PROTOCOL NO. RP6530-1901

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
TRIAL DRUG	Tenalisib (RP6530)
SPONSOR	[redacted]
SPONSOR'S MEDICAL EXPERT	[redacted]
DOCUMENT VERSION	Final, Version 1.0, Dated 12 September 2019

Clinical Trial Protocol Statement of Compliance

This clinical trial shall be conducted in compliance with the protocol, and all applicable local, and international regulatory requirements including 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)
- European Commission - Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C 172/01)
- As the principal investigator (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.
- As the Clinical Research Organization (CRO) Representative, I agree and accept the contracted sponsor responsibilities as defined by the protocol, applicable clinical trial agreements (CTA), and/or business contracts. Additionally, I agree that any changes to the protocol, CTA, or contracts shall be implemented with the Sponsor's review and approval prior to implementation.
- As the Sponsor Representative, I understand that my signature constitutes agreement and understanding of acceptance of the defined and contracted sponsor responsibilities to the CRO as defined by the protocol, applicable clinical trial agreements (CTA), and/or business contracts, but does not in any capacity relieve me of my responsibilities as the Sponsor. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol, CTA, or contracts shall be implemented timely with my review and approval prior to implementation.

Protocol Approval Page

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
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[redacted]

[redacted]

Sponsor's Medical Expert **Signature** **Date**

[redacted]

Sponsor's Representative **Signature** **Date**

[redacted]

Bio-statistician **Signature** **Date**

Protocol Acceptance Page

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
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DOCUMENT VERSION	1.0, Dated 12 September 2019

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

PROTOCOL SYNOPSIS

Study Title	**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
Study Sponsor	Rhizen Pharmaceuticals S.A.
Study Sites	Approximately 10-15 sites.
Study Objectives	**Primary objective:** • To assess the anti-tumor activity of Tenalisib as determined by the objective response rate (ORR) and duration of response (DoR) **Secondary objectives:** • To characterize safety and tolerability of Tenalisib. • To assess progression free survival (PFS)
End points	**Efficacy:** • Overall response rate (ORR): ORR is defined as sum of complete response (CR) and partial response (PR) rates as defined by iwCLL guideline for CLL (Hallek *et al.* 2018). • Duration of response (DoR): DoR is defined as the interval from the first documentation of CR/PR to first documentation of definitive disease progression or death from any cause. • Progression-free survival (PFS): PFS is defined as the interval from first dose to first documentation of definitive disease progression or death from any cause. **Safety:** • Adverse Event (AE), Grade 3/ 4 AEs, Serious Adverse Event (SAE).
Study Design and procedure	The trial is a Phase II, open label, Simon's two stage study design to evaluate the efficacy and safety of Tenalisib in 61 patients with CLL who have relapsed or are refractory after at least one prior therapy. In stage 1, 20 patients will be enrolled. If eight or fewer responders are observed at this stage, the study will be terminated. Else, 41 additional patients will be enrolled into stage 2. The study treatment Tenalisib (800 mg BID) will be administered orally in 28-days of cycle over a period of 7 months (C1D1 to C8D1) in absence of definitive disease progression or unacceptable toxicity. The study will end when all ongoing subjects have reached their third tumor assessment on Cycle 8/Day 1 (C8D1) or have discontinued from the study for any reason, whichever is earlier. At the end of the study, all ongoing patients with no evident disease progression will be given an opportunity to enroll in an open-label compassionate medication use study [Protocol:RP6530-1803; NCT03711604] and will be followed up. The detailed study procedure is presented in Study assessment and Treatment schedule **(Table 1).** Anti-infective prophylaxis (e.g.

	for herpes simplex virus (HSV), pneumocyctis *Jirovecii* pneumonia (PJP), hepatitis B virus (HBV), cytomegalovirus (CMV) are recommeded and will be given at the discretion of study investigator. All safety laboratory assessments, electrocardiogram (ECG) and radiological assessments (e.g. CT) will be performed at the respective sites.
Number of patients	Approximately 61 patients with relapsed/refractory CLL will be enrolled.
Eligibility Criteria	***Patients must meet all the following inclusion criteria to be eligible for participation in this study:*** 1. Patients with diagnosis of B-cell CLL as confirmed by histopathology or flow cytometry. 2. Disease status defined as refractory to or relapsed after at least one prior therapy. 3. Presence of measurable lymphadenopathy, defined as the presence of ≥ 1 nodal lesion that measures ≥ 1.5 cm in the longest diameter (LD) as assessed by computed tomography (CT). 4. ECOG performance status ≤ 2. 5. Male or female ≥ 18 years of age. 6. Life expectancy of at least 3 months. 7. Adequate bone marrow (BM), liver, and renal function as assessed by the following laboratory requirements conducted within 14 calendar days before starting study treatment. a. Adequate bone marrow function. I. Haemoglobin ≥ 9 g/dl II. Absolute neutrophil count (ANC) ≥ 1 x 10^9/L III. Platelets ≥50 x 10^9/L Patients with hemoglobin, neutrophil and platelet counts below the above specified values will be eligible if it is due to tumor dissemination or infiltration to bone marrow and as per physician's discretion. Hemoglobin and platelet requirements should not be met by use of recent transfusion or growth factor support (G-CSF or erythropoietin) within 3 weeks prior to assessment. b. Adequate liver function. I. Total bilirubin ≤1.5 times the upper limit of normal (ULN) II. ALT and AST should be ≤ 3 x ULN. ALT and AST ≤ 5 x ULN if known liver involvement. c. Adequate renal function: Calculated creatinine clearance ≥ 50 mL/min (as calculated by the Cockcroft-Gault method) or Creatinine ≤ 1.5 mg/dl. 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 should have a negative serum pregnancy test within 3 days prior to Cycle 1 Day 1 (C1D1). Female patients of child-bearing potential must consent to use a medically acceptable method of contraception as defined in ***Appendix A*** , throughout the study period and for 30 days after the last dose of study drug.

	10. Male patients willing to use adequate contraceptive measures throughout the study period and for 12 weeks after the last dose of Tenalisib. 11. Willingness and ability to comply with trial and follow-up procedures and give written informed consent.
Exclusion criteria	1. Patient with Richter's (large cell) transformation, or prolymphocytic leukemia (PLL) transformation. 2. Patients receiving any cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy and biologic therapy) or any cancer investigational drug within *3 weeks (21 days)* or *5 half-lives* (whichever is shorter) prior to C1D1. 3. Prior exposure to drug that specifically inhibits PI3K (e.g. idelalisib, copanlisib, duvelisib, umbralisib) 4. Patient with autologous / allogeneic stem cell transplant (ASCT/Allo-SCT) receiving treatment for active graft versus-host disease (GVHD). 5. Evidence of ongoing severe systemic bacterial, fungal or viral infection as assessed by the investigator. 6. Central nervous system (CNS) involvement of leukemia or lymphoma 7. Ongoing immunosuppressive therapy including systemic corticosteroids except as allowed per concomitant medication (***Section 5.2***). 8. Known history of severe liver injury including drug-induced liver injury (e.g. alcoholic liver disease, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver or portal hypertension) as judged by investigator; 9. Any severe and/or uncontrolled medical conditions or other conditions that could affect patient participation in the study, as judged by investigator, such as: a. Symptomatic or history of documented congestive heart failure (New York heart association (NYHA) functional classification III-IV) b. Myocardial infarction within 6 months of C1D1 c. QTcF >470 msec. d. Angina not well-controlled by medication. e. Poorly controlled atherosclerotic vascular disease (e.g. cerebrovascular accident, transient ischemic attack, angioplasty, cardiac/vascular stenting). 10. Patient treated for other malignancy in last 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; and localized prostate cancer with PSA <1.0 mg/dL within 4 weeks of C1D1. 11. Women who are pregnant or lactating. 12. Known seropositive requiring anti-viral therapy for human immunodeficiency virus (HIV) infection. 13. Known seropositive requiring anti-viral therapy for hepatitis B virus (HBV) infection OR evidence of active hepatitis B infection as defined by detectable viral load if the antibody tests are positive. [Note: Subject with

	a positive HBcAb with an undetectable/negative hepatitis B DNA test (e.g., polymerase chain reaction [PCR] test) can be enrolled]. 14. Known seropositive requiring anti-viral therapy for hepatitis c virus (HCV) infection OR patients with positive hepatitis C virus Ab with detectable viral load. [Note: Subject with a positive HCV with an undetectable/negative hepatitis C RNA test (e.g., PCR) can be enrolled]. 15. Known seropositive requiring anti-viral therapy for active CMV infection (Note: A serology positive CMV subject with negative CMV PCR test will be enrolled). 16. Unresolved NCI-CTCAE grade 2 and above toxicity (except as mentioned in adequate organ function (Refer inclusion criteria #7) attributed to any prior therapy/procedure excluding alopecia. 17. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol; 18. Concurrent condition that in the investigator's opinion would jeopardize compliance with the protocol.
Concomitant medication	• Antimicrobial and/or anti-viral prophylaxis should be used according to local standard practice; PJP and herpes zoster prophylaxis is strongly recommended. CMV carriers will be monitored per institutional guidelines and/or will be given anti-CMV therapy (e.g., ganciclovir, valganciclovir). Similarly, chronic carriers of HBV should receive prophylactic anti-viral therapy. • 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 administered at dose ≤ 20 mg per day of prednisone or equivalent. The dose should be stabilized for at least 1 week or *5 half-lives* (whichever is shorter) prior to C1D1. • Patients are permitted to use of topical, ocular, intra-articular, intranasal, and inhaled corticosteroids (with minimal systemic absorption). • 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. • Low molecular weight heparin (LMWH), Dabigatran or Edoxaban is acceptable for prophylaxis and/or treatment of venous thrombosis.
Prohibited medication	The following treatments are prohibited while on the clinical trial: • Any other anti-leukemia/lymphoma therapy

	• Herbal medications. Patients should stop using herbal medications at least 7 days prior to C1D1. • Strong inhibitors or inducers of CYP3A4. Patients should stop using these medications at least 7 days or 5 half-lives (whichever is shorter) prior to C1D1. • Strong inhibitors or inducers of CYP2C9. Patients should stop using these medications at least 7 days or 5 half-lives (whichever is shorter) prior to C1D1. • Substrates of CYP3A4 enzyme with a narrow therapeutic range. Patients should stop using these medications at least 7 days or 5 half-lives (whichever is shorter) prior to C1D1. • Use of heparin, warfarin, apixaban or rivaroxaban for prophylaxis and/or treatment of venous thrombosis is prohibited. These drugs should be stopped at least 7 days or 5 half-lives (whichever is shorter) prior to C1D1. • Live attenuated vaccine (e.g. Flu vaccine, pneumovax, varicella) • Steroids > 20 mg unless it is required for management of toxicity (e.g., transaminitis) during the study.
Estimated Study duration	Approximately 10-12 months for patient accrual plus 7.5 months of treatment and follow up. Estimated clinical duration is about 20 months.
Response assessment	Efficacy will be evaluated by CT scan at C3D1±7 days, C5D1±7 days and C8D1±7 days or at End of the treatment (EOT) visit. The determination of response and progression will be based on iwCLL guidelines for diagnosis and treatment of CLL (Hallek *et al.* 2018). Unilateral bone marrow aspiration and/or biopsy will be performed at investigator discretion in patients for whom assessment of extent of CLL involvement and bone marrow cellularity is important in determining eligibility. However, bone marrow biopsy should be done to confirm potential CR. Radiographic and clinical tumor response as evaluated and confirmed by the site investigator (defined as PI-confirmed response) will be considered for analyses of ORR and other efficacy endpoints.
Sample size	The sample size is derived based on Simon's two stage design to achieve 90% power at alpha of 0.05 for the null hypothesis of ORR ≤ 40%, assuming 60% response rate. Up to 61 patients will be enrolled. In stage 1, 20 patients will be enrolled. If eight or fewer responders are observed in this stage, the study will be terminated without rejecting the null hypothesis. Else, 41 additional patients will be enrolled into stage 2. If 31 or more responders are observed in the study, the null hypothesis of ORR ≤ 40% will be rejected.
Statistical Analysis	Statistical methods to analyze efficacy and safety will be described in statistical analysis plan (SAP). 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 SAP that will 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.

GENERAL INFORMATION	
SPONSOR	[redacted]
SPONSOR'S REPRESENTATIVE	[redacted]
SPONSOR'S MEDICAL EXPERT	[redacted]
STATISTICIAN	[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
Auto-SCT	Autologous 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_{max}	Peak Drug Concentration
CBC	Complete Blood Count
CFR	Code of Federal Regulation
CMV	Cytomegalovirus
CLL	Chronic Lymphocytic Leukemia
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
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
DVT	Deep Vein Thrombosis
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
Hb	Hemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HEENT	Head, Eyes, Ears, Nose and Throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immune Deficiency Virus
IB	Investigator brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IRB/IEC	Institutional Review Board
IWCLL	International Workshop on CLL
IUD	Intrauterine Device
IUS	Intrauterine System
LDH	Lactate Dehydrogenase

LDL	Low-Density Lipoprotein
LLN	Lower Limit of Normal
LMWH	Low Molecular Weight Heparin
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NOAEL	No-Observed-Adverse Effect Level
NYHA	New York Heart Association
ORR	Objective Response Rate
pAKT	PhosphoAKT
PJP	Pneumocystis *Jirovecii* Pneumonia
PD	Progressive disease
PFS	Progression-Free Survival
PI	Principle Investigator
PI3K	Phosphoinositide-3-Kinase
PK	Pharmacokinetics
PP	Per-Protocol
PR	Partial Response
QA	Quality Assurance
QTcF	QTc Fredericia
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Stable Disease
SDV	Source Document Verification
SOP	Standard Operating Procedures
SUV	Standardized Uptake Value
$t_{1/2}$	Plasma Half Life
t_{max}	Time to maximum plasma concentration
TEAE	Treatment-Emergent Adverse Event
TG	Triglyceride
TID	Thrice Daily
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
USP	United States Pharmacopeia
UV	Ultra-violet
WBC	White Blood Cells
WHO	World Health Organization

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1 BACKGROUND INFORMATION

1.1 Tenalisib (RP6530)

The phosphoinositide-3-kinases (PI3Ks) are a family of enzymes involved in various cellular functions, including cell proliferation and survival, cell differentiation, intracellular trafficking and immunity [1, 2, 3]. Tenalisib is a highly specific and orally available dual PI3K δ/γ inhibitor with nano-molar inhibitory potency and several fold selectivity over α and β PI3K isoforms. The specificity of Tenalisib towards PI3K δ and γ is evidenced by >1000 and >100-fold selectivity over α and β isoforms in an enzyme-based assay. Chemically, Tenalisib is an iso-flavone substituted adenine.

1.2 Summary of pre-clinical evaluation

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

Pre-clinical experiments demonstrated that Tenalisib is highly effective at killing primary CLL cells *in vitro*. The effect appeared to be equal to the Bruton tyrosine kinase (BTK) inhibitor- ibrutinib. In fact, the calculated IC_{50} was slightly lower for Tenalisib than ibrutinib (362 nM, versus 567 nM). In comparison, the IC_{50} for Tenalisib was lower than IC_{50} for the conventional chemotherapy agents fludarabine (14.8 μM), bendamustine (382 μM), and chlorambucil (152 μM). Tenalisib also induced 50-60% reduction in chemokine induced migration of Daudi cells (*in vitro* surrogate for CLL patient B-cells), indicating the potential of the molecule in modulating tumor microenvironment [4].

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 [5].

In 28-days toxicity studies in rat and dog, once daily oral administration of Tenalisib was well tolerated. Target organ effects were observed in thyroid and liver. The no-observed-adverse-effect level (NOAEL) was 20 mg/kg/day in rat and 10 mg/kg/day in dog. Refer to Investigator's Brochure (IB) for detailed background information on Tenalisib [4].

1.3 Summary of clinical evaluation

To date, Tenalisib has been evaluated in five clinical trials. Status of the studies as follows:

1. A Phase I Dose Escalation Study Evaluating the Safety and Efficacy of RP6530, a dual PI3K δ/γ inhibitor, in Patients with Relapsed or Refractory Hematologic Malignancies (European study: Protocol Number RP6530-1301). Status: **Completed**
2. A Phase I/Ib, Dose Escalation Study to Evaluate Safety and Efficacy of RP6530, a dual PI3K δ/γ inhibitor, in Patients with Relapsed or Refractory T-cell Lymphoma (US study: Protocol number RP6530-1401). Status: **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 (Food effect study, Protocol no: RP6530-1501). Status: **Completed**

4. 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 no.: RP6530-1802). Status: **Ongoing**
5. 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 no.: RP6530+Romidepsin-1805). Status: **Ongoing**

   In addition, an open-label compassionate medication use study [Protocol:RP6530-1803; NCT03711604] is opened to allow ongoing patients with no evident disease progression to continue Tenalisib treatment.

- **Safety of Tenalisib:**

A total of 95 patients with relapsed/refractory hematologic malignancies were exposed to Tenalisib till date. In RP6530-1301 study, Tenalisib demonstrated acceptable safety profile up to 1200 mg BID and 800 mg TID without any dose limiting toxicity (DLT).

In RP6530-1401 study, a total of 58 patients were treated at Tenalisib 200 mg BID, 400 mg BID, 800 mg BID (Fasting) and 800 mg BID (Fed) in both dose escalation and expansion cohorts. Tenalisib demonstrated acceptable safety and tolerability profile up to 800 mg BID (Fasting). Reported DLTs included Grade 3 transaminitis, and Grade 3 skin rash. Tenalisib 800 mg BID (Fasting) was considered as maximum tolerated dose (MTD). Treatment related SAE were few and included pyrexia, raised international normalized ratio (INR), sepsis, skin infection, hypersensitivity, and diplopia secondary to neuropathy. Overall, Tenalisib has acceptable safety and tolerability profile up to 800 mg BID (Fasting).

- **Pharmacokinetics (PK):**

In RP6530-1301 study, maximum systemic exposures of Tenalisib were assessed on Cycle 1 Day 1 at doses 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 exposures were observed beyond 400 mg. There was no change in t_{max} on increasing doses however there was change in $t_{1/2}$. Steady state PK parameters of Tenalisib as determined on Cycle 2 Day 1 revealed no accumulation of Tenalisib. Similar PK profile was seen in RP6530-1401 study.

- **Efficacy:**

In RP6530-1301 study, Tenalisib demonstrated an ORR ≈ 20% (CR: 7% and PR: 13%) in heavily pre-treated R/R patients with hematological malignancies. In RP6530-1401 study, response assessments of the thirty-five evaluable patients receiving at least two cycles of Tenalisib showed an ORR of 46% (CR: 9% and PR: 37%). Indication specific analysis showed an ORR of 47% (CR: 20%, PR: 27%) in PTCL and 45% (PR: 45%) in CTCL.

1.4 Study Rationale

1.4.1 Rationale for study population

Chronic Lymphocytic Leukemia (CLL) is a myeloproliferative neoplasm characterized by an accumulation of monoclonal mature B-cells (CD5+CD23+) in the blood, bone marrow, and secondary lymphatic organs. CLL is the most common form of adulthood leukemia.

The clinical course of CLL varies but it is typically a slowly progressing disease. The approximate 5-year survival rate for patients with CLL is 81.7% [6]. Due to infiltration of the bone marrow by lymphocytes, the principal complication of CLL is immunodeficiency

related to myelosuppression and as a result, infection is the major cause of death in these patients [7].

Chromosomal abnormalities of 17p del, 11q del, and IGHV unmutated have been found to be markers of poor prognosis with a decrement in overall survival. Other markers of poor prognosis are β2-microglobulin >3.5 mg/L, lymphocyte doubling time <12 months, and age > 60 years [8]. Treatment-related factors associated with poor prognosis include fludarabine refractoriness and relapse after 3 or more prior therapies [9].

Despite high response rates to initial treatment, relapse is common in CLL and relapsed/ refractory disease is often characterized by resistance to chemotherapy. Among patients who either relapse or are refractory to first line treatment, the choice of subsequent therapy depends on age, duration of response to prior therapy, ability to tolerate treatment, disease related manifestations, and the presence of molecular poor-risk features. The majority of CLL patients receive intermittent treatment with periods of remission or stable disease. With each successive treatment regimen, many patients become refractory to treatment with diminished response rates and shorter response durations. Although newer agents Ibrutinib (BTK inhibitor), Venetoclax (BCL-2 inhibitor), Idelalisib (PI3K δ inhibitor), Duvelisib (PI3K δ/γ inhibitor) have become available for the treatment of CLL recently [10], CLL still remains an incurable disease for most patients and is still an unmet medical need.

Further, the safety and tolerability of newer agents remains a concern as there are high incidence of adverse events with use of these agents (e.g., atrial fibrillation, neutropenia, colitis and pneumonitis) leading to discontinuation of drug therapy. Therefore, there is ongoing need for safer and better treatment options.

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. Pre-clinical experiments demonstrated that Tenalisib is highly effective in killing primary CLL cells *in vitro*. The effect appeared to be equal to ibrutinib and higher than conventional chemotherapy agents. Tenalisib also demonstrated reduction in chemokine induced migration of Daudi cells, indicating its potential in modulating tumor microenvironment. Tenalisib has demonstrated clinical activity in patients with hematological malignancies with acceptable safety profile. Therefore, Tenalisib may offer a good treatment option for patient with relapsed/refractory CLL.

1.4.2 Rationale for dose selection

Maximum tolerated dose of Tenalisib (800 mg BID (Fasting)) was established in Phase I/Ib study and showed acceptable safety and promising efficacy in patients with peripheral and cutaneous T-cell lymphoma. Also, the same dose is being tested in a Phase II study in indolent NHL patients. Hence, 800 mg BID (Fasting) dose has been selected for CLL patient population.

1.5 Benefit and Risk

It is expected that the proposed single agent Tenalisib therapy has the potential to improve response rates in the relapsed/refractory CLL 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. In addition, there are certain risk associated with Tenalisib treatment which are described in ***section 3.5.5*** of protocol. 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) and duration of response (DoR)

2.2 Secondary Objective

- To characterize safety and tolerability of Tenalisib.
- To assess progression free survival (PFS)

3 TRIAL DESIGN

3.1 Trial End Points

Efficacy:

- Overall response rate (ORR): ORR is defined as sum of CR and PR rates as defined by iwCLL guideline for CLL (Hallek *et al.* 2018).
- Duration of response (DOR): DOR is defined as the interval from the first documentation of CR/PR to first documentation of definitive disease progression or death from any cause.
- Progression-free survival (PFS): PFS is defined as the interval from first dose to first documentation of definitive disease progression or death from any cause.

Safety:

- Adverse Event (AE), Grade 3/ 4 AEs, Serious Adverse Event (SAE)

3.2 Design of Trial

The trial is a Phase II, open label, Simon's two stage study design to evaluate the efficacy and safety of Tenalisib in 61 patients with CLL who have relapsed or are refractory after at least one prior therapy. In Stage 1, 20 patients will be enrolled and the study treatment Tenalisib (800 mg BID) will be administered orally in 28-days of cycle over a period of 7 months (C1D1 to C8D1) in absence of definitive disease progression or unacceptable toxicity. If 8 or fewer responders are observed in this stage, the study will be terminated. Else, 41 additional patients will be enrolled into stage 2.

Patients will be evaluated for efficacy response by CT at C3D1±7 days, C5D1±7 days and C8D1±7 days and/or at End of the treatment (EOT) visit. The study will end when all ongoing subjects have reached their third tumor assessment on Cycle 8/Day 1 (C8D1) or have discontinued from the study for any reason, whichever is earlier. At the end of the study, all ongoing patients with no evident disease progression will be given the opportunity to enroll in an open-label compassionate medication use study [Protocol:RP6530-1803; NCT03711604] and will be followed up. The details of the study procedures are given in Study Assessments and Treatment Schedule ***(Table 1).***

3.3 Data Review Committee (DRC)

The DRC will be constituted by the sponsor to review the safety and efficacy data. The committee will consist of PI of respective sites, sponsor representative, sponsor's medical expert, and a statistician. The DRC will meet and review the efficacy and safety data at regular intervals to assess the safety and efficacy of study drug and will provide recommendations.

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

Two dose strengths of Tenalisib will be used in the study.

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 appropriately labeled and packaged as per local regulatory requirements and will be supplied by STA Pharma Co. Ltd through Rhizen Pharmaceuticals SA. Tenalisib will be available as 30 tablets per bottle. This must be kept in a secure place at below 25°C (77°F), protected from moisture".

3.5.3 Preparation and administration of the Investigational Product

At each visit, patients will be dispensed enough quantity of Tenalisib until the next visit. Study drug compliance should be reviewed at the beginning of each new treatment cycle. Study drug compliance will 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 treatment of symptoms (see ***section 5.2***).
- Tenalisib tablets will be self-administered orally twice daily one hour before a major meal (e.g. breakfast and dinner). Patients should not consume food during this one-hour period.
- Tenalisib tablets should be taken at approximately same time each day. Tablets should be swallowed; and should NOT be crushed or chewed.
- If a dose of Tenalisib is missed, it should be taken as soon as possible on same day with an interval of 8 hours between two doses. If it is missed for the entire day, it should not be repeated. If vomiting occurs, no attempt should be made to replace the vomited dose.
- Study drug compliance should be reviewed at the beginning of each cycle. Missed doses should be documented.

3.5.4 Accountability of Investigational Products

The site PI/ designee is responsible for accountability of all trial drug supplies (used/unused medication) 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 will be filed at the site and in Trial Master File (TMF).

3.5.5 Precautions and risks associated with the 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, 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, monitor patients for diarrhea/ colitis and pneumonitis as these events are reported with agents of PI3K inhibitor class.
- Patients with CLL are at increased risk for infection (including sepsis and/or opportunistic infection with Pneumocystis *jirovecii* or Herpesviridae (herpes simplex virus, varicella-zoster virus, CMV, Epstein-Barr virus)) because of compromised immune function, which might be related to the disease itself and/or to the consequences of therapy. Therefore, monitor patients for signs and symptoms of infection and interrupt Tenalisib for Grade 3 or higher infection. The severity of infections should be quantified as minor (requiring either oral antimicrobial therapy or symptomatic care alone), major (requiring hospitalization and systemic antimicrobial therapy), or fatal (death as a result of the infection).
- Tenalisib shows 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 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 to be avoided. Low molecular weight heparin (LMWH), Dabigatran or Edoxaban is advised for prophylaxis and treatment of venous thrombosis.
- Strong inhibitor or inducers should be avoided as directed in ***Section 5.3*** 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 is 7 months (C1D1 to C8D1). The study will end when all ongoing subjects have reached their third tumor assessment on Cycle 8/Day 1 (C8D1) or have discontinued from the study for any reason, whichever is earlier. At the end of the study, all ongoing patients with no evident disease progression will be given the opportunity to enroll in an open-label compassionate medication use study [Protocol:RP6530-1803] and will be followed up.

3.7 Study Stopping Rules

The following study stopping rules based on the safety and efficacy will be used.

- **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. In addition, the DRC may recommend for termination of the study in case of major safety concerns.

- **Efficacy:** Once 20 patients are recruited in stage 1 of the study, the DRC will review the efficacy results and may recommend early termination of the study if there are 8 or fewer responders out of 20 patients. Else, 41 additional patients will be enrolled into stage 2.

In addition, Sponsor reserves the right to terminate the study in the interest of patient safety, for noncompliance with the protocol, lack of recruitment or any other administrative reasons. The sponsor and PIs will notify the regulatory authority and respective IRB/IEC 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 the following inclusion criteria to be eligible for participation in this study:

1. Patients with diagnosis of B-cell CLL as confirmed by histopathology or flow cytometry.
2. Disease status defined as refractory to or relapsed after at least one prior therapy.
3. Presence of measurable lymphadenopathy, defined as the presence of $\geq$ 1 nodal lesion that measures $\geq$ 1.5 cm in the longest diameter (LD) as assessed by computed tomography (CT).
4. ECOG performance status $\leq$ 2.
5. Male or female $\geq$ 18 years of age.
6. Life expectancy of at least 3 months.
7. Adequate bone marrow (BM), liver, and renal function as assessed by the following laboratory requirements conducted within 14 calendar days before starting study treatment.
   a. Adequate bone marrow function:
      I. Haemoglobin $\geq$ 9 g/dl
      II. Absolute neutrophil count (ANC) $\geq$ 1 x 10^9/L
      III. Platelets $\geq$50 x 10^9/L

      Patients with hemoglobin, neutrophil and platelet counts below the above specified values will be eligible if it is due to tumor dissemination or infiltration to bone marrow and as per physician's discretion. Hemoglobin and platelet requirements should not be met by use of recent transfusion or growth factor support (G-CSF or erythropoietin) within 3 weeks prior to assessment.
   b. Adequate liver function:
      I. Total bilirubin $\leq$1.5 times the upper limit of normal (ULN)
      II. ALT and AST should be $\leq$ 3 x ULN. ALT and AST $\leq$ 5 x ULN if known liver involvement.
   c. Adequate renal function: Calculated creatinine clearance $\geq$ 50 mL/min (as calculated by the Cockcroft-Gault method) or Creatinine $\leq$ 1.5 mg/dl.
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 should have a negative serum pregnancy test within 3 days prior to Cycle 1 Day 1 (C1D1). Female patients of child-bearing potential must consent to use a medically acceptable method of contraception as defined in ***Appendix A***, throughout the study period and for 30 days after the last dose of study drug.

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

4.2 Exclusion Criteria

Patients should not meet any one of the following exclusion criteria to be eligible for the study

1. Patient with Richter's (large cell) transformation, or prolymphocytic leukemia (PLL) transformation.
2. Patients receiving any cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy and biologic therapy) or any cancer investigational drug within *3 weeks (21 days)* or *5 half-lives* (whichever is shorter) prior to C1D1.
3. Prior exposure to drug that specifically inhibits PI3K (e.g. idelalisib, copanlisib, duvelisib, umbralisib)
4. Patient with autologous / allogeneic stem cell transplant (ASCT/Allo-SCT) receiving treatment for active graft versus-host disease (GVHD).
5. Evidence of ongoing severe systemic bacterial, fungal or viral infection as assessed by the investigator.
6. Central nervous system (CNS) involvement of leukemia or lymphoma
7. Ongoing immunosuppressive therapy including systemic corticosteroids except as allowed per concomitant medication (***Section 5.2***).
8. Known history of severe liver injury including drug-induced liver injury (e.g. alcoholic liver disease, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver or portal hypertension) as judged by investigator.
9. Any severe and/or uncontrolled medical conditions or other conditions that could affect patient participation in the study, as judged by investigator, such as:
    a. Symptomatic or history of documented congestive heart failure (New York heart association (NYHA) functional classification III-IV)
    b. Myocardial infarction within 6 months of C1D1
    c. QTcF >470 msec.
    d. Angina not well-controlled by medication.
    e. Poorly controlled atherosclerotic vascular disease (e.g. cerebrovascular accident, transient ischemic attack, angioplasty, cardiac/vascular stenting).
10. Patient treated for other malignancy in last 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; and localized prostate cancer with PSA <1.0 mg/dL within 4 weeks of C1D1.
11. Women who are pregnant or lactating.
12. Known seropositive requiring anti-viral therapy for human immunodeficiency virus (HIV) infection.
13. Known seropositive requiring anti-viral therapy for hepatitis B virus (HBV) infection OR evidence of active hepatitis B infection as defined by detectable viral load if the antibody tests are positive. [Note: Subject with a positive HBcAb with an undetectable/negative hepatitis B DNA test (e.g., polymerase chain reaction [PCR] test) can be enrolled].
14. Known seropositive requiring anti-viral therapy for hepatitis c virus (HCV) infection OR patients with positive hepatitis C virus Ab with detectable viral load. [Note:

Subject with a positive HCV with an undetectable/negative hepatitis C RNA test (e.g., PCR) can be enrolled].

15. Known seropositive requiring anti-viral therapy for active CMV infection (Note: A serology positive CMV subject with negative CMV PCR test will be enrolled).
16. Unresolved NCI-CTCAE grade 2 and above toxicity (except as mentioned in adequate organ function (Refer inclusion criteria #7) attributed to any prior therapy/procedure excluding alopecia.
17. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol;
18. Concurrent condition that in the investigator's opinion would jeopardize compliance with the protocol.

Note: Relapse is defined as evidence of disease progression in a patient who has previously achieved the criteria of a CR or partial remission for ≥ 6 months. Refractory disease is defined as treatment failure or as progression within 6 months from the last dose of therapy.

4.3 Discontinuation from Study Drug

The following events may be considered for discontinuation of the study drug.

- 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
- Lack of protocol compliance in the opinion of study investigator
- Study completion.

5 TREATMENT OF SUBJECTS

5.1 Administration of Tenalisib

Tenalisib will be dosed continuously twice a day in 28-days cycle up to 7 months (C1D1 to C8D1) unless progression of disease or toxicity warranting discontinuation of therapy. Please refer ***section 3.5.3*** for administration of Tenalisib. Post completion of 7 months, if the patient shows clinical benefit, patient may be enrolled into a compassionate medication use study [Protocol:RP6530-1803] to receive further treatment with Tenalisib.

5.2 Concomitant Medications

In general, patients should not to take any concomitant medications during the study, unless it is required as a standard of care (as necessary supportive care), prophylaxis or for the treatment of adverse event in the opinion of the treating investigator. The following guidance should be followed for concomitant medications and the information including blood transfusion should be recorded in CRF.

- Antimicrobial and/or anti-viral prophylaxis should be used according to local standard practice; PJP and herpes zoster prophylaxis is strongly recommended. CMV carriers will be monitored per institutional guidelines and/or will be given anti-CMV therapy (e.g.,

ganciclovir, valganciclovir). Similarly, chronic carriers of HBV should receive prophylactic anti-viral therapy.

- 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 administered at dose ≤ 20 mg per day of prednisone or equivalent. The dose should be stabilized for at least 1 week or 5 half-lives (whichever is shorter) prior to C1D1.
- Patients are permitted to use of topical, ocular, intra-articular, intranasal, and inhaled corticosteroids (with minimal systemic absorption).
- 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.
- Low molecular weight heparin (LMWH), Dabigatran or Edoxaban is acceptable for prophylaxis and/or treatment of venous thrombosis.

5.3 Prohibited Medications

The following treatments are prohibited while on the clinical trial and should be discontinued:

- Any other anti- leukemia/lymphoma therapy
- Herbal medications. Patients should stop using herbal medications at least 7 days prior to C1D1.
- Strong inhibitors or inducers of CYP3A4. Patients should stop using these medications at least 7 days or 5 half-lives (whichever is shorter) prior to C1D1. Examples of the drugs include but not limited to:
  - Strong inhibitors: Boceprevir, cobicistat, conivaptan, danoprevir, elvitegravir, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, paritaprevir, ritonavir, posaconazole, saquinavir, telaprevir, tipranavir, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir.
  - Strong inducer: Carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort(g)
- Strong inhibitors or inducers of CYP2C9. Patients should stop using these medications at least 7 days or 5 half-lives (whichever is shorter) prior to C1D1. Examples of the drugs include but not limited to:
  - Carbamazepine, rifampin
- Substrates of CYP3A4 enzyme with a narrow therapeutic range. Patients should stop using these medications at least 7 days or 5 half-lives (whichever is shorter) prior to C1D1. Examples of the drugs include but not limited to:
  - Cyclosporine, warfarin, phenytoin, theophylline, procainamide, tacrolimus, fentanyl, dofetilide and imipramine
- Use of heparin, warfarin, apixaban or rivaroxaban for prophylaxis and/or treatment of venous thrombosis is prohibited. These drugs should be stopped at least 7 days or 5 half-lives (whichever is shorter) prior to C1D1.

- Live attenuated vaccine (e.g. Flu vaccine, pneumovax, varicella).
- Steroids > 20 mg unless it is required for management of toxicity (e.g., transaminitis) during the study.

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 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 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 C8D1)
3. End of Treatment (Day +7 from last dose)
4. 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, HBV, HCV and CMV), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with local regulations.

Table 1: Study Assessments and Treatment Schedule												
Day	**Screening**	**C1**		**C2**		**C3**	**C4**	**C5**	**C6**	**C7**	**C8/ EOT[18]**	**EOS[19]**
Day		**D1**	**D15**	**D1**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**-**
Window period	**-28**	0	±1	±1	±1	±3	±3	±3	±3	±3	+7	+30
Study Days	**D-28 to 0**	1	15	29	43	57	85	113	141	169	197	227
Informed consent[1]	X	-	-	-	-	-	-	-	-	-	-	-
Demographics[2]	X	-	-	-	-	-	-	-	-	-	-	-
Medical history[3]	X	-	-	-	-	-	-	-	-	-	-	
Vitals[4]	X	X	X	X	X	X	X	X	X	X	X	-
Height and weight[5]	X	X	X	X	X	X	X	X	X	X	X	-
Complete physical exam[6]	X	-	-	-	-	-	-	-	-	-	X	-
Abbreviated physical exam[6]	-	X	X	X	X	X	X	X	X	X	-	-
ECOG Performance Status	X	X	-	-	-	X	-	X	-	-	X	-
Rai Staging	X	-	-	-	-	-	-	-	-	-	-	-
Laboratory assessment												
Complete blood count[7]	X	X	X	X	X	X	X	X	X	X	X	-
Chemistry panel I[8]	X	X	X	X	X	X	X	X	X	X	X	-
Chemistry panel II[9]	X	X	-	-	-	X	-	X	-	-	X	-
Serology[10]	X	-	-	-	-	-	-	-	-	-	-	
PT and INR[11]	X	X	X	X	X	X	X	X	X	X	X	-
Urinalysis (routine)	X	X	X	X	X	X	X	X	X	X	X	-
Pregnancy test[12]	X	X	-	-	-	-	-	-	-	-	-	-
12-lead ECGs[13]	X	X	-	X	-	X	-	X	-	-	X	-
Bone marrow biopsy/ aspirate[14]	X	-	-	-	-	-	-	-	-	-	-	-

Disease assessment												
Radiological scan/imaging[15]	X	-	-	-	-	X	-	X	-	-	X	-
Treatment administration												
Tenalisib treatment[16]	-	X	X	X	X	X	X	X	X	X	X	-
Tenalisib dispensing	-	X	-	X	-	X	X	X	X	X	X	-
Drug compliance	-	X	X	X	X	X	X	X	X	X	X	-
Safety evaluation												
AE evaluation[17]	X	X	X	X	X	X	X	X	X	X	X	X
SAE evaluation	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X

Foot notes:

1. Patient should be re-consented, if informed consent is obtained >30 days prior to the initiation of study drug.
2. Demographic profile will include age, sex and race.
3. Detailed history will be taken at screening that includes history of cancer, past history, no of prior therapies; prior medication (in last 4 weeks); and other medical history (history of transfusions). Any medical significant history at subsequent visit will be captured as adverse event.
4. Vitals will be done prior to the administration of study drug (Pre-dose) at the days specified above.
5. Weight will be measured at all visits. Height to be recorded at screening only; historical data is acceptable.
6. Physical examination will include lymph node and systemic examination. Complete physical examination will be done at screening and EOT visits. At other visits, abbreviated examination (directed physical examination) will be done depending on the assessment of tumor.
7. Complete blood count: hemoglobin, hematocrit, WBC (total and differential leucocyte count) and platelet count. Additional investigations will be performed if clinically indicated. Hematology should be done ≤ 14 days prior to C1D1. However, if screening assessments are performed within 72 hours of C1D1; these tests need not be repeated on C1D1.
8. Chemistry Panel I include total bilirubin, ALP, AST, ALT, GGT, urea/ blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, phosphorus, CO2/bicarbonate and magnesium. The tests should be done ≤ 14 days prior to C1D1. However, if screening assessments are performed within 72 hours of C1D1; these tests need not be repeated on C1D1. These tests will be performed at supplementary (unscheduled) visits if clinically indicated.

9. Chemistry Panel II includes blood glucose, LDH, albumin, total protein, TSH, T3 (total/free), T4 (free), total Cholesterol, TG, LDL and HDL. These tests will be performed at unscheduled visits if clinically indicated.
10. Serology includes HIV, HBV, HCV and CMV. Historical results in last 12 weeks is acceptable.
11. PT and INR. In case of abnormality, additional tests including aPTT to be done as per investigator discretion. This test will be performed at supplementary visits if clinically indicated.
12. Pregnancy test is required for women of childbearing potential. A serum pregnancy test will be performed at screening; and serum/urine pregnancy test at C1D1 (within 72 hours) of dosing. Urine pregnancy test will be performed at other visits as indicated.
13. 12-lead ECG: ECG will be done at Pre-dose on scheduled timepoints on the day of drug administration. Additional ECGs will be obtained if clinically indicated. Triplicate ECGs will be performed to confirm the significant changes of single ECG.
14. A bone marrow biopsy/aspirate: Unilateral bone marrow aspiration and/or biopsy will be performed at investigator discretion in patients for whom assessment of extent of CLL involvement and bone marrow cellularity is important in determining eligibility. However, post initiation of treatment, bone marrow biopsy should be done to confirm potential CR.
15. Radiological assessment: "Diagnostic quality" CT scan of neck/chest/abdomen/pelvis, as applicable, will be done at the time of screening within 28 days of C1D1. The scan and other investigations to document measurable or evaluable disease should be performed ≤28 days prior to initiation of treatment or as approved by the medical monitor if it is out of 28-days window period. Following screening, CT scans should be repeated at C3D1 (± 7 days), C5D1 (± 7 days) and C8D1 (± 7 days) or at end of the treatment (EOT) visit.
16. Tenalisib will be administered orally twice a day in 28-days of cycle for 7 cycles (C1D1 to C8D1) in absence of disease progression or toxicity warranting discontinuation of therapy.
17. 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.
18. Post C8D1, patient experiencing clinical benefit with no evident disease progression will be given the opportunity to enroll in an open-label compassionate medication use study and will be followed up. Excluding patients who participate in compassionate medication use study [Protocol:RP6530-1803], all other patients will undergo the end-of-treatment (EOT) assessments within 7 days after the last dose of study drug or discontinuation from the study.
19. Patients should be followed for AEs for 30 calendar days after the last dose of study drug. 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 local regulations and Sponsor requirements.

The informed consent must be obtained ≤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 ≤30 days prior to the initiation of study drug.

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 dosing 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

Comprehensive medical history should be taken at least for period of minimum 6 months by the investigator/qualified designee. In addition, information on cytogenetics and immunophenotyping, if available at the screening will be noted. Investigator should note at least 1 of the following criteria to document active disease that warrants initiation of therapy;

a. Evidence of progressive bone marrow failure as manifested by the onset or worsening of anemia (Hb <10 g/dL) and/or thrombocytopenia (count <100 X 10^9/L), OR
b. Massive (lower edge of spleen ≥ 6 cm below the left costal margin) progressive, or symptomatic splenomegaly, OR
c. Massive nodes (≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy, OR
d. Progressive lymphocytosis in the absence of infection, with an increase in blood absolute lymphocyte count (ALC) >50% over a 2-month period or lymphocyte doubling time of <6 months (if initial ALC is ≥30,000/μL), OR

e. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy, OR
f. Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection:
   i. Unintentional weight loss of ≥10% within the previous 6 months, or
   ii. Significant fatigue (≥ Grade 2), or
   iii. Fevers >100.5°F or 38.0°C for ≥2 weeks, or
   iv. Night sweats for >1 month.

6.2.4 Prior and concomitant medication

Prior medication history includes treatment received for disease condition/co-morbidities, supplements, prophylactic treatment, transfusions in last 4 weeks and should be recorded. Anti-cancer-treatment for the disease (prior therapies) should be recorded separately and should not be listed as a prior medication. Concomitant medication includes treatment for disease condition/co-morbidities, supplements, prophylactic treatment, transfusions, given after starting the study drug and should be recorded.

6.2.5 Prior therapies

Prior therapy includes systemic treatments, prior transplantation, radiation, and surgeries received for the treatment of cancer condition. Prior therapies should be recorded from the initial diagnosis and response to each therapy (relapse/refractory) should be noted.

6.2.6 Physical examination

Full physical examination should be performed during the screening period and as defined in Study Assessments and Treatment Schedule ***(Table 1).*** Full physical examination includes lymph node and systemic examination (e.g. General Appearance, neck, cardiovascular, lungs, abdomen, extremities, neurological, skin, and musculoskeletal). The bi-dimensional diameters of the largest palpable lymph nodes in each of the following sites should be recorded: cervical, axillary, and inguinal. The dimensions of the liver and spleen below their respective costal margins, as assessed by palpation, should also be recorded.

For cycles that do not require a full physical exam per the Study Assessments and Treatment Schedule ***(Table 1)***, a directed physical examination (Abbreviated) as clinically indicated depending on assessment of tumor, prior to study drug administration should be performed. After the first dose of study drug new clinically significant abnormal findings should be recorded as AEs.

6.2.7 Vital signs

Vital signs will be taken at screening, prior to the administration of each dose of study drug and at treatment discontinuation as specified in the Study Assessments and Treatment Schedule. Vital signs should include temperature (oral/axillary/tympanic), pulse, respiratory rate, weight and blood pressure. Supine or sitting position is acceptable depending on the patient condition. The window periods for vitals will ±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 Lab
Hematocrit	Total bilirubin	Blood glucose	Blood	Serum β-hCG
Hemoglobin[a]	Alkaline phosphatase	LDH	Glucose	Urine pregnancy test
Platelet count	Alanine aminotransferase	Albumin	Protein	PT
White blood cell count	Aspartate aminotransferase	Total protein	Specific gravity	INR
WBC (Total and differentials)	Urea or blood urea nitrogen[b]	Total Cholesterol	Microscopic exam[d]	
Red blood cell count	Creatinine	Triglyceride (TG)		
Absolute neutrophil count	Gamma-glutamyl transferase	LDL		
Absolute lymphocyte count	Sodium	HDL		
	Potassium	TSH		
	Calcium	T3 (Total or Free)		
	Phosphorous	T4 (free)		
	Carbon Dioxide (CO_2) or bicarbonate[C]			
	Chloride			
	Magnesium			

[a] *Screening and subsequent Hb determinations should be performed before any given transfusions.*
[b] *Blood Urea Nitrogen is preferred; if not available Urea may be tested.*
[C] *One of these tests to be performed depending on standard of care practice followed at the institution.*
[d] *Microscopic exam, if abnormal results are noted.*

Blood drawn for these tests will be specified in informed consent form (ICF). All laboratory investigations will be performed at local laboratory.

Screening laboratory described in ***Table 2*** will be performed, reviewed, and determined to be acceptable by the site PI/designee within ≤ 14 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. Re-screening can be done at the discretion of PI. The scan and other investigations to document measurable or evaluable disease should be performed ≤28 days prior to initiation of treatment or as approved by the medical monitor if it is out of 28-days window period.

During screening, active HBV, HCV, HIV and CMV 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, HCVRNA 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).
- CMV: Negative for anti-CMV IgM antibody or if positive anti-CMV IgG antibody is positive, CMV DNA should be negative. [Note: Carriers will be monitored per institutional guidelines.]

Note: Patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), need to be evaluated for initiation of HBV antiviral prophylaxis and should be closely monitored for HBV reactivation. CMV carriers will be monitored per institutional guidelines and/or will be given anti-CMV therapy (e.g., ganciclovir, valganciclovir).

6.2.9 ECG

A standard 12-lead ECG will be performed using local standard procedures as defined in Study Assessments and Treatment Schedule ***(Table 1).*** Additional ECGs will be obtained if clinically indicated. Triplicate ECGs will be performed to confirm the significant changes of single ECG. If ECG finding is considered as clinically significant, it should be recorded as medical history/adverse event appropriately. On the day of dosing, ECG will be performed prior to dose administration.

6.3 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG performance status will be assessed as below at time points specified in the Schedule of Event.

Score	Description
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

6.4 Disease assessment

The disease assessment will be done by an expert haemato-oncologist/oncologist by evaluating disease-related symptoms/cytopenias, physical examination, lymph nodes assessment, assessment of organomegaly and constitutional symptoms. Based on the disease assessment, Rai staging will be

performed to define risk status of the patients (low risk disease, intermediate-risk disease and high-risk disease) [11].

Table 3:Rai staging system

Stage	Description	Modified Risk Status
0	Lymphocytosis, lymphocytes in blood >5 x 10^9/L clonal B-cells and >40% lymphocytes in the bone marrow	Low
I	Stage 0 with enlarged node (s)	Intermediate
II	Stage 0-I with splenomegaly, hepatomegaly, or both	Intermediate
III	Stage 0-II with hemoglobin <11.0 g/dL or hematocrit <33%	High
IV[c]	Stage 0-III with platelets <100,000/µL	High

[C] *Immune-mediated cytopenias are not the basis for these stage definitions.*

6.5 Radiological assessment

Initial disease assessment of relapsed/refractory CLL patient should be performed within 28 days prior to the first dose of study drug using CT scan of neck/chest/abdomen/pelvis, as applicable (This scan will be considered as baseline scan). The PI should review baseline scan images to confirm the subject has measurable disease as defined in the inclusion criteria. Scan performed as part of routine clinical management is acceptable for use as the baseline scan if it is of diagnostic quality and performed within 28 days prior to the C1D1 or as approved by the medical monitor if it is out of window period. Subsequently, CT scan should be done throughout the study at time-points designated in Study Assessments and Treatment Schedule ***(Table 1).*** Other radiological evaluations (e.g. MRI/USG) will be performed if warranted.

Disease response assessments should be performed at C3D1 (± 7 days), C5D1 (± 7 days) and C8D1 (± 7 days), and/ or at the EOT or as clinically indicated (if clinical progression is suspected). If CT scan at Screening is negative for disease involvement in the neck, subsequent CT scan may not include neck. If CT scan at Screening are positive for disease involvement of the neck, subsequent CT scan must include neck.

Note: Evaluation of radiological assessment will be performed and confirmed by the site investigator (defined as PI-confirmed response). The PI confirmed response will be considered for analyses of efficacy endpoints.

6.6 Bone marrow biopsy

Unilateral bone marrow aspiration and/or biopsy will be performed at investigator discretion in patients for whom assessment of extent of CLL involvement and bone marrow cellularity is important in determining eligibility during screening period (within 28 days prior to the first dose of study drug). However, bone marrow biopsy should be done to confirm potential CR.

To define a CR, the cytological or pathological evaluation of the bone marrow smear or biopsy must be at least normocellular for age, without evidence for typical CLL lymphocytes by morphological criteria.

Note: Bone marrow biopsy/aspirate will be performed at the site (local lab) as a diagnostic procedure as per the site practice.

6.7 Trial Treatment Period

Patients will visit the study center bi-weekly for the first two 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 7 cycles (C1D1 to C8D1). 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.***

6.8 End of Trial Treatment (EOT)

Patients are permitted to continue Tenalisib treatment until C8D1 unless there is disease progression, or discontinuation of patients due to unacceptable toxicity or decision to discontinue treatment by the patient (consent withdrawal)/PI. Follow-up evaluations required after treatment ends are specified in ***Table 1.***

Treatment Beyond Cycle 8: Post C8D1, patient experiencing clinical benefit with no evident disease progression will be given the opportunity to enroll in an open-label compassionate medication use study and will be followed up.

All patients who discontinue Tenalisib will have an End of Treatment visit within 7 days from the last dose of the study drug. If treatment is discontinued because of toxicity or any other reason(s), the date of discontinuation will fulfill the End of Trial Treatment Visit. Patients who will be considered for compassionate use study protocol will have EOT assessment on C8D1.

6.9 End of Study (EOS)

All patients must be followed for adverse events for 30 calendar days after the last dose of study drug. Telephonic follow up is acceptable. Patients who will be considered for compassionate use study protocol will have EOS visit on C8D1. 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.

6.10 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 authorities.

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 related or unrelated 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 initiation of study drug 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 adverse event to the study drug. For this study, the causality assessment will be categorized as related and not related.

- **Related:** All toxicities should be considered 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 study drug 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) 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 during the course of study; 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 dose of 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.

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 dose of study drug 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 dose of study drug 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 dose of study drug and not attributed to study drug (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 e-mail. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines. 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 E6 guidelines, and 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 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 local regulatory authorities (as applicable) 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 Severity of Adverse events

Severity of adverse events will be assessed according to National Cancer Institute (NCI)- CTCAE v5.0 with exceptions for platelet, hemoglobin and ANC that are recommended by iwCLL guidelines for the CLL (see below).

Grade*	Decrease in platelet† or Hb‡ (nadir) from baseline, %	Absolute neutrophil count (nadir)§ x 10^9/L
0	No change to 10	≥ 2
1	11-24	≥1.5 and <2
2	25-49	≥1 and <1.5

3	50-74	≥0.5 and <1
4	≥ 75	<0.5

* Grades: 1-mild; 2-moderate; 3-severe; 4-life-threatening; 5-fatal. Death occurring as a result of toxicity at any level of decrease from baseline will be recorded as grade 5.
† Platelet counts must be below normal levels for grades 1-4. If, at any level of decrease the platelet count is $<20 \times 10^9$/L, this will be considered grade 4 toxicity unless a severe or life-threatening decrease in the initial platelet count (e.g., 20×10^9/L) is present at baseline, in which case the patient is not evaluable for toxicity referable to platelet counts.
‡ Hb levels must be below normal levels for grades 1-4. Baseline and subsequent Hb determinations must be performed as per the schedule of events. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.
§ If the absolute neutrophil count (ANC) reaches $<1 \times 10^9$/L, it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count or in circulating granulocytes are not to be considered because a decrease in the white blood cell count is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC is $<1 \times 10^9$/L before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of G-CSF is irrelevant for the grading of toxicity but should be documented.

7.5 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.

7.5.1 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. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

7.5.2 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. If a persistent AE becomes more severe or lessens in severity, AE should be recorded separately with onset date as date of change of severity in CRF.
A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent events should be recorded separately on an SAE Report Form and/or CRF.

7.5.3 Abnormal laboratory values

Any grade 3/4 laboratory abnormalities or any clinically significant grade 1/2 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.

7.5.4 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.

7.5.5 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 (***See section 7.3)*** that do not require reporting as an SAE.

7.5.6 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.

7.5.7 Pregnancy, abortion, birth defects/congenital anomalies

Pregnancy, abortion, birth defects, and congenital anomalies are events of special interest. Please refer to pregnancy ***Section7.6.1*** for specific instructions.

7.5.8 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 as disease progression.

7.5.9 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 will be considered lack of efficacy and not an AE.

7.6 Protocol-Defined Events of Special Interest

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

7.6.1 Pregnancy, abortion, birth defects/congenital anomalies

Female patients who are not of child-bearing potential (see ***Appendix A*)** and female patients of child-bearing potential who have a negative serum pregnancy test (within 72 hours prior to initiation of study drug) are eligible for the study. Female patients of child-bearing potential (see ***Appendix A***), must consent to use a medically acceptable method of contraception throughout the study period and for 4 weeks after the last dose of Tenalisib. A barrier method of contraception must be included.

During the course of the trial, all female patients of childbearing potential (the definition of "women of *childbearing* potential" is listed in ***Appendix A***) 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.

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 as soon as possible. A pregnancy Form should be completed and emailed to Sponsor.

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 update to reflect the outcome of the pregnancy.

7.6.2 Overdose

Both intentional (misuse/abuse) and unintentional (accidental) overdose must be reported in the CRF. Symptomatic unintentional and intentional overdose must be reported as AE in the CRF (see below). Any accidental overdose with the study drug that is symptomatic, fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within 24 hrs) as SAE. Intentional overdose should be reported as an SAE irrespective of seriousness criteria.

Type of overdose	Document in CRF	Document in AE CRF	Complete SAE form
Unintentional (accidental)	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

7.7 Dose Modifications

In case of the hematologic and non-hematologic toxicities, the dose modifications provided below **(Table 4 and Table 5)** should be used a guidance and should be determined as per PI's clinical judgement. The dose modifications are intended to be applied when the investigator determines the events related to Tenalisib. If events (cytopenia) are deemed related to the underlying disease rather than Tenalisib, dose reduction will be done as per the investigator's discretion.

In case of drug withhold, Tenalisib treatment can be resumed if:

- Patient recovered from grade 3-4 toxicity as defined in dose modification guidance below.
- No clinical or radiographic evidence of disease progression.
- Investigator believes the risk of progression outweighs the risk of further treatment.

If treatment is delayed >2 weeks, treatment continuation should be discussed with Medical monitor. 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.

At the discretion of the investigator, a dose re-escalation may be permitted for patients who earlier has dose reduction. The decision should be taken after evaluating the emerging safety data and benefit and risk of re-escalation. Drug holidays are discouraged. Any patient in whom similar toxicity recurs at the reduced dose, it should be discussed with medical monitor to determine appropriate strategy on treatment continuation.

Table 4: Dose Modifications for Hematologic Toxicity

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 Tenalisib dose. 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 <1.0 X 10^9/L 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 warranted. If the

or a sustained temperature of ≥ 38 ^{0}C (100.4 ^{0}F) for more than one hour.	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.
# Refer iwCLL criteria

Table 5: Dose Modifications for Non-Hematologic Toxicities

Non-Hematologic	Action to be Taken
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.
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
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

Assessment of efficacy includes careful evaluation of blood, lymph nodes and bone marrow by medical history, physical examination, laboratory tests (e.g. CBC and differential count), bone marrow aspirate and/or biopsy (as applicable) and CT scans of neck/chest/abdomen/pelvis, as applicable. Investigator assessed efficacy response will be considered in the study.

8.1 Specification of the Efficacy Parameters

- **ORR** is defined as sum of CR and PR rates as defined by iwCLL guideline for CLL (Hallek *et al.* 2018) [12]. Only those patients who have had a pre-treatment baseline efficacy evaluation and at least one post-treatment efficacy evaluation (that includes confirmed disease progression) will be considered evaluable for response.
- **CR rate** will be assessed by the investigator according to the iwCLL guideline for CLL. Only those patients who have had a pre-treatment baseline efficacy evaluation and at least one post-treatment efficacy evaluation (that includes confirmed disease progression) will be considered evaluable for response.
- **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.
- **Best Overall Response:** The best overall response is the best response, as assessed and confirmed by site PI, from the start of the treatment until disease progression or discontinuation from the study.

Disease parameters:

- **Measurable lesions:** Measurable lesions are defined as those that can be accurately measured in at least two dimensions with conventional techniques with size ≥ 1.5 cm. All tumor measurements should be recorded in centimeters.

- **Non-measurable lesions (evaluable disease):** All other lesions including small lesions (>1 cm) 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

Disease response assessments should be performed at C3D1 (± 7 days), C5D1 (± 7 days) and C8D1 (± 7 days), and/ or at the EOT or as clinically indicated (if clinical progression is suspected). If CT scan at Screening is negative for disease involvement in the neck, subsequent CT scans may not include neck. If CT scan at Screening is positive for disease involvement of the neck, subsequent CT scans must include neck. Disease assessment will be performed as per iwCLL guideline for CLL (Hallek *et al.* 2018) [12].

To define the response to treatment, 2 groups of parameters will be assessed and documented:
- Group A parameters: assess the lymphoid tumor load and constitutional symptoms.
- Group B parameters: assess the hematopoietic system ***(Table 6).***

For complete remission (CR), all criteria given below should be met. For progressive disease, at least 1 of the criteria of group A or group B should be met; For partial remission, at least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve.; For stable disease, all of the criteria have to be met; constitutional symptoms alone do not define PD.

Table 6: Response Criteria for CLL (iwCLL) (Hallek *et al,* 2018)

Group	Parameter	CR	PR	PD	SD
A	**Lymph nodes**	None ≥ 1.5 cm	Decrease ≥ 50% (from baseline) *	Increase ≥ 50% from baseline or from response	Change of -49% to +49%
	Liver and/or spleen size$	Spleen size <13 cm; liver size normal	Decrease ≥ 50% (from baseline)	Increase ≥ 50% from baseline or from response	Change of -49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline	Change of -49% to +49%
B	**Platelet count**	≥ 100 x 10^9/L	≥ 100 x 10^9/L or increase ≥ 50% over baseline	Decrease of ≥ 50% over baseline secondary to CLL	Change of -49% to +49%
	Hemoglobin	≥ 11.0 g/dL (untransfused and without erythropoietin)	≥ 11.0 g/dL or increase ≥ 50% over baseline	Decrease of ≥ 50% over baseline secondary to CLL	Increase <11.0 g/dL or <50% over baseline, or

					decrease <2 g/dL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥ 50% on successive biopsies	No change in marrow infiltrate

[$]spleen size is considered normal if <13cm. There is no firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation and be recorded in CRF.

**Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination). No increase in any lymph node and no new enlarged lymph node (diameter ≥1.5 cm). For small lymph nodes (longest diameter <1.5 cm), an increase <25% is not considered significant.*

Note: *Certain therapies (e.g., kinase inhibitors) may cause lymphocytosis. In the setting of therapy with such agents, an increase in blood lymphocyte count by itself does not uniformly indicate an increased tumor burden but may reflect redistribution of leukemia cells from lymphoid tissues to the blood [12]. As Tenalisib is a kinase inhibitor, increased lymphocytosis alone will not be considered a sign of treatment failure or PD in this study.*

9 STATISTICAL METHOD AND CONSIDERATIONS

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

9.1 General Considerations

Unless otherwise stated, all statistical analyses will be performed using a two-sided hypothesis test at the overall 5% level of significance. 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

The sample size is derived based on Simon's two stage design to achieve 90% power at alpha of 0.05 for the null hypothesis of ORR≤40%, assuming 60% response rate. Up to 61 patients will be enrolled. In stage 1, 20 patients will be enrolled, if 08 or fewer responders are observed in this stage, the study will be terminated without rejecting the null hypothesis. Otherwise, 41 additional

patients will be enrolled into stage 2. If 31 or more responders are observed in the study, the null hypothesis of ORR ≤40% will be rejected.

9.3 Study Population

The following 3 analysis populations are planned in the study.

- Modified Intent-to-Treat Population (mITT): the mITT is the primary efficacy analysis population and will include data from all patients who received at least 1 dose of study medication and provide at least 1 post-baseline efficacy assessment.
- Per-Protocol (PP) Population: the PP Population is a subset of the modified Intent-to-Treat Population and will include patients without major protocol deviations.
- Safety Population: 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 AEs considered to be drug-related
- 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 with exceptions for platelet, hemoglobin and ANC that are recommended by iwCLL guidelines for the CLL.

9.4.3 Efficacy analyses

The efficacy endpoints will include:

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

The analysis will be done as per the disease subtypes and overall. Additional analyses (e.g. CR rates) 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, World Medical Association's Declaration of Helsinki, local regulatory requirement(s), institutional research policies and procedures.

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 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 or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB/IEC. Safety updates for Tenalisib will be prepared by Rhizen or its representative as required, for submission to the relevant IRB/IEC.

10.2 Regulatory Approval

As required by local regulations, Rhizen will ensure 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 for Tenalisib will be prepared by the Sponsor 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 Rhizen and PI or site. 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/investigator undertaking to allow Rhizen to submit the complete and accurate certification or disclosure statements required as per local regulatory requirements. 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 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 the relevant elements required by the local regulatory 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 the 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. 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 Ethical principles that have their origins in the Declaration of Helsinki and local regulatory requirements and good clinical practice.

10.6.3 Investigator and staff training and information

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

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

11 RECORD RETENTION AND DOCUMENTATION OF THE TRIAL

11.1 Amendments to the Protocol

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

11.2 Protocol Deviations

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

the monitor. The IRB/IEC should be notified of all protocol deviations according to IRB/IEC reporting requirements.

11.3 Documentation Required to Initiate Trial

Before the initiation of study, sponsor will ensure that documentation required by the local regulatory authorities and IRB/IEC will be in place. Documents will include, but are not limited to: a signed protocol, copy of regulatory and IRB/IEC approval and; current curricula vitae of the principal investigator; copy of signed agreement, insurance certificate, form FDA 1572/Investigator undertaking (as applicable), IRB-approved consent form; financial disclosure forms for all investigators; site qualification reports, where applicable and study contract.

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 local regulatory requirements. These documents include but not limited to 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 dispensing, medical records and any other trial-related records as per local regulatory requirements for no less than 2 years after the last marketing application has been approved by the regulatory agency; or, in the event that the marketing application has not been approved by local regulatory agency, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and local regulatory agency 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 information collected/documented during 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: 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 Follicular Stimulating Hormone (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 ≤ 72 hours prior to initiating treatment.

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