptance Page**

**An Open label, Phase II study to evaluate the efficacy and safety of Tenalib (RP6530), a novel PI3K  $\delta/\gamma$  dual inhibitor in adult patients with relapsed/refractory indolent Non-Hodgkin's Lymphoma (iNHL)**

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**IND NUMBER**

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**DOCUMENT VERSION**

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**Principal Investigator**

**Signature**

**Date**

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### Amendment History

Amendment#/date	Reference to section	Summary	Rationale
Amendment 1 to Version 1.0, Dated 15 March 2018	General information	Change of Principal investigator and study chair	Administrative change
Amendment Version dated 04 December 2018	Section 4.1 Inclusion criteria	Inclusion criteria # 7 is updated as “The ALT and AST should be $\leq 1.5$ X ULN in absence of liver involvement/ metastasis.”	Patients with history of prior chemotherapy may have altered liver function and therefore inclusion criterion has been defined to set an upper limit of AST/ALT acceptable in this patient population.
	Section 4.2 Exclusion criteria	Inclusion criteria # 9 is updated as “Known history of <u>severe</u> drug-induced liver injury.....	Patient with history of prior chemotherapy may have altered liver function and therefore patients with only severe drug-induced liver injury will be excluded from the study.
	Section 5.2 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 5.3 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 of vitals and visits are clarified.	Protocol clarification
	Section 7.6 dose modifications	Dose modifications are clarified.	Protocol clarification
	Throughout the document	Minor protocol clarifications and administrative changes	

## PROTOCOL SYNOPSIS

<b>Study Title</b>	<b>An Open label, Phase II study to evaluate the efficacy and safety of Tenalisib (RP6530), a novel PI3K <math>\delta/\gamma</math> dual inhibitor in adult patients with relapsed/refractory indolent Non-Hodgkin's Lymphoma (iNHL)</b>
<b>Phase</b>	Phase II
<b>Study Sponsor</b>	████████████████████
<b>Study Centers</b>	Approximately 10 sites.
<b>Study Objectives</b>	<p><b>Primary objective</b></p> <ul style="list-style-type: none"> <li>• To assess the anti-tumor activity of Tenalisib, as determined by the Objective Response Rate (ORR), Duration of Response (DoR) and Progression Free Survival (PFS).</li> </ul> <p><b>Secondary objective</b></p> <ul style="list-style-type: none"> <li>• To characterize safety and tolerability of Tenalisib in patients with iNHL.</li> </ul>
<b>Endpoints</b>	<p><b>Efficacy:</b></p> <ul style="list-style-type: none"> <li>• <b>ORR</b> is defined as sum of CR and PR rates and will be assessed according to the Lugano Classification for initial evaluation, staging, and response assessment of Non-Hodgkin lymphoma. (Cheson-2014)</li> <li>• <b>CR rate</b> will be assessed according to the Lugano Classification for initial evaluation, staging, and response assessment of non-Hodgkin lymphoma.</li> <li>• <b>DoR</b> is calculated as time from the initial response to disease progression or death.</li> <li>• <b>PFS</b> is calculated as time of the first dose of Tenalisib to disease progression or death.</li> </ul> <p><b>Safety:</b></p> <ul style="list-style-type: none"> <li>• Adverse Event (AE), Grade 3/ 4 AEs, Serious and fatal Adverse Event (SAE), graded using NCI CTCAE Version 5.0.</li> </ul>
<b>Study Design and Procedure</b>	<p>The study is designed as a Phase II, open label, two parts study in relapsed/refractory iNHL patients. The mandatory Part 1 of the study will assess the efficacy and safety of Tenalisib in 20 patients with iNHL. After all patients enrolled in Part 1 have had the opportunity to provide at least three tumor outcome assessments, the Data Review Committee (DRC) will evaluate the efficacy (anti-tumor activity) and safety results for each of the subtypes [e.g. follicular lymphoma (FL) or marginal zone lymphoma (MZL) or Waldenstrom macroglobulinemia (WM)]. If the committee believes there are potential clinically meaningful responses for certain subtype, the committee will recommend initiation of Part 2 to evaluate efficacy and safety for that subtype. If not, the study will be terminated without initiating Part 2. The sample size for Part 2 will be derived based on the outcome from Part 1. Data from Part 1 will not be included in the analysis of Part 2 of the study.</p> <p>The study treatment Tenalisib (800 mg BID) will be administered orally in 28-days of cycle over a period of 8 months in absence of definitive disease progression or unacceptable toxicity. Treatment will be continued in patients experiencing clinical benefit until the occurrence of definitive disease progression, unacceptable toxicity, or</p>

	<p>withdrawal from the study due to investigator decision or other reasons; maximum for up to 24 months.</p> <p>The efficacy response will be evaluated on Weeks 8 (C3D1± 7 days), Weeks 16 (C5D1± 7 days) and then every 12 weeks thereafter, and/ or at the EOT or as clinically indicated (if clinical progression is suspected or for confirmation of complete response/disease progression). The details of the study procedures are given in Schedule of Events.</p> <table border="1" data-bbox="410 485 1414 852"> <thead> <tr> <th>Group</th> <th>N</th> <th>Patient population</th> <th>Tenalisib</th> </tr> </thead> <tbody> <tr> <td>Part 1</td> <td>20</td> <td>Refractory/ relapsed iNHL</td> <td>800 mg BID in 28-Days Cycle for 8 Cycles<sup>1</sup></td> </tr> <tr> <td>Part 2 (If initiated)</td> <td>The sample size will be derived based on the outcome from Part 1</td> <td>Refractory/ relapsed iNHL patients of one of the specific subtypes (e.g. FL, MZL, WM)</td> <td>800 mg BID in 28-Days Cycle for 8 Cycles<sup>1</sup></td> </tr> </tbody> </table> <p><sup>1</sup>Post cycle 8, treatment will be continued in patients experiencing clinical benefit up to 24 months unless progression of disease or toxicity warranting discontinuation of therapy. The decision to continue the treatment will be determined by the PI after consultation with Sponsor on case to case basis.</p> <p>The details of the study procedures are given Schedule of Events.</p>	Group	N	Patient population	Tenalisib	Part 1	20	Refractory/ relapsed iNHL	800 mg BID in 28-Days Cycle for 8 Cycles <sup>1</sup>	Part 2 (If initiated)	The sample size will be derived based on the outcome from Part 1	Refractory/ relapsed iNHL patients of one of the specific subtypes (e.g. FL, MZL, WM)	800 mg BID in 28-Days Cycle for 8 Cycles <sup>1</sup>
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<p><b>No. of Patients</b></p>	<p>Part 1: 20 patients with relapsed/refractory iNHL will be enrolled.                  Part 2: The sample size for Part 2 will be determined by the DRC after the committee has completed Part 1 analysis.</p>												
<p><b>Inclusion Criteria</b></p>	<p><b>Patients must meet all of the following inclusion criteria to be eligible for participation in this study:</b></p> <ol style="list-style-type: none"> <li>1. Patients with histologically confirmed diagnosis of <b>indolent B-cell NHL</b>, with histological subtype limited to:                         <ul style="list-style-type: none"> <li>• Follicular lymphoma (FL) G1, G2, or G3a</li> <li>• Marginal zone lymphoma (MZL) (splenic, nodal, or extra-nodal)</li> <li>• Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM)</li> <li>• Small lymphocytic lymphoma (SLL) with absolute lymphocyte count &lt; 5 x 10<sup>9</sup> /L at the time of diagnosis and at study entry.</li> </ul> </li> <li>2. Relapsed or refractory after ≥ 2 prior lines of therapy (refractory defined as not responding to a standard regimen or progressing within 6 months of the last course of a standard regimen). Patients must have received rituximab and alkylating agents.</li> <li>3. Patients must have at least one bi-dimensionally measurable lesion (that has not been previously irradiated) with the longest diameter ≥ 1.5 cm.</li> <li>4. Male or female patients &gt; 18 years of age.</li> <li>5. ECOG performance status ≤ 2.</li> <li>6. Life expectancy of at least 3 months.</li> <li>7. Adequate bone marrow, liver, and renal function as assessed by the following laboratory requirements conducted within 7 days before starting study treatment:                         <ol style="list-style-type: none"> <li>a. Hemoglobin ≥ 9 g/dl</li> <li>b. Absolute neutrophil count (ANC) ≥ 1 x 10<sup>9</sup>/L</li> </ol> </li> </ol>												

	<ul style="list-style-type: none"> <li>c. Platelets <math>\geq 50 \times 10^9/L</math> (patient without BM involvement) and <math>30 \times 10^9/L</math> (patient with BM involvement)</li> <li>d. Total bilirubin <math>\leq 1.5</math> times the upper limit of normal (ULN)</li> <li>e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <math>\leq 2.5 \times</math> ULN if known liver involvement. The ALT and AST should be <math>\leq 1.5 \times</math> ULN in absence of liver involvement/metastasis.</li> <li>f. Calculated creatinine clearance <math>\geq 50</math> mL/min (as calculated by the Cockcroft-Gault method)</li> </ul> <ul style="list-style-type: none"> <li>8. Ability to swallow and retain oral medication</li> <li>9. Female patients who are not of child-bearing potential, and female patients of child-bearing potential who have a negative serum pregnancy test within 72 hours prior to initial trial treatment. Female patients of child-bearing potential, and all male partners must consent to use a medically acceptable two methods of contraception throughout the study period and for 4 weeks after the last dose of Tenalisib. A barrier method of contraception must be included.</li> <li>10. Male patients willing to use adequate contraceptive measures throughout the study period and for 12 weeks after the last dose of Tenalisib.</li> <li>11. Willingness and ability to comply with trial and follow-up procedures, give written informed consent</li> </ul>
<p><b>Exclusion Criteria</b></p>	<ul style="list-style-type: none"> <li>1. Histologically confirmed diagnosis of follicular lymphoma grade 3b or transformed disease or chronic lymphocytic leukemia (CLL).</li> <li>2. Patients receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) or any cancer investigational drug within 3 weeks (21 days) or 5 half-lives (whichever is shorter) prior to C1D1. Corticosteroids (prednisone or equivalent) at a dose of <math>&lt; 20</math> mg daily are allowed. Corticosteroid should be stabilized for at least 1 week prior to C1D1.</li> <li>3. Autologous hematologic stem cell transplant (Auto-SCT) within 3 months from C1D1. Patients must not have active graft versus-host disease;</li> <li>4. History of an allogeneic bone marrow transplant (Allo-SCT)</li> <li>5. Active hepatitis B or C infection. (All subjects must be screened for hepatitis B and C up to 28 days prior to C1D1 using the hepatitis viral panel. Subject positive for HBsAg or HBcAb will be eligible if they are negative for HBV-DNA. Subject positive for HCV IgG will be eligible if they are negative for HCV-RNA);</li> <li>6. Known history of human immunodeficiency virus (HIV) infection;</li> <li>7. Evidence of ongoing severe systemic bacterial, fungal or viral infection;</li> <li>8. Known primary central nervous system lymphoma or known intracranial involvement, leptomeningeal metastases or spinal cord compression due to disease or any preexisting neurologic manifestations;</li> <li>9. Known history of severe drug-induced liver injury; alcoholic liver disease, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver or portal hypertension;</li> <li>10. Patient with any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study as per investigator's judgment;</li> <li>11. Patient with symptomatic or history of documented congestive heart failure (NY Heart Association functional classification III-IV).</li> <li>12. Patient with angina not well-controlled by medication</li> </ul>



	<ol style="list-style-type: none"> <li>13. Patient with poorly controlled or clinically significant atherosclerotic vascular disease (including cerebrovascular accident, transient ischemic attack or have angioplasty, cardiac or vascular stenting) in the past 6 months;</li> <li>14. Prior exposure to drug that specifically inhibits PI3K (e.g. Idelalisib, Copanlisib, Duvelisib and Umbralisib)</li> <li>15. Previous or concurrent malignancy that is distinct in primary site or histology from indolent B-cell NHL within 3 years of study enrollment EXCEPT for adequately treated basal, squamous cell carcinoma or non-melanomatous skin cancer, carcinoma in situ of the cervix, superficial bladder cancer not treated with intravesical chemotherapy or BCG within 6 months, localized prostate cancer with PSA &lt;1.0 mg/dL on 2 consecutive measurements at least 3 months apart with the most recent one being within 4 weeks of study entry;</li> <li>16. Patients with seizure disorder requiring medication.</li> <li>17. Unresolved toxicity higher than CTCAE grade 1 (NCI-CTCAE version 5.0) attributed to any prior therapy/procedure excluding alopecia.</li> <li>18. Myeloid growth factors or red blood cells/ platelet transfusion within 14 days prior to C1D1.</li> <li>19. Administration of any of the following within 1 week prior to C1D1:             <ol style="list-style-type: none"> <li>a. Strong inhibitors or inducers of CYP3A4, including grapefruit products, herbal medications.</li> <li>b. Strong inhibitors or inducers of CYP2C9, including herbal medications.</li> <li>c. Substrates of CYP3A4 enzyme with a narrow therapeutic range (e.g. Warfarin and phenytoin)</li> </ol> </li> <li>20. Pregnant or lactating woman;</li> <li>21. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol;</li> <li>22. Concurrent condition that in the investigator's opinion would jeopardize compliance with the protocol.</li> </ol>
<p><b>Estimated Study duration</b></p>	<p>Part 1: Approximately 12 months for accrual plus 8 months of follow up                  Part 2: To be determined.</p>
<p><b>Assessment of Response</b></p>	<p>Response assessments will be performed as per <b>Lugano Classification (Cheson criteria 2014)</b> at C3D1 (<math>\pm</math> 7 days), C5D1 (<math>\pm</math> 7 days) and approximately every 12 weeks thereafter (<math>\pm</math> 7 days), and/ or at the EOT.</p>
<p><b>Study Treatment</b></p>	<p>For purposes of this study, each cycle of therapy consists of 4 weeks. Tenalisisib will be administered in a cycle of 28 days in absence of disease progression and unacceptable toxicity.                  Tenalisisib 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.</p>
<p><b>Statistical Analysis</b></p>	<p>The sample size for Part 1 is not based on statistical consideration. The sample size for Part 2 will be derived based on ORR data from Part 1.</p>

<b>GENERAL INFORMATION</b>	
<b>SPONSOR</b>	[REDACTED]
<b>PRINCIPAL INVESTIGATOR AND STUDY CHAIR</b>	[REDACTED]
<b>SPONSOR'S REPRESENTATIVE</b>	[REDACTED]
<b>SPONSOR'S MEDICAL EXPERT</b>	[REDACTED]
<b>STATISTICIAN</b>	[REDACTED]

## 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	Area Under the plasma-concentration time curve
BID	Twice Daily
β-HCG	β-human chorionic gonadotropin
C <sub>max</sub>	Peak Drug Concentration
CBC	Complete Blood Count
CLL	Chronic Lymphocytic Leukemia
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
DRC	Data Review Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
FL	Follicular lymphoma
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 brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
INR	International Normalized Ratio
iNHL	Indolent non-Hodgkin's Lymphoma
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IUD	Intrauterine Device
IUS	Intrauterine System
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein

LLN	Lower Limit of Normal
LMWH	Low Molecular Weight Heparin
LPL	Lymphoplasmacytic lymphoma
MCL	Mantle Cell Lymphoma
MM	Multiple Myeloma
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MRI	Magnetic Resonance Imaging
MZL	Marginal Zone Lymphoma
MTD	Maximum Tolerated Dose
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	PhosphoAKT
PCP	Pneumocystis Carinii
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
SUV	Standardized Uptake Value
t <sub>1/2</sub>	Plasma Half Life
t <sub>max</sub>	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
WM	Waldenstrom macroglobulinemia



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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 [1,2,3]. Tenalisib is a highly specific and orally available dual PI3K  $\delta/\gamma$  inhibitor with nano-molar inhibitory potency and several fold selectivity over  $\alpha$  and  $\beta$  PI3K isoforms. The specificity of Tenalisib towards PI3K  $\delta$  and  $\gamma$  is evidenced by >1000 and >100 fold selectivity over  $\alpha$  and  $\beta$  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  $\delta/\gamma$  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.

PI3K  $\delta/\gamma$  isoforms are known to play a role in modulating the tumor microenvironment. PI3K  $\gamma$  is also important for migration and differentiation of tumor-associated myeloid cells. Published data has demonstrated that Tumor-Associated Macrophages (TAMs) are reduced in PI3K $\gamma$  deficient mice resulting in reduced tumor growth. Pre-clinical models demonstrated that selective inactivation of macrophage PI3K $\gamma$  stimulates and prolongs NF $\kappa$ B activation and inhibits C/EBP $\beta$  activation, thus promoting an immuno-stimulatory transcriptional program that restores CD8<sup>+</sup> T cell activation and cytotoxicity. Refer to 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 three clinical trials:

1. A Phase I Dose Escalation Study Evaluating the Safety and Efficacy of RP6530, a dual PI3K  $\delta/\gamma$  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  $\delta/\gamma$  inhibitor, in Patients with Relapsed or Refractory T-cell Lymphoma (US study: Protocol number RP6530-1401). Status: **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**

- **Safety:**

In **RP6530-1301 study**, Tenalisib demonstrated acceptable safety and tolerability profile up to 1200 mg BID and 800 mg TID without any dose limiting toxicity (DLT) in 35 patients with relapsed/refractory haematological malignancies. Treatment related Grade  $\geq 3$  Aes were hypertriglyceridemia, neutropenia and diarrhea. Reported SAEs were assessed to be not related to Tenalisib but attributed to disease under study/concomitant disease conditions. Reported events were consistent with co-morbidities/disease burden in patients with relapsed/refractory hematological malignancies.

In an ongoing **RP6530-1401 study**, a total of 49 patients were treated at 200 mg BID (n=4), 400 mg BID (n=4), 800 mg BID (Fasting) (n=35) 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) is considered as a MTD dose in patients with T-cell lymphoma. Majority of Aes include transaminitis, skin rash and fatigue and nausea. Treatment related Grade  $\geq 3$  includes AST/ALT elevation (n=11), rash (n=3), neutropenia (n=3), hypophosphatemia (n=1), INR Increase (n=1), sepsis (n=1) and diplopia secondary to neuropathy (n=1). Treatment related SAE reported were fever (n=1), raised INR (n=1), sepsis (n=1) and diplopia secondary to neuropathy (n=1).

- **Pharmacokinetics (PK):**

In **RP6530-1301 study**, maximum systemic exposures were assessed by  $AUC_{0-t}$  and  $C_{max}$  as determined on Cycle 1 Day 1 (C1D1) at 25 mg to 1200 mg BID; 600 and 800 mg TID. Based on  $C_{max}$  and AUC dose proportionality was observed up to 400 mg dose. Dose related exposure were observed beyond 400 mg. Up on increasing doses, there is no change in  $T_{max}$  were observed and while there was change in  $T_{1/2}$ . Steady state PK parameters of Tenalisib as determined on Cycle 2 Day 1 (C2D1) revealed no accumulation. Similar findings were seen in ongoing RP6530-1401 study.

- **Efficacy:**

In **RP6530-1301 study**, Tenalisib was evaluated as single agent in 35 heavily pre-treated patients with relapsed/refractory (R/R) hematological malignancies (CLL, DLBCL, FL, MZL, WM, MCL, HL, TCL and MM). Tenalisib demonstrated an ORR  $\approx 20\%$  (CR: 7% and PR: 13%).

In **RP6530-1401 study**, response assessments of the twenty-eight evaluable patients receiving at least two cycles of Tenalisib showed an ORR of 57% (16/28 patients) out of which 3 (11%) were CR and 13 (46%) were PR. Seven patients showed stable disease (25%). Indication specific analysis showed an ORR of 58% (7/12, 3 CR, 4 PR) in PTCL and 56% (9/16, 9 PR) in CTCL.

## 1.2 Study Rationale

### 1.2.1 Rationale for study population

Approximately one third of NHLs are indolent. These indolent NHLs (iNHLs) are slow-growing tumors with a prolonged natural history, and most patients present with advanced disease. iNHLs are highly treatable but rarely cured. [6]

Though iNHLs remain incurable, treatment is markedly advanced after the advent of the anti-CD20 monoclonal antibody rituximab, which now has widespread use both as monotherapy and in chemo-immunotherapy regimens for first-line and relapsed or refractory (R/R) diseases. Recommended first-line regimens for grade 1–2 FL include rituximab monotherapy; rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP/CHOP); CHOP-obinutuzumab; rituximab, cyclophosphamide, vincristine, prednisone (RCVP/CVP); bendamustine-obinutuzumab and rituximab in combination with bendamustine or lenalidomide. [7]

With advances in treatment, iNHL death rates have declined. Although the increased response rates and prolonged progression-free survival (PFS) with rituximab monotherapy and combination therapy are encouraging, as noted earlier, ~20% of patients relapse within 2 years of first-line chemo-immunotherapy, and these patients have lower survival rates compared with patients who did not relapse in the first 2 years (OS at 2 years, 68% vs 97%, respectively). [8] Moreover, responses to second-line therapies are often suboptimal, suggesting that salvage regimens are poorly effective after first-line rituximab. [9]

An analysis of data from the National LymphoCare Study revealed that patients older than 80 years were most likely to be treated with first-line rituximab monotherapy or observation only instead of chemo-immunotherapy, and when combination therapy was used, it was generally RCVP. [10] Although current practice supports the use of rituximab-based regimens in younger, medically fit patients, rituximab monotherapy or watchful waiting is generally recommended for elderly or frail patients. In the National Comprehensive Cancer Network guidelines, recommendations for first-line therapy in the elderly or infirm are limited to rituximab monotherapy, single-agent alkylators, and radio-immunotherapy. [7] Taken together, it is clear that there is a substantial unmet need for effective, well-tolerated treatments in R/R patients and elderly or frail patients with iNHL, despite the recent approvals of Idelalisib and Copanlisib.

### 1.2.2 Rationale for dose selection for Tenalisib

The safety and tolerability of Tenalisib has been established up to doses of 1200 mg BID and 800 mg TID. In an ongoing US study, Tenalisib 800 mg BID (Fasting) is established as a MTD dose in patients with T-cell lymphoma. Therefore, Tenalisib (800 mg BID) is considered for this study.

## 1.3 Benefit and Risk

It is expected that proposed monotherapy has the potential to improve response rates in the proposed patient population. 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 Objective**

- To assess the anti-tumor activity of Tenalisib, as determined by the Objective Response Rate (ORR), Duration of Response (DoR) and Progression Free Survival (PFS).

### **2.2 Secondary Objective**

- To characterize safety and tolerability of Tenalisib in patients with iNHL.

## **3 TRIAL DESIGN**

### **3.1 Trial End Points**

- **Efficacy:**

- **ORR** is defined as sum of CR and PR rates and will be assessed according to the Lugano Classification for initial evaluation, staging, and response assessment of Non-Hodgkin lymphoma. (Cheson-2014)
- **CR rate** will be assessed according to the Lugano Classification for initial evaluation, staging, and response assessment of non-Hodgkin lymphoma.
- **DoR** is measured from the initial response to disease progression or death.
- **PFS** is defined as the time of the first dose of Tenalisib to disease progression or death.

- **Safety:**

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

### **3.2 Design of Trial**

The study is designed as a Phase II, open label, two parts study in relapsed/refractory iNHL patients. The mandatory Part 1 of the study will assess the efficacy and safety of Tenalisib in 20 patients with iNHL. After all patients enrolled in Part 1 have had the opportunity to provide at least three tumor outcome assessments, the Data Review Committee (DRC) will evaluate the efficacy (anti-tumor activity) and safety results for each of the subtypes (e.g. FL, MZL or WM). If the committee believes there are potential clinically meaningful responses for certain subtype, the committee will recommend initiation of Part 2 to evaluate efficacy and safety for that subtype. If not, the study will be terminated without initiating Part 2. The sample size for Part 2 will be derived based on the outcome from Part 1. Data from Part 1 will not be included in the analysis of Part 2 of the study.

The study treatment Tenalisib (800 mg BID) will be administered orally in 28-days of cycle over a period of 8 months in absence of definitive disease progression or unacceptable toxicity. Treatment will be continued in patients experiencing clinical benefit until the

occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to investigator decision or other reasons; maximum for up to 24 months.

The efficacy response will be evaluated on Weeks 8 (C3D1± 7 days), Weeks 16 (C5D1± 7 days) and then every 12 weeks thereafter, and/ or at the EOT or as clinically indicated (if clinical progression is suspected or for confirmation of complete response/disease progression). The details of the study procedures are given in Schedule of Events.

Group	N	Patient population	Tenalisib
Part 1	20	Refractory/ relapsed iNHL.	800 mg BID in 28-Days Cycle for 8 Cycles <sup>1</sup>
Part 2	The sample size will be derived based on the outcome from Part 1	Refractory/ relapsed iNHL patients of one of the specific subtype (e.g. FL, MZL, WM)	800 mg BID in 28-Days Cycle for 8 Cycles <sup>1</sup>

<sup>1</sup>Post cycle 8, treatment will be continued in patients experiencing clinical benefit up to 24 months unless progression of disease or toxicity warranting discontinuation of therapy. The decision to continue the treatment will be determined by the PI after consultation with Sponsor on case to case basis.

### 3.3 Data Review Committee (DRC)

The DRC will be constituted by the sponsor in consultation with PI and will consist of PI, sponsor representative, sponsor's medical expert, medical monitor, and a statistician. The DRC will meet and review the safety and efficacy data at regular interval and as required by the sponsor/investigator to assess the safety and tolerability of study drug.

After all patients enrolled in Part 1 have had the opportunity to provide at least three tumor outcome assessments, the DRC will evaluate the efficacy (anti-tumor activity) and safety results for each of the subtypes. If the committee believes there are potential clinically meaningful responses for certain subtype, the committee will recommend initiation of Part 2 to evaluate efficacy and safety for that subtype.

### 3.4 Randomization and Blinding

This is a non-randomized, open label study.

### 3.5 Investigational Medicinal Product

#### 3.5.1 Dosage form and strengths

Investigational Product	Dosage form, strength	Manufacturer
Tenalisib	Tablets; 200 mg and 400 mg.	STA Pharma Co. Ltd.

**Note:** Please refer Investigator's brochure for additional information of Tenalisib.

### **3.5.2 Labeling, packaging and supply**

Tenalisib will be supplied by STA Pharma Co. Ltd. through Rhizen Pharmaceuticals S.A. Tenalisib will be available as 30 tablets per bottle. All trial drugs must be kept in a secure place at below 25°C (77°F), protected from moisture.

### **3.5.3 Preparation and administration of Investigational Products**

At each visit, patients will be dispensed sufficient quantity of Tenalisib until the next visit. 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.
- Pre-medications: None. No routine prophylactic anti-emetics or pre-medications should be given outside of protocol requirements. However, these medications may be administered for the treatment of symptoms (see Section 5.3).
- 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 hrs 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 at the beginning of each new treatment cycle. Missed doses should be documented.

### **3.5.4 Accountability of Investigational Products**

The PI/ designee are responsible for accountability of all trial drug supplies (used/unused) at the site. The study monitor will verify receipt of investigational product at the sites during monitoring visit(s), 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 verification, returned or expired trial drugs can be destroyed according to local institutional policy with sponsor pre-approval of a site-specific destruction policy. Certificate of destructions must be filed at the site and in Trial Master File.

### **3.5.5 Precautions and risks associated with Investigational Products**

- Monitoring of liver enzymes and levels of TSH, T3, and T4 in subjects receiving Tenalisib is recommended based on target organ toxicity. Patients should be monitored for increased ALT/AST, skin rash, neutropenia as these events are reported with Tenalisib. Monitor patients for signs and symptoms of these events and interrupt

Tenalisib for Grade 3 or higher event. In addition, enteritis (colitis), pneumonia/pneumonitis as these events are reported with other PI3K inhibitors.

- Tenalisib may cause serious infections that may include sepsis and other infections. Monitor patients for signs and symptoms of infection and interrupt Tenalisib for Grade 3 or higher infection.
- 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 demonstrated moderate to high inhibition of CYP3A4 enzymes. Therefore, concomitant administration of Tenalisib with 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. Raised INR has been reported with concomitant warfarin administration. Therefore, use of heparin or warfarin is generally avoided. Low molecular weight heparin (LMWH) is advised for prophylaxis and treatment of venous thrombosis.
- 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.
- In absence of reproductive toxicity and genotoxicity data, the study participants should be advised to follow post treatment contraceptive measures.

### **3.6 The Expected Duration of Subject Participation and Follow-up**

The expected duration of subject participation in the study will be 8 months. Treatment will be continued in patients experiencing clinical benefit up to 2 years unless progression of disease or toxicity warranting discontinuation of therapy. The decision to continue the treatment will be taken by PI after consultation with sponsor on case to case basis.

### **3.7 Study Stopping Rules**

#### **Efficacy:**

After all patients enrolled in Part 1 have had the opportunity to provide at least three tumor outcome assessments, the DRC will evaluate the efficacy (anti-tumor activity) and safety results for each of the subtypes. If the committee believes there are potential clinically meaningful responses for certain subtype, the committee will recommend initiation of Part 2 to evaluate efficacy and safety for that subtype. Else, the study will be terminated.

**Safety:** The DRC will continue to monitor safety of Tenalisib (or toxicity trends that may be of concern) at interval of approximately 3 months from initiation of study until the completion of the study. 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 DRC. The DRC will have discretion to terminate the trial if an additional death occurs that can be attributed to the study drug.

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 respectively if the trial terminates early, with a justification for the early termination.

## 4 SELECTION AND WITHDRAWAL OF SUBJECTS

### 4.1 Inclusion Criteria

*Patients must meet all of the following inclusion criteria to be eligible for participation in this study:*

1. Patients with histologically confirmed diagnosis of **indolent B-cell NHL**, with histological subtype limited to:
  - Follicular lymphoma (FL) G1, G2, or G3a
  - Marginal zone lymphoma (MZL) (splenic, nodal, or extra-nodal)
  - Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM)
  - Small lymphocytic lymphoma (SLL) with absolute lymphocyte count  $< 5 \times 10^9/L$  at the time of diagnosis and at study entry.
2. Relapsed or refractory after  $\geq 2$  prior lines of therapy (refractory defined as not responding to a standard regimen or progressing within 6 months of the last course of a standard regimen). Patients must have received rituximab and alkylating agents.
3. Patients must have at least one bi-dimensionally measurable lesion (that has not been previously irradiated) with the longest diameter  $\geq 1.5$  cm.
4. Male or female patients  $> 18$  years of age.
5. ECOG performance status  $\leq 2$ .
6. Life expectancy of at least 3 months.
7. Adequate bone marrow, liver, and renal function as assessed by the following laboratory requirements conducted within 7 days before starting study treatment:
  - a. Hemoglobin  $\geq 9$  g/dl
  - b. Absolute neutrophil count (ANC)  $\geq 1 \times 10^9/L$
  - c. Platelets  $\geq 50 \times 10^9/L$  (patient without BM involvement) and  $30 \times 10^9/L$  (patient with BM involvement)
  - d. Total bilirubin  $\leq 1.5$  times the upper limit of normal (ULN)
  - e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)  $\leq 2.5 \times$  ULN if known liver involvement. The ALT and AST should be  $\leq 1.5 \times$  ULN in absence of liver involvement/metastasis.
  - f. Creatinine  $\leq 1.5$  mg/dL OR calculated creatinine clearance  $\geq 50$  mL/min (as calculated by the Cockcroft-Gault method)
8. Ability to swallow and retain oral medication.
9. Female patients who are not of child-bearing potential, and female patients of child-bearing potential who have a negative serum pregnancy test within 72 hours prior to initial trial treatment. Female patients of child-bearing potential, and all male partners must consent to use a medically acceptable two methods of contraception throughout



the study period and for 4 weeks after the last dose of Tenofovir. A barrier method of contraception must be included.

10. Male patients willing to use adequate contraceptive measures throughout the study period and for 12 weeks after the last dose of Tenofovir.
11. Willingness and ability to comply with trial and follow-up procedures, give written informed consent.

#### **4.2 Exclusion Criteria**

1. Histologically confirmed diagnosis of follicular lymphoma grade 3b or transformed disease or chronic lymphocytic leukemia (CLL).
2. Patients receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) or any cancer investigational drug within 3 weeks (21 days) or 5 half-lives (whichever is shorter) prior to C1D1. Corticosteroids (prednisone or equivalent) at a dose of < 20 mg daily are allowed. Corticosteroid should be stabilized for at least 1 week prior to C1D1.
3. Autologous hematologic stem cell transplant (Auto-SCT) within 3 months from C1D1. Patients must not have active graft versus-host disease;
4. History of an allogeneic bone marrow transplant (Allo-SCT)
5. Active hepatitis B or C infection. (All subjects must be screened for hepatitis B and C up to 28 days prior to C1D1 using the hepatitis viral panel. Subject positive for HBsAg or HBcAb will be eligible if they are negative for HBV-DNA. Subject positive for HCV IgG will be eligible if they are negative for HCV-RNA);
6. Known history of human immunodeficiency virus (HIV) infection;
7. Evidence of ongoing severe systemic bacterial, fungal or viral infection;
8. Known primary central nervous system lymphoma or known intracranial involvement, leptomeningeal metastases or spinal cord compression due to disease or any preexisting neurologic manifestations;
9. Known history of severe drug-induced liver injury, alcoholic liver disease, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver or portal hypertension;
10. Patient with any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study as per investigator's judgement;
11. Patient with symptomatic, or history of documented congestive heart failure (NY Heart Association functional classification III-IV);
12. Patient with angina not well-controlled by medication;
13. Patient with poorly controlled or clinically significant atherosclerotic vascular disease (including cerebrovascular accident, transient ischemic attack or have angioplasty, cardiac or vascular stenting) in the past 6 months;
14. Prior exposure to drug that specifically inhibits PI3K (e.g. Idelalisib, Copanlisib, Duvelisib and Umbralisib);
15. Previous or concurrent malignancy that is distinct in primary site or histology from indolent B-cell NHL within 3 years of study enrollment EXCEPT for adequately treated basal, squamous cell carcinoma or non-melanomatous skin cancer, carcinoma in situ of the cervix, superficial bladder cancer not treated with intravesical chemotherapy or BCG within 6 months, localized prostate cancer with PSA <1.0 mg/dL on 2 consecutive

measurements at least 3 months apart with the most recent one being within 4 weeks of study entry;

16. Patients with seizure disorder requiring medication;
17. Unresolved toxicity higher than CTCAE grade 1 (NCI-CTCAE version 5.0) attributed to any prior therapy/procedure excluding alopecia;
18. Myeloid growth factors or red blood cells/ platelet transfusion within 14 days prior to C1D1;
19. Administration of any of the following within 1 week prior to C1D1:
  - a. **Strong inhibitors or inducers of CYP3A4**, including grapefruit products, herbal medications.
  - b. **Strong inhibitors or inducers of CYP2C9**, including herbal medications.
  - c. Substrates of CYP3A4 enzyme with a **narrow therapeutic range** (e.g. Warfarin and phenytoin)
20. Pregnant or lactating woman;
21. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol;
22. Concurrent condition that in the investigator's opinion would jeopardize compliance with the protocol.

#### **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.
- Withhold of study drug for > 28 days due to adverse event, unless approved by medical monitor.
- 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
- Confirmed disease progression
- Study completion.

## **5 TREATMENT OF SUBJECTS**

### **5.1 Administration of Tenalib**

Tenalib will be dosed continuously twice a day in 28-days cycle up to 24 months unless progression of disease or toxicity warranting discontinuation of therapy. Please refer [section 3.4.3](#) for administration of Tenalib. Post completion of 24 months, if the patient shows clinical benefit, patient may be enrolled into a compassionate use study protocol to receive Tenalib.

### **5.2 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.
- Transfusions (blood/platelets) may be given, based on standard criteria and clinical judgment.
- No routine prophylactic anti-emetics or pre-medications should be given outside of protocol requirements. However, these medications may be administered for the treatment of symptoms.
- Patient may receive prophylactic allopurinol, in case the risk of tumor lysis syndrome.
- Low doses of steroids are allowed if it stabilized at < 20 mg per day of prednisone or equivalent. If initiated before starting treatment, corticosteroid should be stabilized for at least 1 week prior to C1D1.
- Patients are permitted to use of topical, ocular, intra-articular, intranasal, and inhaled corticosteroids (with minimal systemic absorption). A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) and also for the treatment of drug-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/CYP2C9 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.

### 5.3 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 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 medication (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 medications (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.**

#### **5.4 Procedures for Monitoring Subject Compliance.**

The following measures will be employed to ensure treatment compliance.

Subjects will be asked to bring any unused study drug to the research center at their next 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.

## **6 TRIAL ASSESSMENT AND PROCEDURE**

### **6.1 Overview**

Schedule of Event (**Table 1**) summarizes the trial procedures to be performed at each visit and is divided into following.

1. Screening (Day -28 day to Day 0)
2. On treatment procedures (C1D1 to C8D28)
3. Treatment beyond Cycle 9 (C9D1 to C26)
4. End of Treatment (Day +7 from last dose)
5. End of Study (Day +30 from 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.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the

[REDACTED]

subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

<b>Table 1: Schedule of Events for Part 1</b>															
	Screening	Cycle 1		Cycle 2		Cycle 3		C4	C5	C6	C7	C8	C9-26	EOT <sup>20</sup>	EOS <sup>21</sup>
Day	D-28 to 0	D1	D15	D1	D15	D1	D15	D1	D1	D1	D1	D1	D1	-	-
Window period	-28	±1	±1	±1	±3	±3	±3	±3	±7	±7	±7	±7	±7	+14	+30
Study Days	D-28 to 0	1	15	29	43	57	71	85	113	141	169	197	-	-	-
Informed Consent <sup>1</sup>	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics <sup>2</sup>	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical history <sup>3</sup>	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vitals <sup>4</sup>	X	X	X	X	X	X	X	X	X	X	X	X	-	X	-
Height and weight <sup>5</sup>	X	X	X	X	X	X	X	X	X	X	X	X	-	X	-
Complete Physical exam <sup>6</sup>	X	-	-	-	-	-	-	-	-	-	-	-	-	X	-
Abbreviated Physical exam <sup>6</sup>	-	X	X	X	X	X	X	X	X	X	X	X	-	-	-
ECOG Performance Status	X	X	-	-	-	X	-	-	X	X	X	X	-	X	-
Complete blood count <sup>7</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>19</sup>	X	-
Chemistry panel I <sup>8</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>19</sup>	X	-
Chemistry panel II <sup>9</sup>	X	X	-	-	-	X	-	-	X	-	-	X	-	X	-
Serology <sup>10</sup>	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PT and INR <sup>11</sup>	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	X	X	X <sup>19</sup>	X	-
Pregnancy test <sup>12</sup>	X	X	X	X	X	X	X	X	X	X	X	X	-	X	-
12-lead ECGs <sup>13</sup>	X	X	X	X	X	X	X	X	-	-	-	X	-	X	-
Radiological scan/imaging	X	-	-	-	-	X	-	-	X	-	-	X	X <sup>19</sup>	X	-
CT scan <sup>14</sup>	X	-	-	-	-	-	-	-	X	-	-	X	X <sup>19</sup>	X	-
PET/PET-CT <sup>14</sup>	X	-	-	-	-	X	-	-	-	-	-	-	-	-	-
Disease Response Assessment <sup>15</sup>	X	-	-	-	-	X	-	-	X	-	-	X	X <sup>19</sup>	X	-
Drug Dispensing <sup>16</sup>	-	X	-	X	-	X	-	X	X	X	X	X	X <sup>19</sup>	X	-

Tenalisib treatment <sup>17</sup>	-	X	X	X	X	X	X	X	X	X	X	X	X <sup>19</sup>	X	-
Drug compliance	-	-	X	X	X	X	X	X	X	X	X	X	-	X	-
AE evaluation <sup>18</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>19</sup>	X	X
SAE evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>19</sup>	X	X
Concomitant medication	-	X	X	X	X	X	X	X	X	X	X	X	X <sup>19</sup>	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 Tenalisib 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, number 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 include pulse; blood pressure; respiratory rate and oral temperature that should be done at screening, C1D1 (within 30 minutes prior to dosing) and at the time of clinic visit at all other time points. Supine or sitting position is acceptable depending on the patient condition.
5. Weight will be measured at all visits. Height to be measured at screening only.
6. Physical examination will include lymph node and systemic examination (General Appearance, HEENT, neck, cardiovascular, lungs, abdomen, lymph nodes, genitourinary, extremities, neurological, skin, and musculoskeletal). Complete physical examination will be done at screening visit and EOT. At all other visits, abbreviated examination (directed physical examination) will be done depending on the assessment of tumor.
7. This will include hemoglobin, 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 includes total bilirubin, ALP, AST, ALT, GGT, LDH, sodium, potassium, chloride, calcium, phosphorus, CO<sub>2</sub>/bicarbonate and magnesium. 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 visits if clinically indicated.
9. Chemistry Panel II includes blood glucose, urea/ blood urea nitrogen (BUN), creatinine, albumin, total protein, TSH, T3 (total/free), T4 (free), total Cholesterol, TG, LDL and HDL. 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.
10. Serology includes HIV, HBV and HCV. Historical evidence in the last 4 weeks is acceptable.
11. 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. This is required for women of child bearing potential. A serum 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. A standard 12-lead ECG will be performed at the defined time points. Additional ECGs will be obtained if clinically indicated. Triplicate ECGs will be performed to confirm significant changes of a single ECG.

14. PET/PET-CT 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 C5D1 and at every 12-Weeks thereafter. PET/PET-CT should be repeated at C3D1 and to confirm CR/PD; and as clinically indicated. Tumor imaging should remain consistent throughout study, and should include those thought by investigator to best capture the status of disease. Baseline scans if already available as SOC within 28-days of screening, is accepted as part of study protocol.
15. Disease response assessment will be performed at C3D1 ( $\pm$  7 days), C5D1 ( $\pm$  7 days) and approximately every 12 weeks thereafter ( $\pm$  7 days), and/ or at the EOT or as clinically indicated (if clinical progression is suspected or for confirmation of complete response/disease progression) using Cheson Criteria 2014.
16. Tenalisisib will be dispensed in a HDPE container having 30 tablets of Tenalisisib.
17. Tenalisisib will be administered orally twice a day in 28-days of cycle in absence of disease progression or toxicity warranting discontinuation of therapy. Post cycle 8, Tenalisisib will be continued in patients experiencing clinical benefit up to 24 months unless progression of disease or toxicity warranting discontinuation of therapy. The decision to continue the treatment will be taken by PI after consultation with Sponsor on case to case basis.
18. 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.
19. Post cycle 8, all visits will occur monthly. During these monthly visits, Tenalisisib will be dispensed, medication compliance will be monitored. Safety and efficacy assessments will be done as mentioned below. An EOT visit will be performed within 14 days after treatment ends.
  - Safety assessments: Safety assessment will be done during the monthly visits and AEs will be reported as required by the protocol. There is no specific safety labs or evaluations to be done as per protocol. As part Standard of care, laboratory evaluations will be done and recorded per Investigator’s discretion. Adverse events (AEs, SAEs and deaths) will be recorded and reported for 30 calendar days after discontinuation or completion of protocol-specific treatment. After the 30 day reporting period, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.
  - Efficacy assessments: Disease assessments should be performed at 12 weekly intervals ( $\pm$  7 days), and/ or at the EOT. For example, the appropriate radiological investigation (e.g. CT scan, PET-CT/PET) will be performed patients at C11D1, C14D1, C17D1, C20D1, etc.
  - Drug dispensing: Patients will be given 30 days of drug supply at the beginning of each cycle.
20. All patients will undergo the end-of-treatment (EOT) assessments within 14 days after last dose of study drug or discontinuation.
21. 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.



## **6.2 Screening and on Treatment Procedures**

### **6.2.1 Informed consent**

The investigator/qualified designee must obtain documented 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 a 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.

The informed consent must be obtained  $\leq 30$  days prior to initiation of treatment before any protocol-specific procedures are performed. Patient should be re-consented in case informed consent is not obtained  $\leq 30$  days prior to the initiation of trial treatment.

### **6.2.2 Assignment of screening number**

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

### **6.2.3 Medical history**

A medical history will be obtained by the investigator/qualified designee. Comprehensive history will include but not limited to age; sex; absence/presence of fever 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. Medical history should be taken for period of minimum 6 months.

### **6.2.4 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. 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/qualified designee will record medication, if any, taken by the subject during the trial.

### 6.2.5 Prior therapies details

The investigator/qualified designee will review all prior cancer treatments including systemic treatments, prior transplantation, radiation, and surgeries received for the treatment of cancer condition from the initial diagnosis and record in the source document.

### 6.2.6 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).

**Abbreviated (Directed) physical examination:** For cycles that do not require a full physical exam per the Schedule of Event, the investigator/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.

### 6.2.7 Vital signs

Vital signs will be taken at screening, C1D1 (within 30 minutes prior to dosing) and at the time of clinic visit at all other time points as specified in the Schedule of Event. Vital signs should include temperature (oral/axillary), pulse, respiratory rate, weight and blood pressure. Supine or sitting position is acceptable depending on the patient condition. The window periods for vitals will  $\pm 30$  min for the specified time points.

### 6.2.8 Laboratory safety evaluations

Laboratory tests for hematology, chemistry and urinalysis are specified in **Table 2**.

**Table 2: Laboratory Tests for Hematology, Chemistry and Urinalysis**

Hematology	Chemistry Panel I	Chemistry Panel II	Urinalysis	Other
Hematocrit	Total bilirubin	Blood glucose	Blood	Serum $\beta$ -hCG
Hemoglobin	Alkaline phosphatase (ALP)	Urea or blood urea nitrogen <sup>a</sup>	Glucose	Urine pregnancy test
CBC with differentials	Alanine aminotransferase (ALT)	Creatinine	Protein	PT
Platelet count	Aspartate aminotransferase (AST)	Albumin	Specific gravity	INR
WBC (Total and differentials)	Lactate dehydrogenase (LDH)	Total protein	Microscopic exam	
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		
	Carbon Dioxide (CO <sub>2</sub> ) or bicarbonate <sup>C</sup>	T3 (Total or Free) <sup>d</sup>		
	Chloride	T4 (free)		
	Magnesium			

<sup>a</sup> Blood Urea Nitrogen is preferred; if not available Urea may be tested.

<sup>b</sup> Microscopic exam, if abnormal results are noted.

<sup>c</sup> One of these tests to be performed depending on standard of care practice followed at the institution.

<sup>d</sup> Free or total T3 to be performed depending on standard of care practice followed at the institution.

Blood drawn for these tests will be specified in informed consent form (ICF). The investigations will be performed at the local laboratory as decided by the sponsor and investigator. .

Screening laboratory described in **Table 2** will be performed, reviewed, and determined to be acceptable by the site PI/designee after obtaining informed consent and ≤7 calendar days prior to the initiation of treatment. If these initial examinations are obtained within 72 hours (or as otherwise noted) of Cycle 1 Day 1, the investigations need not be repeated. Rescreening can be done at the discretion of PI. The scan and other investigations to document measurable or evaluable disease should be performed ≤28 weeks prior to initiation of treatment.

During screening, active HBV, HCV or HIV infection 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)

***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 therapy and should be closely monitored for HBV reactivation.*

### 6.2.9 ECG

A standard 12-lead ECG will be performed using local standard procedures as defined in Schedule of Events. Additional ECGs will be obtained if clinically indicated. Triplicate ECGs will be performed to confirm the significant changes of single ECG. Clinically significant abnormal findings should be recorded as an adverse event.

### 6.3 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator/qualified designee will assess ECOG status (see [Appendix A](#)) at screening; prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Schedule of Event.

#### **6.4 Radiological Evaluation**

Initial disease assessment by tumor imaging (baseline scan) must be performed within 28 days prior to the first dose of trial treatment. The site study team must review pre-trial 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. The CT/ PET/PET-CT should be done throughout the study at local imaging centre at time-points designated in Schedule of Events.

#### **6.5 Trial Treatment Period**

Patients will visit the study center bi-weekly for the first three cycles and thereafter every month. All visits should occur as close as possible to the protocol specified time. Complete listings of the assessments that will be performed at each visit during the trial treatment period are specified in **Table 1**.

Trial treatment period is of 8 cycles. Assessments will be performed thereafter if warranted, at the discretion of PI. Patients with progressive disease or unacceptable toxicity should be discontinued from the trial; patients with stable disease or response to therapy will continue treatment. The assessments to be performed are specified in **Table 1**.

#### **6.6 Treatment Beyond Cycle 8 (Cycle 9 onward up to Cycle 26)**

Post cycle 8, all visits will occur monthly in responding patients. During these monthly visits, Tenalisib will be dispensed, medication compliance will be monitored. Safety and efficacy assessments will be done as mentioned below. An EOT visit will be performed within 14 days after treatment ends.

- **Safety assessments:** Safety assessment will be done during the monthly visits and AEs will be reported as required by the protocol. There is no specific safety labs or evaluations to be done as per protocol. As part Standard of care, laboratory evaluations will be done and recorded per Investigator's discretion. Adverse events (AEs, SAEs and deaths) will be recorded and reported for 30 calendar days after discontinuation or completion of protocol-specific treatment. After the 30 day reporting period, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.
- **Efficacy assessments:** Disease assessments should be performed at 12 weekly intervals ( $\pm$  7 days), and/ or at the EOT. For example, the appropriate radiological investigation (e.g. CT scan, PET-CT/ PET) will be performed patients at C11D1, C14D1, C17D1, C20D1, etc.
- **Drug dispensing:** Patients will be given 30 days of drug supply at the beginning of each cycle.

#### **6.7 End of Trial Treatment (EOT)**

Patients are permitted to continue treatment with Tenalisib until disease progression, or the patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the trial physician. Follow-up evaluations required after treatment ends are specified in **Table 1**.

All patients who discontinue study drugs will have an End of Treatment visit within 14 days from the last dose of study drug. If treatment is discontinued because of toxicity or any other reason(s)

at a treatment visit and no trial treatment is administered, that visit may fulfill the End of Trial Treatment Visit.

### **6.8 End of Study (EOS)**

All patients must be followed for adverse events for 30 calendar days after the last dose of study drug. A telephonic follow up is acceptable. In case of drug related AEs, further safety assessments will be performed as warranted, at the discretion of PI. The patient will be followed till resolution or stabilization of related adverse event.

### **6.9 Early Patient Termination / Patient Withdrawal**

Patients who discontinue treatment early due to disease progression or withdrawal will be asked to have all end-of-treatment safety evaluations performed as described in the protocol (see *Table 1*).

## **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, 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 (CRF).

#### **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 CRF. 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 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 (e.g. CT/PET) or clinically confirmed, 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 unit
- 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 Serious adverse event 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 CRF 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 ‘possibly’ or ‘probably’ related to Tenalisib 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 CRF.

The SAE report 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 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 Adverse Events and Serious Adverse Events**

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the SAE Report Forms and AE CRF. Avoid colloquialisms and abbreviations. All AEs, including those that meet SAE reporting criteria, should be recorded on the AE CRF; 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 CRF). 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 CRF, 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 in CRF/SAE Report Form). A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent events should be recorded separately in CRF/SAE Report Form.

#### **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 CRF. 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 CRF.

#### **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” CRF 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 CRF. 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 CRF. 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 CRF, 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 serum 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. > 800 mg).

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 Modifications

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

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

Patients may resume Tenalisib, provided that the toxicity has resolved to Grade  $\leq 2$  or baseline. If study drug is delayed  $> 2$  weeks because of an adverse event, re-initiation of treatment need to be discussed with the medical monitor.

At the discretion of the Investigator, a dose re-escalation may be 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.

#### 7.6.1 Criteria for starting Tenalisib new cycle

If treatment is delayed  $> 2$  weeks due to AE or any other reason, treatment to be resumed with new cycle after discussion with medical monitor as long as:

- Absolute neutrophil count has returned to baseline, or  $> 750/\mu\text{L}$ . Platelet count is  $> 50,000/\mu\text{L}$ .
- 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.

#### 7.6.2 Dose modifications

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

**Table 3: Dose Modifications for Hematologic Toxicity**

Worst CTCAE Grade Toxicity	Action to be Taken
<b>HEMATOLOGIC</b>	
<b>Neutropenia (ANC)</b>	
<b>Grade 3</b> $1.0 \times 10^9/\text{L} < \text{ANC} \leq 0.5 \times 10^9/\text{L}$	Maintain dose level. Monitor ANC at least weekly.
<b>Grade 4</b> $0.5 \times 10^9/\text{L} < \text{ANC}$	<b>First incidence:</b> Hold* dose until resolved to $\leq$ Grade 2 or baseline, Restart Tenalisib at 400 mg BID dose level. <b>Subsequent occurrence:</b> Hold dose until resolved to $\leq$ Grade 2 or baseline, consider growth factor support. Discontinue if further dose modification required.

Grade 3 Febrile neutropenia ANC <1000/mm <sup>3</sup> 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 reduce by 1 dose level.
<b>Thrombocytopenia</b>	
<b>Grade 3</b> (50.0 X 10 <sup>9</sup> /L < PLT ≥ 25.0 X 10 <sup>9</sup> /L)	Maintain dose level. Monitor platelet count at least weekly.
<b>Grade 4</b> 25.0 X 10 <sup>9</sup> /L < PLT	<b>1st occurrence:</b> Hold** dose until resolved to ≤ Grade 2 or baseline, Restart Tenalisib at 400 mg BID dose level. <b>Subsequent Occurrences:</b> Hold dose until to ≤ Grade 2 or baseline, consider platelet transfusion as necessary. Discontinue if further dose modification required. Note: If the count is <50 X 10 <sup>9</sup> /L before initiation of therapy (e.g. in case of marrow involvement), the dose reduction should be done as per investigator's judgement.

\*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 4: Dose Modifications for Non-Hematologic Toxicities**

NON-HEMATOLOGIC	Action to be Taken
<b>Renal*</b>	If serum creatinine 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.
<b>Hepatic*</b>	<p><b>Transaminitis</b></p> <p><b>Grade ≥ 1 Transaminitis (ALT/AST &gt; 1-3 X ULN):</b></p> <ul style="list-style-type: none"> <li>• Maintain Tenalisib dose and initiate <b>prednisone 40 mg daily</b>.</li> <li>• Monitor AST/ALT weekly until resolved.</li> <li>• Withhold Tenalisib in case of development of grade 2 transaminitis or worsening of Grade 1 transaminitis while on steroids.</li> </ul> <p><b>Grade ≥ 3 Transaminitis (ALT/AST &gt;5–20 X ULN):</b></p> <ul style="list-style-type: none"> <li>• Withhold Tenalisib and monitor ALT/AST twice a weekly until Grade ≤1; restart Tenalisib at 400 mg BID dose level.</li> <li>• Initiate <b>prednisone 1 mg/kg</b> in case no improvement with discontinuation of Tenalisib in 1 week.</li> <li>• Monitor ALT/AST twice a weekly until Grade ≤1; restart Tenalisib at 400 mg BID dose level and taper steroid.</li> <li>• If no immediate response to steroids within 7 days, initiate mycophenolate mofetil.</li> <li>• In case of recurrence of transaminitis at reduced doses, discontinue Tenalisib permanently after assessing risk versus benefit.</li> </ul> <p><b>Grade ≥ 4 Transaminitis (ALT/AST &gt;20 X ULN):</b></p> <ul style="list-style-type: none"> <li>• Tenalisib should be permanently discontinued.</li> </ul>

	<p><b>Bilirubin:</b></p> <ul style="list-style-type: none"> <li>• <b>Grade <math>\geq 2</math></b> (<math>&gt; 1.5-3 \times \text{ULN}</math>): Maintain Tenalisib dose. Monitor at least weekly until <math>\leq 1 \times \text{ULN}</math></li> <li>• <b>Grade <math>\geq 3</math></b> (<math>&gt; 3-10 \times \text{ULN}</math>): Withhold Tenalisib. Monitor at least weekly until bilirubin is <math>\leq 1 \times \text{ULN}</math>; restart Tenalisib at 400 mg BID dose level.</li> <li>• <b>Grade <math>\geq 4</math></b> (<math>&gt; 10 \times \text{ULN}</math>): Discontinue Tenalisib permanently</li> </ul>
<b>Infection</b>	<p><b>Grade 3 or higher sepsis or pneumonia</b></p> <ul style="list-style-type: none"> <li>• Interrupt Tenalisib until infection has resolved.</li> </ul>
<b>Diarrhea</b>	<p><b>Moderate:</b></p> <ul style="list-style-type: none"> <li>• Maintain Tenalisib dose. Monitor at least weekly until resolved.</li> </ul> <p><b>Severe diarrhoea or hospitalization</b></p> <ul style="list-style-type: none"> <li>• Withhold Tenalisib dose. Monitor at least weekly until resolved.</li> <li>• Restart Tenalisib at 400 mg BID dose level.</li> </ul> <p><b>Life threatening diarrhoea</b></p> <ul style="list-style-type: none"> <li>• Discontinue Tenalisib permanently.</li> </ul>
<b>Cardiac</b>	<p>If a QTcF <math>&gt;500</math> msec has been demonstrated, hold dose.</p> <p>The patient will be monitored hourly with ECGs until the QTcF <math>&lt;500</math> msec and the QTcF has returned to “<math>&lt;30</math> msec from baseline”. Immediate attention to potassium and magnesium and other clinical factors such as oxygenation and ischemia should be addressed.</p> <p>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.</p>
<b>OTHER NON-HEMATOLOGIC</b>	<b>Action to be Taken</b>
<b>Grade 3/4 CTCAE</b>	<p><b>First occurrence:</b></p> <p>Hold* dose until toxicity Grade <math>\leq 2</math>; restart Tenalisib at 400 mg BID dose level.</p> <p><b>Subsequent Occurrences:</b> Hold dose until to <math>\leq</math> Grade 2 or baseline.</p> <p>Discontinue if further dose modification required.</p>

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

## 8 ASSESSMENT OF EFFICACY

### 8.1 Specification of the Efficacy Parameters

- **ORR** is defined as sum of CR and PR rates, as assessed by the Investigator according to the Lugano Classification for initial evaluation, staging, and response assessment of Non-Hodgkin lymphoma. Only those patients who have had a pre-treatment baseline efficacy evaluation and at least one post-treatment efficacy evaluation or confirmed disease progression will be considered evaluable for response. Subtype specific and overall ORR will be calculated in Part

1 of the study. Criteria for evaluable subjects for Part 2 will be re-defined based on the results of Part 1.

- **CR** rate will be assessed by the investigator according to the Lugano Classification for initial evaluation, staging, and response assessment of non-Hodgkin lymphoma. For assessment of CR, a post-treatment residual mass of any size is permitted if it is negative on positron emission tomography imaging. Only those patients who have had a pre-treatment baseline efficacy evaluation and at least one post-treatment efficacy evaluation or confirmed disease progression will be considered evaluable for response. Subtype specific and overall CR will be calculated in Part 1 of the study.
- **PFS** is defined as time of the first dose of Tenalisib to disease progression or death. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment.
- **DoR** is defined as the time when the measurement criteria are first met for PR or CR (whichever is reported first) until the date of documented disease progression or death. For subjects who neither progress nor die, the duration of response will be censored at the date of their last disease assessment.
- **Evaluation of Best Overall Response:** The “best overall response” is the best response recorded from the start of the treatment until disease progression or discontinuation from the study.

#### **Disease parameters:**

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

## 8.2 Response Evaluations and Measurements

During Screening, the disease will be staged and confirmed by an expert hematologist as per the appropriate staging. Ann-Arbor staging or Follicular Lymphoma International Prognostic Index (FLIPI) will be performed as appropriate. Clinical assessments will include ECOG performance status (Appendix A), lymph nodes, organomegaly and “B” symptoms.

Disease response assessments should be performed at C3D1 ( $\pm 7$  days), C5D1 ( $\pm 7$  days) and approximately every 12 weeks thereafter ( $\pm 7$  days), and/ or at the EOT or as clinically indicated (if clinical progression is suspected). If PET/PET-CT and CT scan at Screening are negative for disease involvement in the neck, subsequent CT scans may not include neck. If PET/PET-CT and CT scans at Screening are positive for disease involvement of the neck, subsequent CT scans must include neck. Disease assessments and imaging should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Disease assessment will be performed as per the **Lugano Classification** (Cheson criteria 2014) [11] (refer Appendix C).

## 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.

After all patients enrolled in Part 1 had the opportunity to provide at least three tumor outcome assessments, the DRC will evaluate the efficacy (anti-tumor activity) and safety results for each of the subtypes. If the committee believes there are potential clinically meaningful benefits for certain subtype, the committee will recommend initiation of Part 2 to evaluate efficacy and safety for that subtype. Data from Part 1 will not be included in the analysis of Part 2 of the study.

### 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. 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**

Since study Part 1 was exploratory in nature. The sample size for Part 1 is not based on statistical considerations. After all patients enrolled in Part 1 had the opportunity to provide at least three tumor outcome assessments, the DRC will evaluate the efficacy and safety results for each of the subtypes. If the committee believes there are potential clinically meaningful benefits for certain subtype, the committee will recommend initiation of Part 2 to evaluate efficacy and safety for that subtype. The sample size for Part 2 will be derived based on ORR data from Part 1.

## **9.3 Study Population**

The following 3 analysis populations are planned for Part 1 of the study. Analysis population for Part 2 will be redefined based on the results of Part 1.

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

The safety endpoints will be listed and/or summarized. 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:

- Objective Response Rate
- CR rates
- Duration of response
- Progression free survival (PFS)

The analysis will be done as per the disease subtypes and overall. Additional analyses may also be performed as appropriate. These analyses will be performed from time to time for presentation/publication purposes.

### **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 trial protocol, ICF, IB, available safety information, patient documents, patient recruitment procedures (e.g., advertisements), information about payments (i.e., PI payments) and 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 the trial 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/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 or 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/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; original Form FDA 1572 (Statement of Investigator), appropriately completed and signed; 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 trial staffs are responsible for maintaining a comprehensive and centralized filing system (Site Trial File/SSF or ISF) of all trial-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF/SSF 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/SSF 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., CRFs and medical records), all original, signed informed consent forms, and copies of all CRFs, 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 (CRF). The CRF 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 CRF 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 CRF, 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 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 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  $\leq 72$  hours prior to initiating treatment.

<b>Fertile Males</b>
Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment, <u>plus additional 12 weeks after stopping treatment</u> and should not father a child in this period.
<b>Pregnancies</b>
<p>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.</p> <p>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.</p> <p>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.</p>

**Appendix C: Response Criteria for iNHL- (Cheson et. al. 2014)**

<b>Response and Site</b>	<b>PET-CT–Based Response</b>	<b>CT-Based Response</b>
<b>COMPLETE</b>	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
<b>PARTIAL</b>	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

<b>NO RESPONSE OR STABLE DISEASE</b>	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
<b>PROGRESSIVE DISEASE</b>	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  $\leq$  mediastinum; 3, uptake  $>$  mediastinum but  $\leq$  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.