PROTOCOL NO. RP6530-1803

An Open label, Compassionate Use Study of Tenalisib (RP6530) in Patients currently receiving treatment on Tenalisib trials in Hematological Malignancies

PROTOCOL NUMBER	RP6530-1803
TRIAL DRUG	Tenalisib (RP6530)
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DOCUMENT VERSION	Version 2.0, Dated October 15, 2019

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PROTOCOL SYNOPSIS

Study Title	An Open label, Compassionate Use Study of Tenalisib (RP6530) in Patients currently receiving treatment on Tenalisib trials in Hematological Malignancies.
Study Sponsor	Rhizen Pharmaceuticals S.A.
Study Rationale	Compassionate use provides an important avenue for patients with life-threatening conditions to gain access to unapproved investigational drugs, biologics and medical devices. Currently, Tenalisib has been evaluated as an investigational new drug in number of early clinical studies in patients with relapsed/refractory hematological malignancies. Tenalisib demonstrated acceptable safety and promising efficacy in these patients. Since these advanced relapsed/refractory patients have limited therapeutic options, it is reasonable to continue Tenalisib in responding patients post completion of their participation in previous clinical studies. It is anticipated that Tenalisib would not expose patients to an unreasonable and significant risk or injury. Therefore, this trial is designed to offer patients benefited by Tenalisib and who completed study without progression an opportunity to continue Tenalisib as compassionate medication and followed up on treatment for safety and disease progression.
Study Objectives	1. To evaluate the safety and tolerability of Tenalisib as single agent or in combination until the withdrawal of subject from the study due to disease progression, unacceptable toxicity or any other reason including consent withdrawal or investigator's decision. 2. Time to disease progression
Endpoints	1. Adverse Events (AEs), Grade 3/ 4 AEs and Serious Adverse Event (SAEs). 2. Date of disease progression.
Study Design	This is an open label, compassionate use study in patients who have completed a clinical trial of Tenalisib sponsored by Rhizen Pharmaceuticals S.A. This trial offers an opportunity to patients who have responded (either have CR, PR or SD on Tenalisib treatment) to receive Tenalisib as compassionate medication following their completion of previous study. Patients will continue to receive Tenalisib (schedule and dose) as they received in previous protocols, unless dose adjustments or delays are necessary for toxicity management. Trials evaluating Tenalisib as a single agent or in combination with other therapies will be part of this compassionate study protocol. The patients of these studies will be rolled over to compassionate use study once they complete the participation in original study.
No. of Patients	Approximately 50 patients
Inclusion Criteria	***Patients must meet all inclusion criteria to be eligible for participation in this study:*** 1. Patients must be currently receiving treatment with Tenalisib either as monotherapy or in combination with another agent on a previously approved protocol for hematological malignancies including but not limited to indications DLBCL, iNHL, PTCL, CTCL, CLL and HL. 2. Patients must have had at least one efficacy evaluation following the initiation of Tenalisib in previous study and should have achieved either SD, PR or CR. 3. Patients must have completed at least 6 cycles of Tenalisib in previous study 4. Ability to swallow and retain oral medication.

	5. Female patients of child-bearing potential must consent to use two medically acceptable 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. 6. Male patients must be willing to use adequate contraceptive measures throughout the study period and for 12 weeks after the last dose of Tenalisib. 7. Willingness and ability to comply with trial and follow-up procedures. 8. Willingness to provide new written informed consent.
Exclusion Criteria	***Patients must meet none of the following exclusion criteria to be eligible for participation in this study:*** 1. Patient has been discontinued from their previous Tenalisib study 4 weeks prior to entering the compassionate use trial. 2. Patient progressed while receiving Tenalisib therapy in his/her previous study. 3. Pregnant or lactating woman. 4. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol. 5. Concurrent condition that in the investigator's opinion would jeopardize compliance with the protocol.
Study Procedure	Once rolled over to compassionate use study, patients will visit the study center every 3 months until documented disease progression or treatment discontinuation due to toxicity or consent withdrawal. During these visits, Tenalisib will be dispensed and medication compliance will be monitored. In case of roll over from a combination study, the investigator has a choice to continue with the combination therapy or to maintain the patient on Tenalisib monotherapy. If combination agent is continued, it will be administered as a part of SOC. Safety and efficacy assessments will be done as mentioned below. • **Safety assessments:** Safety assessments will be done during these visits and AEs will be reported as required by the protocol. There are no specific safety labs or evaluations (including vitals, physical examinations, pregnancy tests and ECGs) required as per protocol. As part of SOC, laboratory tests or other evaluations will be done per Investigator's discretion. Adverse events (AEs, SAEs and deaths) will be recorded and reported until 30 calendar days after last dose or until a new anti-cancer treatment is initiated, whichever is earlier. After this period, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported. • **Efficacy assessments:** Disease assessments should be performed as part of SOC. Date of disease progression will be recorded in the CRF. • **Drug dispensing:** Patients will be given drug supply of 3 months.
Estimated Study duration	Approximately 5 years
Assessment of Response	Efficacy evaluations will be performed as per physician's discretion as part of SOC. These evaluations (e.g. measurement of lymph node, mSWAT) will not be recorded in CRF, however the date of disease progression will be reported.
Study Treatment	Patients showing clinical benefit will continue to receive Tenalisib as they are currently receiving in previous protocols. The treatment plan will be the same dosing schedule unless dose adjustments or delays are necessary for toxicity management. In case of roll over from a combination study, the investigator has a choice to continue with the combination therapy or to maintain the patient on Tenalisib monotherapy. If combination agent is continued, it will be administered as a part of SOC.

Statistical Analysis	The primary purpose of this study is to offer patients who completed a Rhizen sponsored clinical study without progression the opportunity to continue to receive Tenalisib on a compassion basis. The safety and progression status will be summarized as appropriate.

List of Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BID	Twice Daily
C_{max}	Peak Drug Concentration
CBC	Complete Blood Count
cHL	Classical Hodgkin's lymphoma
CLL	Chronic Lymphocytic Leukemia
CR	Complete Response
CrCl	Creatinine Clearance
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T cell Lymphoma
CYP	Cytochrome P450
DLBCL	Diffuse Large B Cell Lymphoma
ECG	Electrocardiogram
CRF	Case Report Form
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
FSH	Follicular Stimulating Hormone
GCP	Good Clinical Practices
Hb	Hemoglobin
HDPE	High-density Polyethylene
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
LMWH	Low Molecular Weight Heparin
ORR	Objective Response Rate
pAKT	PhosphoAKT
PCP	Pneumocystis Carinii Pneumonia
PET	Positron Emission Tomography
PTCL	Peripheral T cell Lymphoma
PI	Principle Investigator
PI3K	Phosphoinositide-3-Kinase
PR	Partial Response
SAE	Serious Adverse Events
SD	Stable Disease
SDV	Source Document Verification
SOC	Standard of Care

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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. Tenalisib is a highly specific and orally available dual PI3K δ/γ inhibitor with nano-molar inhibitory potency and several fold selectivity over α and β PI3K isoforms. The specificity of Tenalisib towards PI3K δ and γ is evidenced by >1000 and >100 fold selectivity over α and β isoforms in an enzyme based assay. Chemically, Tenalisib is an iso-flavone substituted adenine. Refer to Investigator's Brochure (IB) for detailed background information on Tenalisib.[1]

1.2 Summary of Clinical Evaluation

In the clinical setting, Tenalisib demonstrated a promising single agent activity with objective response rate (ORR) of 19.4 % (CR: 6.5% and PR: 12.9 %) in patients with hematological malignancies; and 46% (CR: 8.5% and PR: 37%) in evaluable R/R TCL patients with a manageable safety profile.[1] Below is the summary of clinical studies of Tenalisib.

1. A Phase I Dose Escalation Study Evaluating the Safety and Efficacy of RP6530, a dual PI3K δ/γ inhibitor, in Patients with Relapsed or Refractory Hematologic Malignancies (Protocol Number RP6530-1301) Status: **Completed**
2. A Phase I/Ib, Dose Escalation Study to Evaluate Safety and Efficacy of RP6530, a dual PI3K δ/γ inhibitor, in Patients with Relapsed or Refractory T-cell Lymphoma (Protocol number RP6530-1401). Status: **Completed**
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 (Protocol no: RP6530-1501). Status: **Completed**
4. An Open label, Phase I/II study to evaluate the safety and efficacy of RP6530, a novel PI3K δ/γ dual inhibitor given in combination with an anti-PD-1 therapy, Pembrolizumab in adult patients with relapsed or refractory Classical Hodgkin's lymphoma (cHL). (Protocol Number: RP6530+Pembrolizumab-1701). Status: **Terminated.**
5. An Open label, Phase II study to evaluate the efficacy and safety of Tenalisib (RP6530), a novel PI3K δ/γ dual inhibitor in adult patients with relapsed/refractory indolent Non-Hodgkin's Lymphoma (iNHL). (Protocol number: RP6530-1802). Status: **Ongoing.**
6. An Open label, Phase I/II study to evaluate the safety and efficacy of Tenalisib (RP6530), a novel PI3K δ/γ dual inhibitor given in combination with a histone deacetylase (HDAC) inhibitor, Romidepsin in adult patients with relapsed/refractory T-cell Lymphoma. (Protocol number: RP6530+Romidepsin-1805). Status: **Ongoing.**
7. A Phase 2, Open label Study to Assess the Efficacy and Safety of Tenalisib (RP6530), a Novel PI3K Dual δ/γ Inhibitor, in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL) (Protocol number: RP6530-1901). Status: **Planned.**

1.3 Study Rationale

Compassionate use provides an important avenue for patients with life-threatening conditions to gain access to unapproved investigational drugs, biologics and medical devices.[2] Currently, Tenalisib is being evaluated as an investigational new drug in number of early clinical studies in patients with relapsed/refractory hematological malignancies. Tenalisib demonstrated acceptable safety and promising efficacy in these patients.

Since these advanced relapsed/refractory patients have limited therapeutic options, it is reasonable to continue Tenalisib in responding patients post completion of their participation in previous (original) clinical studies. It is anticipated that Tenalisib would not expose patients to an unreasonable and significant risk or injury. Therefore, this trial is designed to offer patients benefitted by Tenalisib and who completed previous study without progression an opportunity to continue Tenalisib as compassionate medication and followed up on treatment for safety and disease progression.

1.4 Benefit and Risk

It is anticipated that Tenalisib would not expose patients to an unreasonable and significant risk or injury. 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

- To evaluate the safety and tolerability of Tenalisib as single agent or in combination until the withdrawal of subject from the study due to disease progression, unacceptable toxicity or any other reason including consent withdrawal or investigator's decision.
- Time to disease progression

3 TRIAL DESIGN

3.1 Trial End Point

- Adverse Event (AE), Grade 3/ 4 AEs and Serious Adverse Event (SAE)
- Date of disease progression

3.2 Design of Trial

This is an open label, compassionate use study in patients who have completed a clinical trial of Tenalisib sponsored by Rhizen Pharmaceuticals S.A. This trial offers an opportunity to patients who have responded (either have CR, PR or SD on Tenalisib treatment) to receive Tenalisib as compassionate medication following their completion of previous study. Patients will continue to receive Tenalisib (schedule and dose) as they received in previous protocols unless dose adjustments or delays are necessary for toxicity management.

Trials evaluating Tenalisib as a single agent or in combination with other therapies will be part of this compassionate study protocol. The patients of these studies will be rolled over to compassionate use study once they complete their participation in original study.

3.3 Randomization and Blinding

This is a non-randomized, open label study.

3.4 Investigational Medicinal Product

3.4.1 Dosage form and strengths

Investigational Product	Dosage form, strength
Tenalisib	Tablets; 200 mg and 400 mg.

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

In case of roll over from the combination study, the combination agent (e.g. romidepsin) will be administered as part of SOC and will not be supplied/provided by Rhizen Pharmaceuticals SA.

3.4.2 Labeling, packaging and supply

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

3.4.3 Preparation and administration of Investigational Products

At each visit, patients will be dispensed sufficient quantity of Tenalisib until the next visit. Study drug compliance will be reviewed with the patient at the beginning of cycle. Study drug compliance will be documented, including missed doses.

Guidelines 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 will be given outside of protocol requirements. However, these medications may be administered for treatment of symptoms/adverse events.
- 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. ***Please note, patients will continue to receive the same dose they were receiving in previous protocols. (e.g. If patient is receiving Tenalisib 400 mg BID while rolling over, he/she will continue to receive 400 mg BID dose in compassionate study protocol).***
- 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 with the patient at the beginning of cycle. Missed doses should be documented.

3.4.4 Accountability of Investigational Products

The PI/ designee is responsible for accountability of all trial drug supplies (used/unused) at the site. The study monitor will verify receipt of investigational product at the site 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 after sponsor approval. Certificate(s) of destructions must be filed at the site and in Trial Master File.

3.4.5 Precautions and Risks associated with Investigational Product

- 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/drug reaction, 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 is 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.

3.5 The Expected Duration of Subject Participation and Follow-up

The expected duration of subject participation in the study is variable. Participation in the study will be continued until withdrawal of the subject from the study due to disease progression, unacceptable toxicity or any other reason including consent withdrawal by patient or investigator's decision.

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 IRBs 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 inclusion criteria to be eligible for participation in this study:

1. Patients must be currently receiving treatment with Tenalisib either as monotherapy or in combination with another agent on a previously approved protocol for hematological malignancies including but not limited to indications DLBCL, iNHL, PTCL, CTCL, CLL and HL.
2. Patients must have had at least one efficacy evaluation following the initiation of Tenalisib in previous study and should have achieved either SD, PR or CR.
3. Patients must have completed at least 6 cycles of Tenalisib in previous study
4. Ability to swallow and retain oral medication.
5. Female patients of child-bearing potential must consent to use two medically acceptable 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.
6. Male patients must be willing to use adequate contraceptive measures throughout the study period and for 12 weeks after the last dose of Tenalisib.
7. Willingness and ability to comply with trial and follow-up procedures.
8. Willingness to provide new written informed consent.

4.2 Exclusion Criteria

Patients must meet none of the following exclusion criteria to be eligible for participation in this study:

1. Patient has been discontinued from their previous Tenalisib study 4 weeks prior to entering the compassionate use trial.
2. Patient progressed while receiving Tenalisib therapy in his/her previous study.
3. Pregnant or lactating woman.
4. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol.
5. 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 v4.0 Grade 3/4 non-hematological toxicity related to study drug that necessitate withdrawal in the opinion of investigator.
- Development of an intercurrent illness, condition or procedural complication, which could interfere with the patient’s continued participation.
- Voluntary patient withdrawal from study treatment (all patients are free to withdraw from participation in this study at any time, for any reasons, specified or unspecified, and without prejudice).
- Any other situation where, in the opinion of the investigator, continued participation in the study would not be in the best interest of the patient

- Confirmed disease progression

5 TREATMENT OF SUBJECTS

5.1 Administration of Study drugs

Patients showing clinical benefits (have achieved either SD, PR or CR) will continue to receive Tenalisib as they were receiving in previous protocols. The treatment plan will be the same dosing schedule unless dose adjustments or delays are necessary for toxicity management.

In case of roll over from a combination study, the investigator has a choice to continue with the combination therapy or to maintain the patient on Tenalisib monotherapy. If combination agent is continued, it will be administered as a part of SOC.

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 or at the discretion of the investigator.
- Transfusions (blood/platelets) may be given, based on standard criteria and clinical judgment.
- Patient may receive prophylactic anti-emetics at the discretion of the investigator if required for a combination agent.
- Patient may receive prophylactic allopurinol, in case risk of tumor lysis syndrome.
- Low doses of steroids are allowed if it stabilized at < 20 mg per day of prednisone or equivalent.
- 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. Refer prohibited medication section **[Sec 5.3].** Use of heparin or warfarin for prophylaxis and treatment of venous thrombosis is prohibited. Low molecular weight heparin (LMWH) is acceptable.
- 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 compassionate study protocol:

- 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. Patients should stop using these medications at least 7 days prior to C1D1.
- **Strong inhibitors or inducers of CYP2C9** including herbal medications. 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). Patients should stop using these medications at least 7 days prior to C1D1.
- 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 by case basis, after reviewing ongoing clinical benefit and risk. The decision to allow a patient to continue will be documented.

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 study center at their next visit. Site 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 patient.

6 TRIAL ASSESSMENT AND PROCEDURE

6.1 Overview

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

1. Screening (Day -14 to Day C1D1)
2. On treatment procedures (C1D1 to EOT)
3. End of Treatment (EOT)
4. End of Study (EOS) (Day +30 from last dose)

6.2 Screening Procedure

6.2.1 Informed Consent

The investigator/qualified designee must obtain written informed consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial. Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on an IRB/IEC approved consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the trial.

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

6.2.2 Enrollment of patient

During the screening period, the investigator/designee will complete the patient enrollment form and submit to the Sponsor for review and approval prior to enrolling the patient in the study.

6.2.3 Screening Procedure

Medical history, ECOG status and weight will be taken. Information on prior medication use, prior therapies including Tenalisib treatment will also be obtained to confirm eligibility of the patient.

6.3 Treatment and Study Procedures

Patients will visit the study center every three months until documented disease progression or treatment discontinuation due to toxicity or consent withdrawal. During these visits, Tenalisib will be dispensed and medication compliance will be monitored. Safety and efficacy assessments will be done as mentioned below.

- **Safety assessments:**
  - Safety assessment will be done during the visits and AEs will be reported as required by the protocol.
  - Concomitant medications may be administered as clinically indicated.
  - A medication history should be reviewed at each clinic visit to assure no potential adverse events are noted.
  - There are no specific safety labs or evaluations (including vitals, physical examinations, pregnancy tests and ECGs) required as per protocol. As part of SOC, laboratory tests or other evaluations can be done per Investigator's discretion. Adverse events (AEs, SAEs and deaths) will be recorded and reported for 30 calendar days after last dose or until a new anti-cancer treatment is initiated, whichever is earlier. After this period, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.
- **Efficacy assessments:**
  - Disease assessments [e.g. radiological imaging (e.g. CT, PET-CT) or any other appropriate evaluation tool (e.g. mSWAT in case of skin involvement)] should be performed as part of SOC. These evaluations (e.g. measurement of lymph node, mSWAT) will not be recorded in the CRF, however, date of disease progression will be reported .
- **Drug dispensing:**
  - Patients will be given drug supply for 3 months.

Table 1: Schedule of Events						
	Screening and Eligibility	**Cycle 1**	**Cycle 4**	**Cycle 7 Through EOT**	**EOT**	**EOS[11]**
Day	**D-14 to D1**	D1	D1	D1	-	-
Window period	**-14**	-	±7	±7	-	+30
Study Days	**D-14 to D1**	1[1]	85	169	-	-
Informed Consent	X	-	-	-	-	-
Eligibility Confirmation	X	-	-	-	-	-
Demographics[2]	X	-	-	-	-	-
Medical history[3]	X	-	-	-	-	-
Vitals	-	SOC*	SOC*	SOC*	SOC*	-
Weight[4]	X	SOC*	SOC*	SOC*	SOC*	-
Physical exam	-	SOC*	SOC*	SOC*	SOC*	-
ECOG Performance	X	SOC*	SOC*	SOC*	SOC*	-
Complete blood count	-	SOC*	SOC*	SOC*	SOC*	-
Chemistry	-	SOC*	SOC*	SOC*	SOC*	-
PT/INR	-	SOC*	SOC*	SOC*	SOC*	-
Urinalysis (routine)	-	SOC*	SOC*	SOC*	SOC*	-
Pregnancy test[4]	-	SOC*	SOC*	SOC*	SOC*	-
12-lead ECGs	-	SOC*	SOC*	SOC*	SOC*	-
Disease assessment[5]	-	SOC*	SOC*	SOC*	SOC*	-
Date of discontinuation[6]	-	-	-	-	X	-
Drug Dispensing[7]	-	X	X	X	-	-
Tenalisib treatment[8]	-	X	X	X	-	-
Drug compliance	-	-	X	X	X	-
AE evaluation[9]	X	X	X	X	X	X
SAE evaluation[10]	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X

Note: *There are no specific safety labs or evaluations (including vitals, physical examinations, pregnancy tests, ECGs and radiological evaluation/mSWAT scoring) required as per protocol. As part Standard of care (SOC), laboratory tests or any evaluations can be done per Investigator's discretion.

Foot notes:

1. Depending on the feasibility, screening/eligibility assessment and dispensing of the study drug can be done on same day. Assessment performed in previous study (e.g. Medical history, vital signs demographics, Weigh and ECOG) can be used for eligibility evaluation. The first day of Tenalisib administration will be considered as C1D1
2. Demographic profile will include age, sex and race.
3. Medical history will include history of cancer, past history of Tenalisib, no of prior therapies and prior medication (last 4 weeks); and other medical history. Any medical significant history at subsequent visit will be captured as adverse event.
4. Applicable only for women of child-bearing potential.
5. Disease assessment may include evaluation of disease condition by radiological imaging (e.g. CT, PET, PET-CT or MRI) or by any other appropriate evaluation tool depending on the disease condition (e.g. mSWAT in case of skin involvement, bone marrow biopsy in case of marrow involvement). Disease evaluation will be performed at the discretion of study investigator.
6. The day of the last dose of study drug will be considered as EOT.
7. Tenalisib will be dispensed in a HDPE container having 30 tablets of Tenalisib. A 3-month supply of study drug will be dispensed at each visit. In case of roll over from the combination study, the combination agent (e.g.

romidepsin) will be administered as part of SOC and will not be supplied/provided by Rhizen Pharmaceuticals S.A.

8. Patients showing clinical benefit (have achieved either SD, PR or CR) will continue to receive Tenalisib as they are currently receiving in previous protocols. The treatment plan will be the same dosing schedule unless dose adjustments or delays are necessary for toxicity management.
   In case of roll over from a combination study, the investigator has a choice to continue with the combination therapy or to maintain the patient on Tenalisib monotherapy. If combination agent is continued, it will be administered as a part of SOC.
9. All AEs should be recorded spanning from the informed consent drug until 30 calendar days after the last dose of study drug or till new anti-cancer treatment is initiated whichever is earlier.
10. All events that meet the definition of serious but, in the opinion of the treating investigator, are clearly expected from the Patient's disease or related to disease progression (i.e. there exists no reasonable possibility that they were caused by the study drug) should be reported on the case report forms and do not require expedited reporting. In addition, 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.
11. Patients should be followed for AEs for 30 calendar days after the last dose of study treatment or till new anti-cancer treatment is initiated whichever is earlier. 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.

6.4 End of Trial Treatment (EOT)

The day of the last dose of study drug will be considered as EOT. Reason of discontinuation should be recorded.

6.5 End of Study (EOS)

All patients will be followed for adverse events until 30 calendar days after the last dose of study drug or until new anti-cancer treatment is initiated whichever is earlier. 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 until resolution or stabilization of related adverse event.

7 ASSESSMENT OF SAFETY

7.1 Adverse Events

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.

7.1.2 Recording of adverse events

All adverse events should be graded as per the CTCAE v5.0. and should be recorded in the case report form. 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 or till new anti-cancer treatment is initiated whichever is earlier. 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. 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

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

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, is a congenital anomaly/birth defect or an important medical event.

All events that meet the definition of serious but, in the opinion of the treating investigator, are clearly expected from the Patient's disease or related to disease progression (i.e. there exists no reasonable possibility that they were caused by the study drug) should be reported on the case report forms and do not require expedited reporting. In addition, 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

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 dose of study drug. 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. The SAE report should be sent to the sponsor/sponsor representative **via e-mail.** 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. 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 fax/mail 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.

7.3.4 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

Pregnancy, abortion, birth defects, and congenital anomalies are events of special interest. Please refer to pregnancy *section 7.4.1* for specific instructions.

7.4 Protocol-Defined Events of Special Interest

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

7.4.1 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

Female patients of child-bearing potential (see ***Appendix A*****)** must consent to use two medically acceptable method of contraception throughout the study period and for 4 weeks after the last dose of Tenalisib.

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 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 mailed to the Sponsor. The outcome of the pregnancy will be monitored as outlined in ***Appendix A***.

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.

7.4.2 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 twice a day).

Symptomatic and non-symptomatic overdose must be recorded in the CRF. Any accidental or intentional overdose with the trial treatment that is symptomatic, and 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.

7.5 Dose Modifications

The dose modification should be performed for the drug toxicity or underlying disease conditions. Guidelines (Refer Table 2 and 3) are intended to be applied when the investigator determines the event related to Tenalisib. Please note the dose modifications provided below should be used as a guidance and should be determined as per PI's clinical judgement.

Patients may resume Tenalisib, provided that the toxicity has resolved to Grade ≤2 or baseline and there is no clinical or radiographic evidence of disease progression. If study drug is delayed >2 weeks because of an adverse event, strategy of re-initiation of study drug should be discussed with 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.

Table 2: Dose Modifications for Hematologic Toxicity

Worst CTCAE Grade Toxicity	Action to be Taken
HEMATOLOGIC	
Neutropenia (ANC)	
Grade 3 1.0 X 10^9/L<ANC ≥ 0.5 X 10^9 /L	Maintain dose level. Monitor ANC at least weekly.
Grade 4 0.5 x 10^9 /L<ANC	**First incidence**: Withhold* dose until resolved to ≤ Grade 2 or baseline. Monitor ANC at least weekly. Resume treatment at the same dose level. **Subsequent occurrence**: Hold dose until resolved to ≤ Grade 2 or baseline. Consider growth factor support. Resume treatment at the reduced dose level (Tenalisib 400 mg BID) if warranted.
Grade 3 Febrile neutropenia ANC <1000/mm3 with a single temperature of > 38.3 ^{0}C (101^{0}F)	Withhold* dose until resolved to ≤ Grade 2 or baseline, consider growth factor support, then reduce by 1 dose level (Tenalisib 400 mg BID), if

or a sustained temperature of ≥ 38 ^{0}C (100.4 ^{0}F) for more than one hour.	warranted. If the ANC is <1 X 10^9/L (1000/µL) before therapy, the dose shall not be modified as long as ANC >0.5 X 10^9/L.
Thrombocytopenia	
Grade 3 thrombocytopenia with Grade 1 bleeding	Maintain Tenalisib dose. Monitor platelet count at least weekly.
Grade 3 thrombocytopenia with Grade 2 bleeding OR Grade 4 thrombocytopenia (20.0 X 10^9/L< PLT)	**1st occurrence**: Withhold** dose until to ≤ Grade 2 or baseline or resolution of bleeding. Consider platelet transfusion as necessary. Resume treatment at the same dose level. **Subsequent Occurrences**: Withhold dose until to ≤ Grade 2 or baseline or resolution of bleeding. Consider platelet transfusion as necessary. Resume treatment at the reduced dose level (Tenalisib 400 mg BID) if warranted. Doses should not be modified if Grade 4 thrombocytopenia is present at baseline.

* The treatment should be permanently discontinued if withhold of study drug due to drug related toxicity is for > 28-days unless approved by medical monitor.
** Patient receiving concomitant medication (e.g. anti-platelets, aspirin, or low molecular weight heparin) should be discussed with the medical monitor for further management.

Table 3: Dose Modifications for Non-Hematologic Toxicities

NON-HEMATOLOGIC	Action to be Taken
Hepatic*	**Transaminitis** **Grade 1-2 Transaminitis (**ALT/AST >1-3 x ULN if baseline is normal; 1.5 - 3 x baseline if baseline is abnormal)**:** • Maintain Tenalisib dose and initiate **prednisone 40 mg daily**. • Monitor AST/ALT weekly until resolved and then taper steroid. • Withhold Tenalisib in case of development of grade 2 transaminitis or worsening of Grade 1 transaminitis while on steroids. **Grade 3 Transaminitis (**ALT/AST >5–20 x ULN; >5-20 x baseline if baseline is abnormal)**:** • Withhold Tenalisib and monitor ALT/AST twice a weekly until Grade ≤1; restart Tenalisib at one dose lower (Tenalisib 400 mg BID). • Initiate **prednisone 1 mg/kg** in case no improvement after withholding Tenalisib for 1 week. • Monitor ALT/AST twice a weekly until Grade ≤1; restart Tenalisib at one dose lower (Tenalisib 400 mg BID). and taper steroid. • If no immediate response to steroids within 7 days, initiate mycophenolate mofetil. • In case of recurrence of transaminitis at reduced doses, discontinue Tenalisib permanently after assessing risk versus benefit. **Grade 4 Transaminitis (**ALT/AST >20 x ULN; >20 x baseline if baseline is abnormal)**:** • Tenalisib should be permanently discontinued. **Bilirubin:** • **Grade 2** (> 1.5-3 x ULN; >1.5- 3 x baseline if baseline is abnormal): Maintain Tenalisib dose. Monitor at least weekly until ≤ 1x ULN

	• **Grade 3** (> 3-10 x ULN; >3 - 10 x baseline if baseline is abnormal): Withhold Tenalisib. Monitor at least weekly until bilirubin is≤ 1x ULN; Restart Tenalisib at one dose lower (Tenalisib 400 mg BID). • **Grade 4** (> 10 x ULN; >10 x baseline if baseline is abnormal): Discontinue Tenalisib permanently
Infection	**Grade 3 or higher sepsis or pneumonia** • Withhold Tenalisib until infection has resolved. • Restart at the same or at the reduced dose (Tenalisib 400 mg BID)
Skin rash **(Cutaneous reactions)**	**Grade 1-2** • Maintain Tenalisib dose. Initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids • Monitor closely until resolved. **Grade 3** • Withhold Tenalisib dose. Initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids • Monitor at least weekly until resolved. • Restart Tenalisib at the reduced dose level (Tenalisib 400 mg BID). • If severe cutaneous reaction does not improve, worsens, or recurs, discontinue Tenalisib **Life threatening or SJS, TEN, DRESS (any grade)** • Discontinue Tenalisib permanently.
Pneumonitis without suspected infectious cause	**Moderate (Grade 2) symptomatic pneumonitis** • Withhold Tenalisib dose. Initiate systemic steroid therapy. If pneumonitis recovers to Grade 0 or 1, Tenalisib may be resumed at reduced dose. • If non-infectious pneumonitis recurs or patient does not respond to steroid therapy, discontinue Tenalisib. **Severe (Grade 3) or life-threatening pneumonitis** Discontinue Tenalisib. Treat with systemic steroid therapy.
Non-infectious Diarrhea	**Moderate diarrhea and responsive to antidiarrheal agents:** • Maintain Tenalisib dose. Monitor at least weekly until resolved. **Moderate diarrhea and unresponsive to antidiarrheal agents:** • Withhold Tenalisib dose. Initiate supportive therapy with enteric acting steroids (e.g., budesonide). • Monitor at least weekly until resolved. • Restart Tenalisib at the reduced dose level (Tenalisib 400 mg BID). **Severe diarrhea or hospitalization** • Withhold Tenalisib dose. Initiate supportive therapy with enteric acting steroids (e.g., budesonide) or systemic steroids. • Monitor at least weekly until resolved. • Restart Tenalisib at the reduced dose level (Tenalisib 400 mg BID). **Life threatening diarrhoea** • Discontinue Tenalisib permanently. •
Cardiac	If a QTcF >500 msec has been demonstrated, hold dose.

	The patient will be closely monitored until the QTcF <500 msec and the QTcF has returned to <30 msec from baseline. Immediate attention to potassium and magnesium and other clinical factors such as oxygenation and ischemia should be addressed. All cardiac events should be treated as per the local standard of care and referral to a specialist if clinically indicated. Any final decisions concerning dose modifications or permanently discontinuing the patient from study drug due to QTcF prolongation will occur after discussion with medical monitor.
OTHER NON-HEMATOLOGIC	**Action to be Taken**
Grade 1 or 2	None
Grade 3	Withhold Tenalisib dose until toxicity Grade ≤2. Restart Tenalisib at one dose lower (Tenalisib 400 mg BID) if warranted.
Recurrence of grade 3 toxicity	Withhold Tenalisib dose until toxicity Grade ≤2; Restart Tenalisib at one dose lower or discontinue treatment
Grade 4	Withhold Tenalisib dose until toxicity Grade ≤2; Restart Tenalisib at one dose lower (Tenalisib 400 mg BID) or discontinue Tenalisib
Recurrence of grade 4 toxicity	Discontinue Tenalisib

*The treatment should be permanently discontinued if withhold of study drug due to drug related toxicity is for > 28-days unless approved by medical monitor.

8 ASSESSMENT OF EFFICACY

Efficacy evaluations will be performed at the physician's discretion as part of standard of care (SOC). These evaluations (e.g. measurement of lymph node, mSWAT) will not be reported in CRF, however the date of disease progression will be reported.

9 STATISTICAL METHOD AND CONSIDERATIONS

The primary purpose of this study is to offer patients who completed a Rhizen sponsored clinical study without progression the opportunity to continue to receive Tenalisib on a compassion basis. The safety and progression status will be summarized as appropriate. No formal sample is determined for this study and final sample size will depend on the number of patients who benefitted and completed the Tenalisib study.

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 any other local applicable regulatory requirement(s).

All potential serious breaches must be reported to Rhizen 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 documents (e.g, protocol, ICF, IB, available safety information, patient documents, patient recruitment procedures, 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.

10.2 Regulatory Approval

As required by local regulations, Rhizen will ensure 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.

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/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

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 US FDA 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, 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- only a unique trial number and initials will identify patients on CRF, or other documents 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. Therefore, absolute confidentiality cannot be guaranteed.

10.6.2 Investigator's responsibilities

Medical supervision is the responsibility of the Principal Investigator named on the FDA Form 1572. 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 (FDA), sound medical practices, and in compliance with applicable regulations (21 CFR, ICH).

10.6.3 Investigator and Staff training

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

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. The written amendment must be submitted and approved by the IRB/IEC.

11.2 Protocol Deviations

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

11.3 Documentation Required to Initiate Trial

Before the trial may begin, documentation required by US FDA will be provided by the Sponsor. At minimum, documents required to begin a trial in the US include, but are not limited to: a signed protocol acceptance page, and contract; a copy of the official IRB/IEC approval of the trial and the IRB/IEC membership list; current Curricula Vita for the Principal Investigator and any sub-investigator 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; completed signed Form FDA 1572 (Statement of Investigator), 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 site staff are responsible for maintaining a comprehensive and centralized filing system (Site Trial File/SSF or Investigator Site File (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, IRB/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 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; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA 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

Data will be captured via Case Record Form (CRF). 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. The Principal Investigator will sign and date each CRF 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 verifying 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. Monitoring will be done in the form of on-site visits, remote monitoring and other communication and will include review of original source documents and CRFs. 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 or its representatives and government regulatory authorities 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.

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 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.

14 REFERENCES

1. Tenalisib (RP6530) Investigator's brochure. Version 10. Dated 15 October 2019.
2. Expanded Access (Compassionate Use). https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm#Expanded_Access_to_Investigational_Drugs_and_Biologics. Accessed on 23 March 2018

15 APPENDICES

Appendix A: 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

Fertile Males

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

STATISTICAL ANALYSIS PLAN

PROTOCOL NO. RP6530-1803

An Open label, Compassionate Use Study of Tenalisib (RP6530) in Patients currently receiving treatment on Tenalisib trials in Hematological Malignancies

1 STATISTICAL METHOD AND CONSIDERATIONS

The primary purpose of this study is to offer patients who completed a Rhizen sponsored clinical study without progression the opportunity to continue to receive Tenalisib on a compassion basis. The safety and progression status will be summarized as appropriate. No formal sample is determined for this study and final sample size will depend on the number of patients who benefitted and completed the Tenalisib study.

2 DISPOSITION OF PATIENTS

A tabular presentation of the patient disposition will be provided by type of cancer and previous study protocol and dose of tenalisib. All patients' data will be used for this analysis.

3 ASSESSMENT OF EFFICACY

3.1 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.

All adverse events should be graded as per the CTCAE v5.0. and should be recorded in the case report form. 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 or till new anti-cancer treatment is initiated whichever is earlier. 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. 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.

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.

3.2 Serious Adverse Events

- Definitions of serious adverse events

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, is a congenital anomaly/birth defect or an important medical event.

All events that meet the definition of serious but, in the opinion of the treating investigator, are clearly expected from the Patient's disease or related to disease progression (i.e. there exists no reasonable possibility that they were caused by the study drug) should be reported on the case report forms and do not require expedited reporting. In addition, 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.

3.3 Protocol-Defined Events of Special Interest

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

- Pregnancy, Abortion, Birth Defects/Congenital Anomalies

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.

- 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 twice a day).

The safety endpoints will include:

- Incidence of AEs and related AEs
- Incidence of grade 3, grade 4 and grade 5 AEs
- Incidence of SAEs and deaths

The analyses of safety will be based on the frequency of adverse events for patients who received at least one dose of study treatment.

4 ASSESSMENT OF EFFICACY

Efficacy evaluations will be performed at the physician's discretion as part of standard of care (SOC). These evaluations (e.g. measurement of lymph node, mSWAT) will not be reported in CRF, however, the date of disease progression will be reported.

The duration of disease progression will be calculated for patients who received at least one dose of study treatment.