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PROTOCOL NO. RP6530-2101

A Phase II, Multi-center, Randomized, Open label, two arm Study to Assess the Efficacy and Safety of Tenalisib (RP6530), a PI3K δ/γ and SIK3 Inhibitor, in patients with Locally Advanced or Metastatic Breast Cancer

PROTOCOL NUMBER	RP6530-2101
TRIAL DRUG	Tenalisib (RP6530)
[redacted]	[redacted]
[redacted]	[redacted]
DOCUMENT VERSION	**Version 1.0, Dated June 29, 2021**

Clinical Trial Protocol Statement of Compliance

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

- **International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- 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.

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Protocol Approval Page

A Phase II, Multi-center, Randomized, Open label, two arm Study to Assess the Efficacy and Safety of Tenalisib (RP6530), a PI3K δ/γ and SIK3 Inhibitor, in patients with Locally Advanced or Metastatic Breast Cancer

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Protocol Acceptance Page

A Phase II, Multi-center, Randomized, Open label, two arm Study to Assess the Efficacy and Safety of Tenalisib (RP6530), a PI3K δ/γ and SIK3 Inhibitor, in patients with Locally Advanced or Metastatic Breast Cancer

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TRIAL DRUG(S)	Tenalisib (RP6530)
DOCUMENT VERSION	**Version 1.0, Dated June 29, 2021**

[redacted]

PROTOCOL SYNOPSIS

Study Title	A Phase II, Multi-center, Randomized, Open label, two arm Study to Assess the Efficacy and Safety of Tenalisib (RP6530), a PI3K δ/γ and SIK3 Inhibitor, in patients with Locally Advanced or Metastatic Breast Cancer
Phase	Phase II
Study Sponsor	Rhizen Pharmaceuticals AG
Study Centers	Approximately 05 study centers in Georgia
Study Objectives	**Primary Objective** • To assess the anti-tumour activity of tenalisib in patients with locally advanced or metastatic breast cancer **Secondary Objective** • To evaluate the safety and tolerability of tenalisib **Exploratory Objectives** • Changes in serum cytokines/chemokines and tumour tissue gene expression post treatment with tenalisib.
Endpoints	**Primary Endpoint** • Percentage of patients without disease progression at the end of 6 months. **Secondary Endpoints** • Overall Response Rate (ORR), Clinical Benefit Rate (CBR) and Progression Free Survival (PFS). • Adverse Event (AE), Grade 3/4 AEs, Serious Adverse Event (SAE) evaluated and graded using NCI-CTCAE Version 5.0. **Exploratory Endpoints** • Change from baseline in cytokine/chemokine levels post treatment with tenalisib • Change in gene expression profiles as measured by RNA sequencing from tumour biopsy samples post treatment with tenalisib.
Study Design	This is a Phase II, randomized, open label study, designed to evaluate the preliminary efficacy and safety of tenalisib at two dose levels (800 mg BID and 1200 mg BID) in 40 patients with locally advanced or metastatic breast cancer. 20 patients each, will be enrolled in Group 1 (Tenalisib 800 mg BID) and Group 2 (Tenalisib 1200 mg BID). Both groups will be run in parallel.
Study Procedure	The study treatment will be administered orally in 28 days of cycle until disease progression or unacceptable toxicity for a maximum duration of 24 months. The detailed study procedure is presented in Study assessment and Treatment schedule **(Table 5).** Safety including laboratory assessments and electrocardiogram (ECG), and radiological assessments including CT and/or MRI will be performed at the protocol specified timepoints at the respective sites.
No. of Patients	40 patients (20 patients per group) will be enrolled in two parallel groups.
Estimated Study Participation	The subject will participate in the study until disease progression, consent withdrawal or unacceptable toxicity for a maximum duration of 24 months.

Inclusion Criteria	***Individuals should meet all the following criteria to be considered eligible to participate in the study:*** 1. Provision of full informed consent prior to any study-specific procedures. 2. Patients must be ≥18 years of age, at the time of signing informed consent. 3. Female patients who have histologically and/or cytologically confirmed locally advanced or metastatic breast cancer that has progressed following at least one line of therapy. 4. Patients with at least one measurable lesion per RECIST version 1.1 at baseline that can be accurately assessed by CT scan or MRI and is suitable for repeated assessment at follow up-visits. 5. ECOG performance status 0 to 2. 6. Life expectancy of at least 3 months. 7. Adequate bone marrow, liver and renal functions as assessed within 7 (±2) days before the first dose of study drug with the following laboratory requirements: a. Hemoglobin ≥ 8.0 g/dL (should not be transfused or treated with erythropoietin to maintain or exceed this level) b. Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L without growth factor support c. Platelet count ≥ 75 x 10^9/L d. Total bilirubin ≤ 1.5 times the ULN (or ≤ 3 x ULN, if the patient has Gilbert syndrome) e. ALT and AST ≤ 3 x ULN (≤ 5 x ULN for patients with liver metastasis or liver involvement) f. Creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault formula) for patients with creatinine levels above ULN. 8. Female patient of childbearing potential should be willing to use a medically acceptable method of contraception as defined in Appendix B while participating in the study and for 30 days after the last dose of study drug AND must have a negative serum pregnancy test within 3 days prior to Cycle 1 Day 1 (C1D1). 9. Ability to swallow and retain oral medication. 10. Willingness and capability to comply with the study requirements.
Exclusion Criteria	***Individuals who meet any of the following criteria will be considered ineligible to participate in the study:*** *1.* Patients with HER-2 positive breast cancer. 2. Patients receiving anticancer therapy (e.g., chemotherapy, biologic therapy, hormonal therapy or any other investigational product) within 4 weeks or 5 half-lives of the drug prior to C1D1, whichever is shorter. Treatment interval will be 6 weeks for nitrosoureas or mitomycin C. 3. Patient who has not recovered from acute toxicities (defined as NCI-CTCAE grade > 1) of previous therapy except treatment-related alopecia. (Note: Patient with any unresolved toxicities which in the opinion of PI are stable and controlled with medication can be enrolled in the study). 4. Patients who have had disease progression within 8 weeks of platinum chemotherapy. (Note: Patients who have had a disease-free interval of more than 8 weeks following platinum chemotherapy; and patients with previous neoadjuvant OR adjuvant platinum-based therapy can participate in the study). 5. Prior exposure to investigational or marketed PI3K inhibitors (e.g., idelalisib, copanlisib, duvelisib, umbralisib, alpelisib, buparlisib) given for the treatment of breast cancer. 6. Major surgery within 4 weeks of starting study treatment OR any patient who has not recovered from the effects of major surgery.

	7. Patient with symptomatic uncontrolled brain metastasis. (Note: A scan to confirm the absence of brain metastases is not required. Patients whose brain metastatic disease has remained stable for ≥ 4 weeks (prior to the start of study treatment) following treatment of brain metastases are eligible. The patient can receive a stable dose of corticosteroids before and during the study if steroids were started at least 4 weeks prior to C1D1). 8. HIV positive patients who are on antiretroviral therapy OR active hepatitis C OR active hepatitis B virus infections. 9. Ongoing immunosuppressive therapy including systemic corticosteroids except as allowed per concomitant medication. 10. Known history of severe 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. (Note: Exception will be the patients with liver metastasis who can be enrolled in the study). 11. History of severe cutaneous reactions (e.g., Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) in the past. 12. Active gastrointestinal tract disease with malabsorption syndrome or uncontrolled inflammatory gastrointestinal disease such as Crohn's disease or ulcerative colitis. 13. Myocardial infarction within 6 months before starting therapy, symptomatic congestive heart failure (New York Heart Association > Class II), unstable angina, or unstable cardiac arrhythmia requiring medication or clinically relevant findings in the ECG such as second-or third-degree AV block, significant prolongation of the QTcF interval, unless agreed between the investigator and the medical monitor. 14. Concurrent disease or condition that would interfere with study participation or safety, such as the following: o Active, clinically significant infection requiring parenteral antimicrobial agent. o Clinically significant bleeding diathesis or coagulopathy, including known platelet function disorder. o Mood disorders like OCD, severe depression, history of suicidal attempt, schizophrenia etc. as per the investigator's discretion. 15. Concurrent medications or substances with the potential to affect the activity or pharmacokinetics of tenalisib, as reviewed and confirmed by medical monitor. 16. Pregnancy or lactation. 17. Patient with other active malignancies at the time of screening except for adequately treated in situ carcinoma of the cervix uteri or carcinoma in situ of breast, basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin. (Note: Patients with prior malignancies which are treated and are in remission without requiring active treatment are allowed in the study.) 18. A serious uncontrolled medical disorder or active infection which would impair the ability of the patient to receive protocol therapy or whose control may be jeopardized by the complications of this therapy. *Note: Post eligibility confirmation, tumour biopsy will be performed in approximately 10-12 patients who have consented for biopsy, prior to the first dose on C1D1. Eligible patients who do not consent for biopsy will also be enrolled into the study. Blood will be collected in all patients for cytokine/chemokine analysis.*

Administration of Tenalisib	Tenalisib will be administered orally daily in 28-day cycle (Day 1-28). 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. If a dose of tenalisib is missed, it should be taken as soon as possible on the same day with an interval of minimum 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.
Concomitant Medications	In general, any concomitant medications should be avoided during study, unless it is required as a standard of care (necessary supportive care), prophylaxis or for the treatment of adverse event in the opinion of the treating investigator. Below recommendations should be followed, and concomitant medication should be clearly documented. 1. Antimicrobial and/or anti-viral prophylaxis should be used according to local standard/institutional practice; Pneumocystis *jirovecii* pneumonia (PJP) and herpes zoster prophylaxis is strongly recommended. Similarly, chronic carriers of HBV should receive prophylactic anti-viral therapy. 2. Hematopoietic growth factors (e.g., erythropoietin, GM-CSF and G-CSF) can be used for the management of acute toxicities such as febrile neutropenia when clinically indicated or at the discretion of the investigator. 3. Prophylactic anti-emetic treatment is discouraged at the start of study treatment; however, patients can receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local standard/institutional practice. 4. Transfusions may be given, based on standard criteria and clinical judgment. 5. Corticosteroids are allowed for the symptomatic control of brain metastases provided the dose is stable before and during the study and they are started at least 4 weeks prior to the start of study treatment. 6. Bisphosphonates (e.g., zoledronic acid and pamidronate) and monoclonal antibody denosumab are allowed for bone metastases/bone pain. 7. Concurrent palliative radiotherapy for pain relief is allowed at the site of bone metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period; and radiotherapy is limited to an area other than the sole site of measurable or evaluable disease. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes palliative radiation. 8. If concomitant treatment of drugs metabolized by CYP3A4/CYP2C9 enzymes are clinically warranted, careful observation of the patient is advised. 9. Low molecular weight heparin (LMWH) and Direct Oral Anticoagulant (DOA) such as dabigatran and edoxaban are acceptable for prophylaxis and/or treatment of venous thrombosis. Careful observation of the patient is advised while using apixaban and rivaroxaban. 10. Any Covid-19 vaccine (e.g., mRNA, viral vector and inactivated vaccine), and other inactivated vaccines are allowed and can be given as per the institutional guidance. 11. Any other treatment (except anti-cancer therapy as mentioned in the prohibited medication) which is required as a part of standard of care of the institution. However, this should be discussed with Medical Monitor and documented.

Prohibited medication	The following treatments are prohibited while on the clinical trial: • Any other anti-cancer therapy (e.g., radiation therapy, hormonal, immunotherapy or biologic therapy). • Strong inhibitors or inducers of CYP3A4. Patients should stop using these medications at least 48 hrs or 5 half-lives (whichever is shorter) prior to C1D1. • Strong inhibitors or inducers of CYP2C9. Patients should stop using these medications at least 48 hrs 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 48 hrs or 5 half-lives (whichever is shorter) prior to C1D1. • Use of heparin and warfarin for prophylaxis and/or treatment of venous thrombosis is prohibited. These drugs should be stopped at least 48 hrs prior to C1D1. • Herbal or alternative medicines are not allowed throughout the trial. Patients should stop using these medications at least 48 hrs prior to C1D1. • Live attenuated vaccine (e.g., Flu vaccine, pneumovax, varicella) should not be administered whilst the patient is receiving study treatment. • Concurrent medications or substances with the potential to affect the activity of tenalisib as reviewed and confirmed by medical monitor. • Any other investigational agent.
Discontinuation Criteria	***The patient will be discontinued from the study if any adverse event or procedure poses increased risk to the patient or interferes with the study conduct;*** examples include but are not limited to the following: - NCI CTCAE v5.0 Grade 3/4 non-hematological toxicity related to study drug that necessitates withdrawal in the opinion of investigator. - Development of an intercurrent illness, condition, or procedural complication, which could interfere with the patient's continued participation. - 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. In addition, patients will be discontinued from the study in the following circumstances: - Consent withdrawal by the patient (all patients are free to withdraw from participation in this study at any time, for any reasons, specified or unspecified, and without prejudice). - Pregnancy - Non-compliance by study patient. - Confirmed disease progression during therapy. - Discontinuation of the study by the Sponsor
Safety assessment:	AEs will be recorded and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 5.0). Physical examination, vital signs, ECGs and clinical laboratory tests will be performed at screening and at specific time points during the study. Clinical and laboratory evidence of AEs will be monitored routinely throughout the study and for 30 days following discontinuation of the study drug.

Efficacy Assessment	• Computed tomography (CT) with IV contrast will be the primary modality for assessment, unless the patient has an allergy to contrast that cannot be controlled with pre-medications. If patients are unable to receive iodinated CT contrast, the preferred imaging is non-contrast CT of the chest, and MRI of the abdomen and pelvis with contrast. • Disease will be re-assessed by the site investigator/radiologist using RECIST version 1.1 at C3D1 (± 7 days) and approximately 8 weeks thereafter (± 7 days), and/or at the EOT and/or as clinically indicated (if clinical progression is suspected). Investigator-assessed response will be used for analysis.
Sample size calculation:	A sample size of 20 per group will provide a precision of 13% for a two-sided 90% confidence interval based on Exact (Clopper-Pearson) method assuming the percentage of patients without progression at the end of 6 months is 20%. Thus, a total of 40 patients (20 patients in each group) will be enrolled in the study.
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. The following two analysis populations are planned for this study: • Intent-to-Treat Population (ITT): The ITT is the primary analysis population and will include data from patients who have received at least 1 dose of study medication. • Per-Protocol (PP) Population: The PP Population is a subset of the ITT population and will include patients without major protocol deviations. Membership in the analysis populations will be determined before database lock.

GENERAL INFORMATION	
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List of Abbreviations

AE	Adverse Event
AI	Aromatase Inhibitor
ALP	Alkaline Phosphatase
ALT (SGOT)	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AST (SGPT)	Aspartate aminotransferase
AUC_{0-t}	Area Under the plasma-concentration time curve from zero up to the last measurable concentration
BID	Twice Daily
BRCA	Breast Cancer gene
β-HCG	β-human chorionic gonadotropin
C_{max}	Peak Drug Concentration
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CDK	Cyclin Dependent Kinase
CLL	Chronic Lymphocytic Leukemia
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
DSB	Double Strand Break
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EOS	End of Study
EOT	End of Treatment
GCP	Good Clinical Practices
GGT	Gamma Glutamyl Transferase
G-CSF	Granulocyte Colony-Stimulating Factor
Hb	Hemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDPE	High-density Polyethylene
HIV	Human Immunodeficiency Virus
HL	Hodgkin's Lymphoma
HR	Homologous Recombinant
IB	Investigator's Brochure
ICF	Informed Consent Form
ITT	Intent-to-Treat
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IUD	Intrauterine Device
IUS	Intrauterine System

LAR	LAR Legally Acceptable Representative
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LMWH	Low Molecular Weight Heparin
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
iNHL	Indolent Non-Hodgkin's Lymphoma
NOAEL	No-Observed-Adverse Effect Level
NSAID	Non-Steroidal Anti-Inflammatory Drug
ORR	Overall Response Rate
PD	Progressive Disease
PARP	Poly-ADP Ribose polymerase
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI	Principle Investigator
PI3K	Phosphoinositide 3-kinase
PJP	Pneumocystis *Jirovecii* Pneumonia
PK	Pharmacokinetics
PP	Per-Protocol
PR	Partial Response
PTCL	Peripheral T-cell lymphoma
PTEN	Phosphatase and Tensin Homolog
QA	Quality Assurance
QTcF	Frederica's (QTcF)
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Stable Disease
SDV	Source Document Verification
SIK	Salt-inducible Kinase
SOP	Standard Operating Procedures
$t_{1/2}$	Plasma Half Life
TG	Triglyceride
TCL	T-cell lymphoma
TGI	Tumour Growth Inhibition
ULN	Upper Limit of Normal
UV	Ultra-violet
WBC	White Blood Cells

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1 BACKGROUND INFORMATION

1.1 Background

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. In hematological malignancies, inhibition of δ isoform is known to dampen the responsiveness of the tumour cells to supportive stimuli from the microenvironment. PI3K δ inhibitors act to a large extent by disrupting the interactions between the malignant B-cells, their protective stromal cells and immune cells, without directly killing the cancer cells. In solid tumours (e.g., breast and prostate cancer) p110 δ is shown to dampen the activity of PTEN tumour suppressor. Inactivation of p110 δ in these cells leads to PTEN activation, suppression of Akt phosphorylation, and inhibition of cell proliferation. Likewise, forced overexpression of p110 δ in cells with low p110 δ expression reduces PTEN activity, resulting in increased Akt phosphorylation.[1] This is exemplified by the frequent activating mutations in PIK3CA and the loss of PTEN functionality in common cancers such as breast, colon and ovary. In addition, the expression levels of p110δ protein seem to act as an intrinsic cancer-causing driver in various solid tumours including breast, prostate, colorectal, liver, merkel-cell carcinoma, glioblastoma and neuroblastoma.[1] Multiple p110δ selective inhibitors are being studied as potential single agent or in combination for treatment of solid tumours. **(Table 1)**

The immunosuppressive microenvironment in tumour tissue is partly mediated by non-tumoural stromal cells, most notably tumour associated macrophages (TAMs)**.** These tumour-reprogramed macrophages shut down effector T and NK cell activities with soluble immunosuppressive factors and membrane-bound immune checkpoint molecules. Data has shown that PI3Kγ acts as a molecular switch turning on immunosuppression while shutting down immune-stimulatory activities. Inhibitors of PI3Kγ, can cause a shift/re-programming leading to enhanced adaptive immunity, including increased recruitment and cytotoxicity of T cells.[2] This change in the immune environment significantly inhibit the growth and metastasis of tumours.[3] The PI3Kγ inhibitor (Eganelisib) is being studied as potential single agent or in combination for treatment of solid tumours. **(Table 1)**

Activation of the PI3K/AKT pathway has been implicated in *de novo* and acquired treatment resistance to targeted therapies in multiple solid tumour.[4,5] In addition, PI3K also stabilizes and preserves double strand break (DSB) repair by interacting with the human recombinant complex under normal conditions[6] and is necessary for DNA repair during ionizing radiation.[7] PI3K inhibitors have shown to induce DNA damage in tumours that have defects in DNA damage-repair pathways, by disproportionately affecting the nonoxidative pentose phosphate pathway that delivers ribose-5-phosphate required for base ribosylation.[8] PI3K blockade also promotes Homologous Recombinant (HR) deficiency by downregulating *BRCA*1/2 and sensitizes *BRCA*-proficient tumours to poly-ADP Ribose polymerase (PARP) inhibition.

Salt-inducible kinases (SIKs) are highly conserved serine/threonine protein kinases that belong to a family of AMP-activated protein kinases (AMPKs) and have a role in steroidogenesis, adipogenesis and regulation of tumour malignancy. SIKs are dysregulated in various cancers, including ovarian, breast, prostate, and lung cancers, indicating that SIKs may have role in tumour occurrence or progression.[9, 10] SIK-3 facilitates tumour cell resistance against cytotoxic T cell attack by shifting TNF signaling from apoptosis to survival. SIK3-specific inhibitors alone sensitize a wide array of human and murine cancer cell lines to TNF-induced apoptosis by engaging HDAC4/NFkB pathway.[11]

SIK3 also governs G1/S process through upregulating the gene expression of cyclin D and cyclin E, downregulating the expression of p21 and p27, and increasing the Cyclin Dependent Kinase 2 (CDK2) activity. The absence of SIK3 leads to prolongation of mitosis in mice and human cells, thus increasing the sensitivity of cancer cells to a variety of anti-mitotic drugs.[12] SIK3 also plays a positive role in mediating the high salt-induced inflammatory signal response that leads to cancer cell proliferation. SIK3 induces the upregulation of inflammatory arginine metabolism factors, such as iNOS and ass-1, and the downregulation of anti-inflammatory enzymes, such as arginase-1 and ornithine decarboxylase in breast cancer.[13] Multiple SIK-3 inhibitors are being studied for treatment of solid tumours. **(Table 1)**

Table 1: PI3K δ, γ and SIK-3 inhibitors in clinical development for solid tumours

Drug name	Selectivity	Combination agent	Indication	Phase of the study
PI3K δ inhibitor				
AZD8835	PI3K α, δ	Fulvestrant	ER+, HER2-ve breast cancer	Phase 1
Parsaclisib	PI3K δ	INCMGA00012	Advanced Solid Tumours	Phase 1b
BGB-10188	PI3K δ	Tislelizumab	Advanced solid tumours.	Phase 1/2
Copanlisib	PIK3 α, δ	Eribulin	TNBC	Phase 1/2
		Trastuzumab	HER2-positive Breast Cancer.	Phase 1b/2
PI3K γ inhibitor				
Eganelisib (IPI-549)	PI3K γ	Atezolizumab/ Nab Paclitaxel	Triple-Negative Breast Cancer	Phase 2
SIK3 inhibitor				
GRN-300/ ARN-3261	SIK2/3	Paclitaxel	Ovarian Cancers	Phase I
OMX-0370/ IMT-07	SIK3	-	Advanced Solid Tumours	Preclinical
ARN-3236	SIK2	-	Advanced Solid Tumours	Preclinical

1.2 Tenalisib (RP6530)

Tenalisib is a highly specific and orally available dual PI3K δ/γ and SIK-3 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.

1.3 Pre-clinical Studies with RP6530

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 the potential in modulation of the tumour microenvironment. Studies using immortalized B and T lymphoma cell lines demonstrated the anti-proliferative effect of tenalisib coupled with induction of apoptosis and a concomitant inhibition of the downstream biomarker, pAKT. Similarly, cytokine induced pAKT was inhibited in malignant primary CTCL cells isolated from patient donors.[14]

In case of solid tumours, in MC38 syngeneic murine colon carcinoma model in immunocompetent C57BL/6 female mice, treatment with tenalisib showed tumour growth inhibition (TGI) of 29% as compared to control. The combination of tenalisib and anti-PD1 reduced a mean tumour volume by 63% as compared to control.

Combination of tenalisib and IN0385 (the major metabolite of tenalisib) potentiated the activity of taxol and doxorubicin in attenuating the growth of breast cancer cell lines. In another study, IN0385 demonstrated its activity as a single agent and in combination with a PARP inhibitor, talazoparib in ovarian cancer cell lines. Addition of IN0385 potentiated the activity of talazoparib. Similarly, IN0385 demonstrated its activity in combination with olaparib in breast cancer cell lines. IN0385 also potentiated the TNF-α mediated inhibition and apoptosis in breast cancer, AML and pancreatic cancer cell lines, and combination of TNF-α and IN0385 resulted in GI_{50} shift of IN0385 to left and significant inhibition of cell proliferation. Refer to the Investigator's Brochure (IB) for detailed background information on tenalisib.[14]

1.4 Clinical Experience

As of 20th April 2021, a total of 169 patients with relapsed/refractory hematological malignancies (viz. CLL, PTCL, CTCL and iNHL) have been exposed to tenalisib in either single agent or combination studies; 35 patients in RP6530-1301 study, 58 patients in RP6530-1401 study, 2 patients in RP6530+Pembrolizumab-1701 study, and 33 patients RP6530+Romidepsin-1805 study, 20 patients in RP6530-1802 study, 21 patients in RP6530-1901 study. A total of 16 patients have been rolled over to compassionate study (RP6530-1803); 4 from RP6530-1401 study, 5 from RP6530+Romidepsin-1805 study and 7 from RP6530-1901 study. In addition, 18 healthy volunteers were exposed to tenalisib in food effect study (RP6530-1501).

- **Safety:**

169 patients have received tenalisib at doses ranging from 25-1200 mg BID. Tenalisib is generally well tolerated in patients with hematological malignancies (at doses ranging from 25 mg BID to 1200 mg BID) and aggressive lymphomas such as TCL (at doses ranging from 200 mg BID to 800 mg BID). The most frequently reported related AEs (all grades) that occurred in more than 10% of patients included alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased (15.6% each) and diarrhea (11.9%). The most frequently reported related Grade ≥3 AEs were ALT increased, AST increased (7.4% each) and neutropenia (4.4%). Other Grade ≥3 laboratory abnormalities included gamma-glutamyl transferase (GGT) increased, International normalized ratio (INR)

increased, hyperglycemia and hypertriglyceridemia reported in one patient each. Hypophosphatemia and thrombocytopenia were reported in two patients.

- **Pharmacokinetics:**

In RP6530-1301 study, pharmacokinetics (PK) was evaluated in patients with hematological malignancies at doses ranging from 25-1200 mg BID and in TCL at doses ranging from 200 to 800 mg BID. Maximum systemic exposures assessed by AUC_{0-t} as determined on Cycle 1 Day 1 (C1D1) were found at these doses. Tenalisib showed rapid absorption (between 0.5 and 2 h), with C_{max} and AUC_{0-t} increasing proportionately with dose on C1D1. There was no significant accumulation between C1D1 and C2D1. Trough concentrations did not show any specific trends from one day to the other even though concentrations increased generally with doses. $T_{1/2}$ were similar for all dose levels.

Clinically relevant concentrations of IN0385, a major metabolite of tenalisib, were observed in patients treated with tenalisib. Exposures (C_{max}) for IN0385 ranged between 1.2 to 2.2 times of tenalisib (the parent compound). Elimination kinetics of IN0385 were however similar to tenalisib with half-life ranging between 2 - 4.5 hours.

- **Efficacy:**

In Phase I study (RP6530-1301 study) in hematological malignancies, two patients (6.5 %) showed CR and 4 patients (12.9%) showed PR in 31 efficacy evaluable patients. The ORR was 19.4 % with a DCR of 61.3%. Duration of response was 5.68 (1.5-15.7) months. The time to onset of response was 3.49 months (1.4-11.9 months). PFS was 4.62 months (1.0-17.5 months).

In patients with TCL (RP6530-1401 study), a total of 16 out of 35 evaluable patients responded to tenalisib with ORR of 45.7% and a median DOR being 4.37 months. The best response of CR was noted in a total three (8.6%) patients while PR was noted in 13 (37.1%) patients. The ORR among CTCL and PTCL patients were similar and were 45.0% and 46.7% respectively. The median DOR among PTCL patients was 4.9 months whereas it was 3.83 months in CTCL patients.

In patients with indolent NHL (RP6530-1802 study), 20 patients received tenalisib in Part 1. Only one FL patient showed a PR out of 19 evaluable patients in the study. In patients with CLL (RP6530-1901 study), seven patients showed PR with ORR of 33% in 21 evaluable patients of Part I. Remaining 14 patients showed a stable disease. The median DOR was 5.23 months.

1.5 Rationale

1.5.1 Study Rationale

Breast cancer is the most common cancer diagnosed in women and is the second leading cause of cancer-related deaths. It is categorized into different histopathological subtypes based on expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). HR-positive, HER2-negative breast cancer is the most common subtype. Most patients with HR-positive, HER2-negative breast cancer are initially diagnosed and treated at an early stage with a combination of surgery with or without radiation and adjuvant endocrine therapy with or without adjuvant chemotherapy.

Approved therapies for patients with HR-positive, HER2-negative advanced or metastatic breast cancer include hormonal-based (aromatase inhibitor [AI], fulvestrant) therapies in combination with CDK 4/6 inhibitors (abemaciclib, palbociclib, ribociclib), everolimus with exemestane, alpelisib with fulvestrant, hormonal monotherapy (AI, fulvestrant, tamoxifen), and chemotherapy (capecitabine, eribulin, ixabepilone, paclitaxel protein-bound, gemcitabine, etc.).[15] Metastatic breast cancer is incurable and has a 5-year survival rate of approximately 25%. Treatment options for all patients remain an area of significant unmet need.

The PI3K pathway is a central oncogenic pathway that regulates cell proliferation, cell metabolism, growth, survival, and apoptosis. Constitutive activation of PI3K down signaling is a critical step in mediating the transforming potential of oncogenes and tumour suppressors in many tumour types. Constitutive activation of the PI3K pathway has also been linked to resistance for a variety of therapeutic interventions, including chemotherapy, hormonal therapy, and anti-HER2 therapies. Similarly, activation of the PI3K pathway has been linked to *de novo* or acquired resistance to endocrine therapy, chemotherapy, and radiotherapy. Targeting PI3K pathway is therefore a potential therapeutic strategy for breast cancer.

Furthermore, in some solid tumours p110 δ is shown to dampen the activity of PTEN tumour suppressor. Given that PTEN somatic mutations occur in a small percentage of human breast cancers and that p110 δ is highly expressed in this tumour type, PI3K δ inhibitors may provide an excellent opportunity in the intervention of breast cancer. PI3Kγ plays major role in immunosuppressive microenvironment. PI3Kγ inhibitors plays major role modulation tumour micro-environment leading to inhibition of tumour growth and metastasis.

Overexpression of SIK is found in specific types of cancer such as ovarian and breast cancers. SIK3 is highly expressed in around 55% breast cancer patients. Elevated SIK3 expressions in breast cancer cells are shown to contribute to tumourigenesis. Mechanistic studies have demonstrated that SIK3 played a crucial role in induction of G1/S-phase release of cell cycle, along with enhanced expression of metastasis specific chemokine CXCR4 in breast cancer cells. The phosphorylation of HDAC4, a well-documented downstream target of SIK3, is known to induce cell proliferation and malignancy.[16] Also, high expression of SIK3 stimulates mTOR-mediated aerobic glycolysis and cell proliferation of breast cancer cells.[17]

These evidences suggest the role of PI3K and SIK in oncogenesis and its maintenance and hence its inhibition can potentially lead to inhibition of growth of locally advanced or metastatic breast cancers. Several PI3K inhibitors, most of which are orally administered, either with broad activity against all PI3K isoforms or selectivity for specific isoforms, are in clinical development **(Table 1)**.

Tenalisib is a highly selective PI3K δ/γ and SIK3 inhibitor with a differentiated safety profile. In addition to PI3K class effects, anti-tumour activity of tenalisib is through three distinct and non-overlapping mechanisms; a) inhibition of δ isoform enhances an anti-tumour cytotoxic T-cell response by reducing the immune-suppressive function of regulatory T cells (Tregs), b) inhibition of γ isoform decreases tumour growth by modulating tumour micro-environment, c) Inhibition of SIK3 potentiates the activity of TNF-α and thus increases apoptosis.

Tenalisib has been evaluated in >150 patients with haematological malignancies and demonstrated encouraging activity in indications such as T-cell lymphoma (TCL) and Hodgkin's Lymphoma (HL). The added influence of SIK-3, which is relevant to solid tumours, could potentially augment the activity of tenalisib in aggressive tumours.

Tenalisib demonstrated pre-clinical activity as a single agent and in combination in multiple cell lines and syngeneic model representative of various solid tumours. In MC38 syngeneic murine colon carcinoma model in immunocompetent C57BL/6 female mice, treatment with tenalisib reduced a mean tumour volume with TGI of 29% as compared to control. The combination of tenalisib and anti-PD1 reduced a mean tumour volume with TGI of 63% as compared to control, possibly indicating modulation of tumour micro-environment through inhibition of γ isoform by tenalisib.[14]

Combination of tenalisib and IN0385 potentiated the activity of taxol and doxorubicin in attenuating the growth of breast cancer cell lines. In another study, IN0385 demonstrated its activity as a single agent and also in combination with talazoparib in ovarian cancer cell lines. Addition of IN0385 at 5μM potentiated the activity of talazoparib. Similarly, IN0385 demonstrated its activity in combination with olaparib in breast cancer cell lines. Addition of IN0385 potentiated the TNF-α mediated inhibition and apoptosis in breast cancer, AML and pancreatic cancer cell lines, and combination of TNF-α and IN0385 resulted in GI_{50} shift of IN0385 to left and significant inhibition of cell proliferation. [14]

Based on these pre-clinical evidences with tenalisib and clinical evidences from other PI3K inhibitors, it is proposed that tenalisib has the potential to treat the patients with locally advanced and metastatic breast cancer.

1.5.2 Rationale for Dose Selection

The safety and tolerability of tenalisib has been established up to doses of 1200 mg BID (total daily dose of 2400 mg) in patients with relapsed/refractory hematologic malignancies.[18] No dose limiting toxicity was seen at this dose level. The efficacy of tenalisib at 800 mg BID has been evaluated as a single agent as well as in combination in patients with TCL and showed impressive response in this patient population. [19,20]

In this study of breast cancer, the objective is to evaluate two doses of tenalisib and thus identify the optimal dose amongst the two which shows signal of clinical efficacy with an acceptable safety profile. This dose can be thus taken ahead for further development. Hence doses of 800 mg BID and 1200 mg BID are proposed in this Phase II study.

1.6 Benefit and Risks of participation in the study

It is expected that proposed doses of tenalisib have the potential to improve response rates and benefit rates, and also increase the progression free survival. 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 effectiveness and safety of an investigational medicine. Additional details regarding specific benefits and risks for subjects participating in this clinical trial can be found in the accompanying IB and Informed Consent documents.

This protocol is written considering the impact of COVID-19 on trial participants, site staff and sponsor staff. The protocol includes the following adaptations to minimize risk while prioritizing the overall well-being and best interests of all involved in the trial. With these priorities in mind, the protocol design still permits assessment of safety and efficacy of tenalisib.

- Minimize the number of study visits to align with the trial endpoints.
- Minimize the number of trial specific activities. The trial is designed to align with standard of care protocols for locally advanced and metastatic breast cancer. For example, obtaining data from standard of care assessments conducted during routine care, for the collection and reporting of some safety outcomes (vital signs, laboratory results) and imaging outcomes.
- Conduct visits by telemedicine or by telephone at EOS visit, where permitted, when a participant is unable to attend the site physically. This will permit the timely collection of efficacy endpoints (example: response to treatment or progression) and safety data (e.g., AE, SAE, lab assessment).
- Use of remote electronic consent, where permitted.

In addition to the above items included in the protocol, ongoing risk assessments and monitoring of the COVID-19 situation will be conducted by the sponsor with input from the local investigators at both a site and country level. These ongoing assessments include changes to any of the following:

- Potential impact on trial participants
- Potential impact on trial site staff, including local or central IRBs/ECs.
- Potential impact on sponsor/CRO staff conducting site monitoring and central review of data.

The outcome of these ongoing assessments could result in site-specific or country-specific mitigation plans, which could include:

- Suspension of enrollment in that site or country
- Suspension of on-site visits by participants in that site or country, replacing the physical data capture with some remote measures (telephone or telemedicine, where permitted)

- Suspension of on-site visits being conducted by the study monitor, replacing the monitoring with remote review of data and telephone contacts with the site.
- Other mitigation plans, as appropriate.

2 TRIAL OBJECTIVES

2.1 Primary Objective

– To assess the anti-tumour activity of tenalisib in patients with locally advanced or metastatic breast cancer.

2.2 Secondary Objective

– To evaluate the safety and tolerability of tenalisib.

2.3 Exploratory Objective

– Changes in serum cytokines/chemokines and tumour tissue gene expression post treatment with tenalisib.

3 TRIAL DESIGN

3.1 Trial End Points

3.1.1 Primary Endpoint

– Percentage of patients without disease progression at the end of 6 months.

3.1.2 Secondary Endpoints

– Overall Response Rate (ORR), Clinical Benefit Rate (CBR) and Progression Free Survival (PFS).
– Adverse event (AE), Grade 3/4 AEs, serious adverse event (SAE) evaluated and graded using NCI-CTCAE Version 5.0.

3.1.3 Exploratory Endpoints

– Change from baseline in cytokine/chemokine levels post treatment with tenalisib.
– Change in gene expression profiles as measured by RNA sequencing from tumour biopsy samples post treatment with tenalisib.

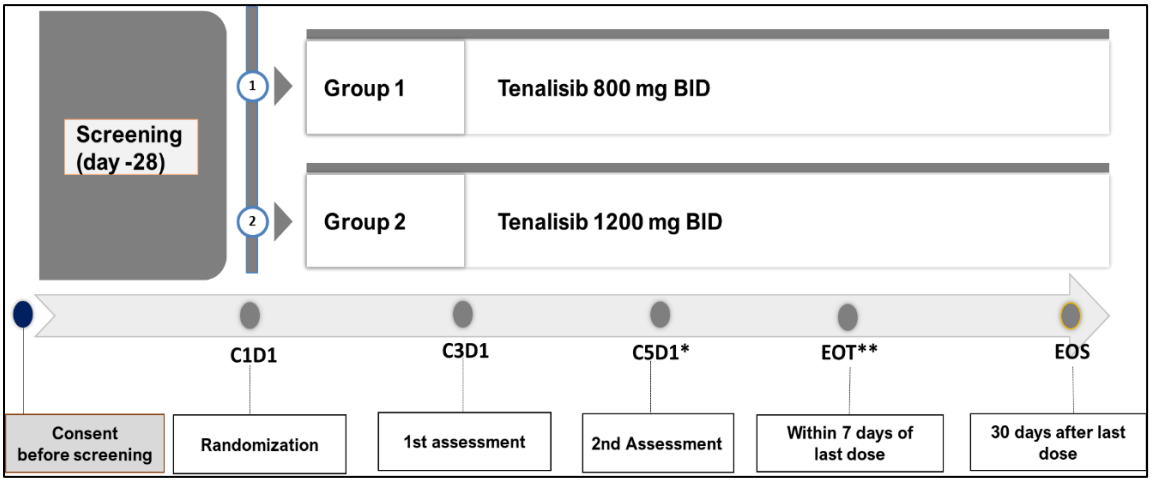
3.2 Design of Trial

This is a Phase II, randomized, open label study, designed to evaluate the preliminary efficacy and safety of tenalisib at two dose levels (800 mg BID and 1200 mg BID) in 40 patients with locally advanced or metastatic breast cancer. Twenty patients each, will be enrolled in Group 1 (Tenalisib 800 mg BID) and Group 2 (Tenalisib 1200 mg BID). Both groups will be run in parallel.

Table 2 : Dosing Scheme

Groups	Number of Patients	Dose of Tenalisib
Group 1	20	Tenalisib 800 mg BID
Group 2	20	Tenalisib 1200 mg BID

Figure 1: Study Design



Note:
* Disease will be re-assessed at C3D1 (± 7 days) and approximately 8 weeks thereafter (± 7 days), and/or at the EOT and/or as clinically indicated (if clinical progression is suspected).
** Patients will undergo the end-of-treatment (EOT) assessments within 7 days after last dose of study drug or discontinuation.

3.3 Randomization

This is a randomized, open label study. Eligible subjects will be randomized to one of the two groups (Group 1: Tenalisib 800 mg BID and Group 2: Tenalisib 1200 mg BID) in 1:1 ratio based on the central randomization list generated by a validated software.

3.4 Investigational Medicinal Product

3.4.1 Dosage Form and Strengths

A single strength of tenalisib tablet will be used in the study.

Investigational Product(s)	Dosage form, strength
Tenalisib (RP6530)	Tablets 400 mg

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

3.4.2 Labeling, Packaging and Supply

Tenalisib will be appropriately labeled and packaged as per local regulatory requirements and will be supplied to the sites through Rhizen Pharmaceuticals/designee. Tenalisib will be available as 30 tablets per bottle. Recommended storage condition is "Store at 20 to 25°C, excursions permitted between 15°C and 30°C".

3.4.3 Guidelines for administration of Tenalisib

- Method of administration: Tenalisib will be administered orally twice daily in a 28-day cycle (Day 1-28).
- Premedication: None.
- 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 minimum 8 hours between two doses. If it is missed for the entire day, it should not be repeated.
- If vomiting occurs, no attempt should be made to replace the vomited dose.
- Study drug compliance should be reviewed with the patient at the beginning of each new treatment cycle. Missed doses should be documented.

3.4.4 Accountability of Investigational Medicinal Products

The PI/designee is responsible for the receipt of investigational medicinal product (tenalisib) and accountability of supplies at the site. During monitoring visit, the study monitor will ensure that all IMP related documentation is current and accurate. Study monitor will verify the drug accountability logs to ensure that the IMP has been dispensed as per the protocol and all the relevant information is documented. He will conduct an inventory of the remaining IMP at the site. All tenalisib inventories must be made available for verification by the monitor, sponsor representatives and regulatory agency inspectors/monitor upon request.

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

3.4.5 Precautions and Risks Associated with Investigational Product

- Monitoring of liver enzymes and levels of TSH, T3, and T4 in patients receiving tenalisib is recommended based on target organ toxicity. Patients will be monitored for increased ALT/AST, skin rash, neutropenia as these are reported with tenalisib. In addition, events like enteritis (colitis), pneumonia/pneumonitis would also be looked for as they have been reported with other PI3K inhibitors. Tenalisib elicits no photo instability upon exposure to ultraviolet (UV) radiations. However, in absence of in-vitro data, possibility of photo-toxicity with tenalisib cannot be ruled out.
- Tenalisib shows inhibition of CYP3A4 enzyme. Therefore, concomitant administration of tenalisib with predominant CYP3A4 substrates (e.g., calcium channel blockers,

warfarin, carbamazepine, macrolide antibiotics, lovastatin, simvastatin, terfenadine) may reduce clearance of these drugs increasing the risk of adverse events.
- Similarly, as tenalisib is inhibited by CYP3A4/5 and CYP2C9, there is possibility of drug interaction with inhibitors or inducers of CYP3A4 and CYP2C9. If concomitant treatment with these drugs is clinically warranted, careful observation of the patient is advised. 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.[14]

3.5 The Expected Duration of Patient Participation and Follow-up

The expected duration of patient participation in the study will be approximately 24 months, unless the patient is discontinued from the study due to disease progression, drug toxicity or consent withdrawal.

3.6 Study Stopping Rules

The study will be terminated if emerging safety findings confirm increased risk to the patients or a significantly altered risk-benefit assessment. Examples include but are not limited to the following:

- New toxicological or pharmacological findings that significantly alter the risk benefit assessment or more SAEs of similar nature which in the opinion of the investigator, are the result of tenalisib, and hence place remaining patients at risk.
- The sponsor may decide to discontinue the study if it becomes apparent that patient enrollment is unsatisfactory, and/or for administrative reasons.

Regulatory authorities and respective IRB(s)/EC's will be notified if the trial terminates early with a justification for the early termination.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

Individuals should meet all the following criteria to be considered eligible to participate in the study:

1. Provision of full informed consent prior to any study-specific procedures.
2. Patients must be ≥18 years of age, at the time of signing informed consent.
3. Female patients who have histologically and/or cytologically confirmed locally advanced or metastatic breast cancer that has progressed following at least one line of therapy.
4. Patients with at least one measurable lesion per RECIST version 1.1 at baseline that can be accurately assessed by CT scan or MRI and is suitable for repeated assessment at follow up-visits.
5. ECOG performance status 0 to 2.
6. Life expectancy of at least 3 months.
7. Adequate bone marrow, liver and renal functions as assessed within 7 (±2) days before the first dose of study drug with the following laboratory requirements:
   a. Hemoglobin ≥ 8.0 g/dL (should not be transfused or treated with erythropoietin to maintain or exceed this level)
   b. Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L without growth factor support

c. Platelet count ≥ 75 x 10^9/L
d. Total bilirubin ≤ 1.5 times the ULN (or ≤ 3 x ULN, if the patient has Gilbert syndrome)
e. ALT and AST ≤ 3 x ULN (≤ 5 x ULN for patients with liver metastasis or liver involvement)
f. Creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault formula) for patients with creatinine levels above ULN.

8. Female patient of childbearing potential should be willing to use a medically acceptable method of contraception as defined in ***Appendix B*** while participating in the study and for 30 days after the last dose of study drug AND must have a negative serum pregnancy test within 3 days prior to Cycle 1 Day 1 (C1D1).
9. Ability to swallow and retain oral medication.
10. Willingness and capability to comply with the study requirements.

4.2 Exclusion Criteria

Individuals who meet any of the following criteria will be considered ineligible to participate in the study:

1. Patients with HER-2 positive breast cancer
2. Patient receiving anticancer therapy (e.g., chemotherapy, biologic therapy, hormonal therapy or any other investigational product) within 4 weeks or 5 half-lives of the drug prior to C1D1, whichever is shorter. Treatment interval will be 6 weeks for nitrosoureas or mitomycin C.
3. Patient who has not recovered from acute toxicities (defined as NCI-CTCAE grade > 1) of previous therapy except treatment-related alopecia. (Note: Patient with any unresolved toxicities which in the opinion of PI are stable and controlled with medication can be enrolled in the study).
4. Patients who have had disease progression within 8 weeks of platinum chemotherapy. (Note: Patients who have had a disease-free interval of more than 8 weeks following platinum chemotherapy; and patients with previous neoadjuvant OR adjuvant platinum-based therapy can participate in the study).
5. Prior exposure to investigational or marketed PI3K inhibitors (e.g., idelalisib, copanlisib, duvelisib, umbralisib, alpelisib, buparlisib) given for treatment of breast cancer.
6. Major surgery within 4 weeks of starting study treatment OR any patient who has not recovered from the effects of major surgery.
7. Patient with symptomatic uncontrolled brain metastasis. (Note: A scan to confirm the absence of brain metastases is not required. Patients whose brain metastatic disease has remained stable for ≥ 4 weeks (prior to the start of study treatment) following treatment of brain metastases are eligible. The patient can receive a stable dose of corticosteroids before and during the study if steroids were started at least 4 weeks prior to C1D1).
8. HIV-positive patients who are on antiretroviral therapy OR active hepatitis C OR active hepatitis B virus infections.
9. Ongoing immunosuppressive therapy including systemic corticosteroids except as allowed per concomitant medication.
10. Known history of severe 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. (Note: Exception will be the patients with liver metastasis who can be enrolled in the study).

11. History of severe cutaneous reactions (e.g., Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) in the past.
12. Active gastrointestinal tract disease with malabsorption syndrome or uncontrolled inflammatory gastrointestinal disease such as Crohn's disease or ulcerative colitis.
13. Myocardial infarction within 6 months before starting therapy, symptomatic congestive heart failure (New York Heart Association > Class II), unstable angina, or unstable cardiac arrhythmia requiring medication or clinically relevant findings in the ECG such as second-or third-degree AV block, significant prolongation of the QTcF interval unless agreed between the investigator and the medical monitor.
14. Concurrent disease or condition that would interfere with study participation or safety, such as the following:
    - Active, clinically significant infection requiring parenteral antimicrobial agent.
    - Clinically significant bleeding diathesis or coagulopathy, including known platelet function disorder.
    - Mood disorders like OCD, severe depression, history of suicidal attempt, schizophrenia etc. as per the investigator's discretion.
15. Concurrent medications or substances with the potential to affect the activity or pharmacokinetics of tenalisib, as reviewed and confirmed by medical monitor.
16. Pregnancy or lactation.
17. Patient with other active malignancies at the time of screening except for adequately treated in situ carcinoma of the cervix uteri or carcinoma in situ of breast, basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin. (Note: Patients with prior malignancies which are treated and are in remission without requiring active treatment are allowed in the study).
18. A serious uncontrolled medical disorder or active infection which would impair the ability of the patient to receive protocol therapy or whose control may be jeopardized by the complications of this therapy.

Note: *Post eligibility confirmation, biopsy will be performed in approximately 10-12 patients who have consented for biopsy, prior to the first dose on C1D1. Eligible patients who do not consent for biopsy will also be enrolled into the study. Blood will be collected in all patients for cytokine/chemokine analysis.*

4.3 Discontinuation from Trial Treatment

The patient will be discontinued from the study in case of any adverse event or procedure that poses increased risk to the patient or interferes with the study conduct; examples include but are not limited to the following:

- NCI CTCAE version 5.0 Grade 3/4 non-hematological toxicities related to study drug that necessitate withdrawal in the opinion of investigator.
- Development of an intercurrent illness, condition, or procedural complication, which could interfere with the patient's continued participation.
- 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.

In addition, patients will be discontinued from the study in the following circumstances.:

- Consent withdrawal by patient (all patients are free to withdraw from participation in this study at any time, for any reasons, specified or unspecified, and without prejudice).
- Non-compliance by study patients.
- Pregnancy
- Confirmed disease progression during therapy.
- Discontinuation of the study by the Sponsor.

Each patient discontinuation should be discussed with Medical Monitor and the reason for discontinuation should be documented. For all discontinued patients, the end of study safety assessment should be completed at the time of discontinuation. In case of discontinuation due to an AE, patient should be followed up for 30 calendar days from dosing or until resolution/stabilization of AE, whichever is earlier. Patients who have drug related CTCAE grade ≥ 3 laboratory abnormalities should be followed until the laboratory values have returned to CTCAE grade ≤ 2.

Patients who are discontinued from the study at any stage will be considered for safety analysis. Patients who are discontinued from the study for reasons other than safety may be replaced as advised by the Medical Monitor, unless the Medical Monitor deems it unnecessary based on duration of the follow-up completed by the patient.

5 TREATMENT OF PATIENTS

5.1 Administration of Tenalisib

Tenalisib will be administered orally twice daily in a 28-day cycle (Day 1-28) up to 2 years until progression of disease or toxicity warranting discontinuation of therapy.

5.2 Concomitant Medications

In general, any concomitant medications should be avoided during the course of the study, unless it is required as a standard of care (necessary supportive care), prophylaxis or for the treatment of adverse event in the opinion of the treating investigator. The below recommendations should be followed, and concomitant medication should be clearly documented.

- Antimicrobial and/or anti-viral prophylaxis should be used according to local standard practice; Pneumocystis *jirovecii* pneumonia (PJP) and herpes zoster prophylaxis is strongly recommended. Similarly, chronic carriers of HBV should receive prophylactic anti-viral therapy.
- Hematopoietic growth factors (e.g., erythropoietin, GM-CSF and G-CSF) can be used for the management of acute toxicities such as febrile neutropenia when clinically indicated or at the discretion of the investigator.
- Prophylactic anti-emetic treatment is discouraged at the start of study treatment; however, patients can receive appropriate anti-emetic treatment at the first onset of

nausea or vomiting and as required thereafter, in accordance with local standard practice.
- Transfusions may be given, based on standard criteria and clinical judgment.
- Corticosteroids are allowed for the symptomatic control of brain metastases provided the dose is stable before and during the study and they are started at least 4 weeks prior to the start of study treatment.
- Bisphosphonates (e.g., zoledronic acid and pamidronate) and monoclonal antibody denosumab are allowed for bone metastases/bone pain.
- Concurrent palliative radiotherapy for pain relief is allowed at the site of bone metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period; and radiotherapy is limited to an area other than the sole site of measurable or evaluable disease. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes palliative radiation.
- 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) and Direct Oral Anticoagulant (DOA) such as dabigatran and edoxaban are acceptable for prophylaxis and/or treatment of venous thrombosis. Careful observation of the patient is advised while using apixaban and rivaroxaban.
- Any Covid-19 vaccine (e.g., mRNA, viral vector and inactivated vaccine), and other inactivated vaccines are allowed and can be given as per the institutional guidance.
- Any other treatment (except anti-cancer therapy as mentioned in the prohibited medication) which is required as a part of standard of care of the institution. However, this should be discussed with Medical Monitor and documented.

5.3 Prohibited Medications

The following treatments are prohibited while on clinical trial:
- Any other anti-cancer therapy (e.g., radiation therapy, hormonal, immunotherapy or biologic therapy).
- Strong inhibitors or inducers of CYP3A4. Patients should stop using these medications at least 48 hrs or 5 half-lives (whichever is shorter) prior to C1D1.
- Strong inhibitors or inducers of CYP2C9. Patients should stop using these medications at least 48 hrs 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 48 hrs or 5 half-lives (whichever is shorter) prior to C1D1.
- Use of heparin and warfarin for prophylaxis and/or treatment of venous thrombosis is prohibited. These drugs should be stopped at least 48 hrs prior to C1D1.
- Herbal or alternative medicines are not allowed throughout the trial. Patients should stop using these medications at least 48 hrs prior to C1D1.
- Live attenuated vaccine (e.g., Flu vaccine, pneumovax, varicella) should not be administered whilst the patient is receiving study medication.
- Concurrent medications or substances with the potential to affect the activity of tenalisib as reviewed and confirmed by medical monitor.
- Any other investigational agent.

Decision on discontinuation of the patient who received concomitant/prohibited medication will be taken by the PI in consultation with Medical Monitor on a 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 Patient Compliance.

The following measures will be employed to ensure treatment compliance.

- The study staff will instruct patients to bring any unused study drug to the site.
- The study staff/designee will count and record the number of used and unused study drug tablets.
- The study coordinator will confirm adherence to the dosing regimen with the patient.
- He/she will record the number of tablets 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

The Schedule of Event summarizes the trial procedures to be performed at each visit and is divided into following:

1. Screening (Day -28 to Day 0)
2. On treatment procedures (C1D1 to EOT)
3. End of Treatment (within 7 days from the last dose)
4. End of Study (Day +30 from the last dose)

Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Multiple procedures may be scheduled at the same time point relative to tenalisib.

6.2 Informed Consent

The investigator or qualified designee must obtain written consent from each potential patient or each patient's Legally Acceptable Representative (LAR) prior to participating in a clinical trial. Consent must be documented on an IRB/EC approved consent form. A copy of the signed and dated consent form should be given to the patient before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the patient must receive the IRB/EC's approval/favorable opinion in advance before use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient'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 patient's dated signature or by the patient's legally acceptable representative's dated signature. Specifics about a trial and the trial population will be added to the consent form template.

The informed consent will adhere to IRB/EC requirements, applicable laws and regulations and Sponsor requirements.

6.3 Screening

During screening period, written informed consent must be obtained prior to the initiation of trial treatment and before any protocol-specific procedures are performed. A*n additional consent for tumour biopsy will be requested.* Screening vitals, laboratory tests, as described in the Schedule of Events, will be performed as per institutional practice and will be reviewed by the site PI/designee. The laboratory tests should be done ≤ 7 calendar days prior to the initiation of trial treatment. Re-screening can be done at the discretion of PI.

Radiological assessment and other investigations to document presence of disease should be performed within 28 days prior to C1D1. Documentation of serology status (HIV, HBV and HCV) will be done based on historical information. 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).

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.

Covid-19 testing prior to enrollment may be done as per the institutional practice/local requirements.

6.3.1 Assignment of screening and randomization numbers

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 during screening. Post confirmation of the eligibility, subject will be assigned a randomization number.

Figure 2: Schema for screening

Screening period			Dosing
Day -28 to Day 0			Day 1
Patient consent	• Disease assessment • Radiological assessment • Laboratory assessment • Other assessments as part of eligibility assessment	• Eligibility confirmation • Collection of blood sample for cytokine/chemokines • Tumour biopsy in consented patients	First Dose of the study drug

Note: Post eligibility confirmation, the biopsy will be performed in approximately 10-12 patients who have consented for biopsy, prior to the first dose on C1D1. Eligible patients who do not consent for biopsy will also be enrolled into the study. Blood will be collected in all patients for cytokine/chemokine analysis.

6.3.2 Medical history

Basic demographic and baseline characteristics will be collected during screening. In addition to the evaluation of a patient's medical history in terms of study eligibility, all relevant medical conditions will be documented on the appropriate eCRF. Events occurring after signing of informed consent but prior to initiation of tenalisib, unless serious and due to a protocol mandated procedure, should be recorded on the Medical History eCRF.

The patient's entire oncology history will be collected on the appropriate eCRF including date of diagnosis for cancer (and other malignancy, if applicable), prior surgeries / treatments received for cancer, dates of treatment administration, best response achieved, date of progression and its assessment, and *BRCA* mutation status (if known).

6.3.3 Prior and Concomitant Medication Review

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

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

6.3.4 Physical Examination

Full physical examination: The investigator/qualified designee will perform a complete physical exam during the screening period and as defined in Schedule of Events. Physical examination will include systemic examination (General Appearance, HEENT, neck,

cardiovascular, lungs, abdomen, lymph nodes, genitourinary (as applicable), extremities, neurological, skin, and musculoskeletal). Physical examination also includes measurement of accessible nodes and the size of the spleen and liver. Clinically significant abnormal findings should be recorded as medical history.

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

6.3.5 Vital Signs

Vital signs include temperature, pulse, respiratory rate, weight and blood pressure and should be recorded as per institutional practice. Historical data can be used for height. Vitals will be done prior to the administration of study treatments, at the time points specified in schedule of events.

6.4 Laboratory Investigations

Laboratory tests for hematology, chemistry and urinalysis are specified in **Table 3.**

Table 3 : Laboratory Tests for Hematology, Chemistry and Urinalysis

Hematology	Chemistry Panel I	Chemistry Panel II	Urinalysis	Other
Hematocrit	Total bilirubin	Total Cholesterol	Blood	Serum β-hCG
Hemoglobin	Alkaline phosphatase	Triglyceride (TG)	Glucose	Urine pregnancy test
Platelet count	ALT	LDL	Protein	PT and INR
WBC (Total and differentials)	AST	HDL	Specific gravity	Serology (Hepatitis B, Hepatitis C, HIV)- Historical data is acceptable.
Absolute neutrophil count	LDH	T3, T4, TSH	Microscopic exam[b]	
	GGT			
-	Blood glucose			
	Albumin			
	Total protein			
	Urea or BUN[a]			
	Creatinine			
	Sodium			
	Potassium			
	Calcium			
	Phosphorous			
	Chloride			

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

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are out of reference range, the

investigator may opt to retest the patient and the subsequent within range screening result may be used to confirm eligibility.

Blood drawn for these tests will be specified in informed consent form (ICF) as per the site ICF requirements. *All safety laboratory investigations will be performed locally at the site.* Screening labs will be done within 7 calendar days prior to the initiation of trial treatment. If these initial examinations are obtained within 72 hours of Cycle 1 Day 1, the labs need not be repeated on C1D1 again.

6.5 12-Lead Electrocardiograms

A single 12-lead electrocardiogram (ECG) will be obtained at designated time points using local ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals. ECG will be performed after the patient has at least a 5-minute rest. Additional ECGs will be obtained if clinically indicated.

Table 4 : ECG time points

Days	Time points
Screening	Within last 28 days
C1D1	Pre-dose
At other time points	Pre-dose C2D1, C3D1 and at EOT visit

6.6 Tumour Biopsy

When patient presents with a biopsiable tumour/nodes/metastatic lesion, an on-study tumour biopsy will be performed (only in patients who agree to provide consent for the biopsy). The biopsy will be done after eligibility confirmation and prior to first dose on C1D1. A second biopsy sample will be taken at C3D1.
Tumour tissue collected during the study will be fixed and processed to a FFPE block. Details on shipping the FFPE block to the central genomics lab will be detailed in the laboratory manual

6.7 Serum Cytokines/Chemokines

Correlative serum for cytokines/chemokines (refer ***Appendix C***) will be collected at screening and at the C3D1. Blood samples will be obtained in all patients at baseline and at C3D1. Processed serum samples will be stored at the specified temperature until analysis. The analyses of correlative markers are exploratory evaluation and will not be used to guide treatment decisions in the dose escalation and expanded cohort of the study. See laboratory manual for blood/serum processing instructions.

6.8 End of Trial Treatment (EOT) Visit

All discontinued patients will undergo the end-of-treatment (EOT) assessments within 7 days after the last dose of study drug or discontinuation from the study. Radiological assessment will not be performed if done earlier within 28 days.

6.9 End of Study (EOS) Visit

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

Table 5 : Schedule of Events

Cycle	Screening	C1		C2		C3	Monthly visits (C4 onward up to 2 year)[19]	Efficacy Visits (C5, C7, C9… up to 2 year)[20]	EOT[21]	EOS[22]
Day	**D-28 to 0**	**D1**	**D15**	**D1**	**D15**	**D1**	**D1**	**D1**	**-**	**-**
Window period	**-**		**±1**	**±1**	**±3**	**±3**	**±3**	**±7**	**+7**	**+30**
Study Days	**D-28 to 0**	**1**	**15**	**29**	**43**	**57**	**-**	**-**	**-**	**-**
Informed Consent[1]	X	-	-	-	-	-	-	-	-	-
Demographics[2]	X	-	-	-	-	-	-	-	-	-
Medical history[3]	X	X	-	-	-	-	-	-	-	-
Vitals[4]	X	X	X	X	X	X	X	-	X	-
Height and weight[5]	X	X	X	X	X	X	X	-	X	-
Physical examination[6]	X	X	X	X	X	X	X	-	X	-
ECOG Performance Status	X	X	-	X	-	-	X	-	X	-
Complete blood count[7]	X	X	X	X	X	X	X	-	X	-
Chemistry panel I[8]	X	X	X	X	X	X	X	-	X	-
Chemistry panel II[9]	X	X	-	X	-	X	X	-	X	-
HIV, HBV, HCV status	X	-	-	-	-	-	-	-	-	-
PT and INR[10]	X	X	-	X	-	X	-	-	X	-
Cytokines/chemokines analysis[11]	X	-	-	-	-	X	-	-	-	-
Urinalysis (routine)	X	X	X	X	X	X	X	-	X	-
Pregnancy test[12]	X	X	-	-	-	-	-	-	-	-
12-lead ECGs[13]	X	X	-	X	-	X	-	-	X	-
Tumour biopsy [14]	X	-	-	-	-	X	-	-	-	-
Radiological assessment (CT and/or MRI) [15]	X	-	-	-	-	X	-	X	X	-
Bone scan[16]	X	-	-	-	-	-	-	-	-	-
Drug Dispensing[17]	-	X	-	X	-	X	X	-	-	-

Tenalisib administration[18]	-	X	X	X	X	X	X	-	-	-
Drug compliance	-	X	X	X	X	X	X	-	X	-
AE evaluation	X	X	X	X	X	X	X	-	X	X
SAE evaluation	X	X	X	X	X	X	X	-	X	X
Concomitant medication	X	X	X	X	X	X	X	-	X	X

Foot notes:

1. Patient should be re-consented, if informed consent is obtained > 30 days prior to the initiation of trial treatment. The first day of tenalisib administration will be considered as C1D1.
2. Demographic profile will include age, sex and race.
3. Detailed history will be taken at screening that includes history of cancer, past history, no of prior therapies and prior medication (in last 4weeks); and other medical history. Patient's medical record must include prior treatments received, dates of administration, response to prior therapies and date of progression.
4. Vitals will include pulse (sitting/supine); blood pressure (sitting/supine); respiratory rate and oral temperature. Vitals will be done at pre-dose at all visits.
5. Weight will be measured at all visits. Height to be measured at screening only.
6. Physical examination will include systemic examination (General Appearance, HEENT, neck, cardiovascular, lungs, abdomen, extremities, neurological, skin, and musculoskeletal). Complete physical examination will be done at screening visit. At subsequent visits, abbreviated examination will be done depending on the assessment of tumour.
7. This will include Hb, complete blood count, total leucocyte and differential count and platelet count. Additional investigations will be performed if clinically indicated. Hematology must be done ≤ 7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated.
8. Chemistry Panel I include blood glucose, albumin, total protein, total bilirubin, ALP, AST, ALT, GGT, LDH, urea or blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, phosphorus. These tests must be done ≤ 7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated. These tests will be performed at supplementary visits if clinically indicated.
9. Chemistry Panel II includes total cholesterol, TG, LDL, HDL, T3, T4 and TSH. These tests must be done ≤ 7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated. These tests will be performed at supplementary visits if clinically indicated.
10. The tests must be done ≤ 7 days prior to initiation of treatment. However, if initial examination is obtained within 72 hours of C1D1; this does not have to be repeated. This test will be performed at supplementary visits if clinically indicated.
11. Blood will be collected in all patients for serum cytokine/chemokine estimation at screening (baseline) and at C3D1.
12. This is required for women of child-bearing potential. A serum pregnancy test will be performed at screening and 72 hours prior to dosing. Urine pregnancy test will be performed at other visits as indicated.
13. ECGs will be performed at screening and C1D1 pre-dose to establish baseline cardiac activity. Additional ECGs will be obtained if clinically indicated. All ECGs will be performed on local equipment.
14. A tumour biopsy will be performed in 10-12 patients who have consented for the biopsy. The biopsy will be done after eligibility confirmation prior to the first dose on C1D1. A second tumour biopsy sample will be taken at C3D1.
15. CT and/ or MRI will be performed at the time of screening within 28 days of screening. Disease will be re-assessed at C3D1 (± 7 days) and approximately 8 weeks thereafter (± 7 days), and/or at the EOT (not required if done within last 28 days) and/or as clinically indicated (if clinical progression is

suspected). If a CR or PR is noted, confirmatory scans should be performed at least 4 weeks after the initial response was first documented. Tumour imaging should remain consistent throughout the study and should include those thought by investigator to best capture status of disease. (Baseline scan, if already available as SOC within 28-days of screening is accepted as part of study protocol). Any other sites at which new disease is suspected should also be appropriately imaged.

16. Bone scan will be done at the baseline when progression in bone is suspected. Bone scans need to be repeated only when complete response is reported in target disease or when progression in bone is suspected.
17. Tenalisib will be dispensed in a HDPE container having 30 tablets of tenalisib.
18. Tenalisib will be administered orally twice a day in 28-days of cycle. Tenalisib will be continued in patients experiencing clinical benefit for 24 months unless progression of disease or toxicity is observed warranting discontinuation of therapy.
19. All visits will be done monthly from Cycle 3 onwards for 24 months (e.g. C4, C5, C6…. C26).
20. All visits for efficacy assessments will be done at 8-weekly intervals (± 7 days) for 24 months (e.g.C5, C7…. C26).
21. All patients will undergo the end-of-treatment (EOT) assessments within 7 days after last dose of study drug or discontinuation.
22. Patients must be followed telephonically for adverse events for 30 calendar days after the last dose of study drug.

7 ASSESSMENT OF SAFETY

7.1 Adverse Events

7.1.1 Definitions of Adverse Events

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

7.1.2 Recording of Adverse Events

All adverse events of any patient during the course of the trial will be reported in the electronic Case Record Form (eCRF), and the investigator will give his or her opinion as to the relationship of the adverse event to trial drug treatment (i.e., whether the event is related or unrelated to trial drug administration). If the adverse event is serious, it should be reported immediately to Sponsor. Other untoward events occurring in the framework of a clinical trial are also to be recorded as AEs (i.e., AEs that occur prior to assignment of trial treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in). All AEs regardless of seriousness or relationship to tenalisib, spanning from the informed consent drug until 30 calendar days after the last dose of study drug are to be recorded in the electronic Case Record Form (eCRF).

7.1.3 Handling of Adverse Events

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

7.2 Adverse Event/Serious Adverse Event Causality Assessment

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

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

7.3 Serious Adverse Events

7.3.1 Definitions of Serious Adverse Events

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

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

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. ***Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST version 1.1 criteria), should not be reported as a serious adverse event.***

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

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

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

7.3.2 SAE Reporting by Investigators

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

Adverse events classified by the treating investigator as **serious** require expeditious handling and reporting to sponsor in order to comply with regulatory requirements. Serious adverse events may occur at any time from the signing of the informed consent form through the 30-day follow-up period after the last trial treatment. Sponsor/sponsor representative must be notified of all SAEs, regardless of causality, within 1 day of the first knowledge of the event by the investigator.

To report an SAE, the SAE Report Form should be completed with the necessary information. All SAEs occurring from the signing of consent until 30 calendar days of last trial treatment must

be reported to the Sponsor as SAEs on the SAE Report and followed until resolution (with autopsy report if applicable).

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

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

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

7.3.3 Sponsor's SAE Reporting Requirements

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

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

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

7.4 Recording of AE and SAE

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the SAE Report Forms and AE eCRF. Avoid colloquialisms and abbreviations. All AEs, including those that meet SAE reporting criteria, should be recorded on the AE eCRF; AEs that meet the definition of an SAE should additionally be reported following the procedures noted in above sections.

7.4.1 Diagnosis vs. Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Coordinating Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or

syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF). If a diagnosis is subsequently established, it should be reported as follow-up information. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

7.4.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form. If a persistent AE becomes more severe or lessens in severity, AE should be recorded separately with new onset date in eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent events should be recorded separately on an SAE Report Form and eCRF and should be reconciled later as a one event. Example of recurrent AEs include, but not limited to recurrent fall, recurrent transaminitis, recurrent elevated GGT.

7.4.3 Abnormal Laboratory Values

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

7.4.4 Deaths

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

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

7.4.5 Hospitalization, Prolonged Hospitalization, or Surgery

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

7.4.6 Pre-existing Medical Conditions

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

7.4.7 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

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

7.4.8 New Cancers

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

7.4.9 Lack of Efficacy

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

7.5 Protocol-Defined Events of Special Interest

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

7.5.1 Pregnancy, Abortion, Birth defects/Congenital anomalies

Female patients who are not of child-bearing potential (see ***Appendix B***) and female patients of child-bearing potential who have a negative pregnancy test within 72 hours prior to C1D1 are eligible for the study. Female patients of child-bearing potential (see ***Appendix B***)) must consent to use a medically acceptable method of contraception throughout the study period and for 30 days after the last dose of tenalisib.

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

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

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

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

7.5.2 Overdose

An overdose is defined as accidental or intentional administration of any dose of product that is considered both excessive and medically important. For purposes of this trial, an overdose will be defined as any dose exceeding the proposed dose of tenalisib (i.e 1200 mg BID).

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

7.6 Dose Modifications

In case of hematologic and non-hematologic toxicities, the dose modifications provided below **(Table 6** and **Table 7)** should be used as 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 recovers 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 6 : Dose modifications for hematologic toxicity

CTCAE Grade	Action to be Taken
Hematologic toxicity	
Grade 3 Neutropenia (1.0×10^9/L<ANC ≥ 0.5×10^9 /L)	• Maintain dose level. • Monitor ANC at least weekly.
Grade 4 Neutropenia (0.5×10^9 /L<ANC)	• First incidence: Hold 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 one dose lower* if warranted. • Discontinue if further dose modification required at lowest dose.
Grade 3 Febrile neutropenia ANC <1.0×10^9/L with a single temperature of > 38.3^0C (101^0F) or a sustained temperature of ≥ 38^0C (100.4^0F) for more than one hour.	• Withhold dose until resolved to ≤ Grade 2 or baseline, consider growth factor support, then reduce by 1 dose level*, if warranted. • If the ANC is <1×10^9/L (1000/μL) before therapy, the dose shall not be modified as long as ANC >0.5×10^9/L.
Grade 3 Thrombocytopenia (50.0×10^9 /L< PLT ≥ 25.0×10^9 /L) **with Grade 1 bleeding**	• Maintain dose level. • Monitor platelet count at least weekly.
Grade 4 thrombocytopenia (20.0×10^9/L< PLT) OR **Grade 3 thrombocytopenia with Grade 2 bleeding**	• 1st occurrence: Hold 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: Hold dose until to ≤ Grade 2 or baseline or resolution of bleeding. Consider platelet transfusion as necessary. Resume treatment at one dose lower* if warranted. • Discontinue if further dose modification required at lowest dose*.

Note: The drug interruption and dose modification should be discussed with medical monitor.
**See 'Guidelines for dose reduction' below.*

Table 7 : Dose modifications for non-hematologic toxicity

Non-Hematologic Toxicity	
Infection	**Grade 3 or higher sepsis or pneumonia** • Withhold tenalisib until infection has resolved. • Restart at the same or at the reduced dose level*, if warranted.
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*. • 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, responsive to antidiarrheal agents:** • Maintain tenalisib dose. Monitor at least weekly until resolved. **Moderate diarrhea, 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*. **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*. **Life threatening diarrhea:** • 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*. • 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* and taper steroid. • If no immediate response to steroids within 7 days, initiate mycophenolate mofetil. • Discontinue if further dose modification required at lowest dose. **Grade 4 Transaminitis** (ALT/AST >20 x ULN; >20x 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*. **Grade 4** (> 10 x ULN; >10 x baseline if baseline is abnormal): • Discontinue tenalisib permanently.
Other non-hematologic toxicities	
Grade 1 or 2	None
Grade 3	Withhold tenalisib dose until toxicity Grade ≤2. Restart tenalisib at one dose lower* 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* or discontinue tenalisib.
Recurrence of grade 4 toxicity	Discontinue tenalisib

**See 'Guidelines for dose reduction' below.*

Note: The drug interruption and dose modification should be discussed with medical monitor.

Table 8 : Guidance on Tenalisib Dose reduction

Group	1st Dose reduction	2nd Dose reduction	3rd Dose reduction
Group 1 (Tenalisib 800 mg BID)	400 mg BID	Discontinue	-
Group 2 (Tenalisib 1200 mg BID)	800 mg BID	400 mg BID	Discontinue

8 ASSESSMENT OF EFFICACY

8.1 Specification of the Efficacy Parameters

Initial disease assessment of patients should be performed within 28 days prior to the first dose of study drug using computed tomography (CT) and/or magnetic resonance imaging (MRI). 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.

Subsequent scan (CT and/or MRI as applicable) should be done at C3D1 (± 7 days) and approximately 8 weeks thereafter (± 7 days), and/ or at the EOT and so on or as clinically indicated (if clinical progression is suspected). If a CR or PR is noted, confirmatory scans should be performed at least 4 weeks after the initial response was first documented. The scan should be reviewed by site investigator/radiologist/designee and tumour response will be assessed according to the revised Response Evaluation Criteria in Solid Tumour guideline (RECIST) version 1.1.[21]

8.2 Images included in the assessment.

A CT with IV contrast will be the primary modality for assessment, unless the patient has an allergy to contrast that cannot be controlled with pre-medications. If patients are unable to receive iodinated CT contrast, the preferred imaging is non-contrast CT of the chest, and MRI of the abdomen and pelvis with contrast. Tumour imaging should remain consistent throughout study and should include those thought by investigator to best capture status of disease. For skin nodules, CT or MRI will be the preferred modality of assessment. Digital photography will not be acceptable as a method of assessment for skin lesions.

8.3 Measurable and non-measurable disease:

Eligibility of lesions for quantitative assessment will be determined at baseline, with target lesions selected from the measurable lesions identified. After baseline, target lesions will always be assessed quantitatively, and non-target lesions will be assessed qualitatively, with no further evaluation of measurability according to these definitions.

8.3.1 Measurable Disease

A lesion is considered measurable, if it meets one of the measurability criteria described above.

- A lesion is considered measurable if it has a diameter of ≥ 10 mm in the axial plane on CT or MRI, assuming that the slice thickness is 5 mm or less. If the slice thickness is greater than 5 mm, the minimum size increases to two times the slice thickness.
- Pathological lymph nodes are considered measurable if the short axis (greatest dimension perpendicular to the longest diameter) is ≥ 15 mm at baseline.
- Skin nodules will be considered measurable lesion if they are assessed on CT or MRI. Digital photography will not be acceptable as a method of assessment for skin lesions. Discrete skin nodules that are not visible on CT or MRI should be considered non-measurable lesions.
- Bone lesions that are lytic or mixed lytic-blastic, which have soft tissue components seen on CT or MRI, and which meet size criteria above, may be measurable.
- Cystic metastases may be considered measurable, but solid lesions are preferred for selection as target.

8.3.2 Non-Measurable Disease

A lesion is considered non-measurable, if it does not meet the measurability criteria described above. Example of non-measurable lesion included.

- A lymph node that has a short axis diameter of 10-14 mm is considered evaluable, but not measurable. Nodes with a short axis diameter of < 10 mm are considered normal.
- Palpable skin nodules that are not discernible using CT or MRI are considered evaluable but not measurable for this study.
- Bone lesions that are blastic are non-measurable.
- Simple cysts are considered benign by default.
- Malignant ascites or pleural/pericardial effusions, lymphangitic infiltration of skin or lung, leptomeningeal disease, inflammatory breast disease, and infiltrative disease without clear borders.
- Lesions seen on bone scan, or modalities other than CT or MRI (plain X-ray [with the exception for lung lesions], PET etc.) cannot be measured. These modalities can be used only to determine whether a lesion is present or absent.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of previous treatment.

8.4 Baseline Lesion Selection and Documentation

Target lesions will be chosen from among the measurable lesions. The lesions chosen should be the largest, most reproducible, and most representative of the overall disease distribution.

- **Target lesions:** All measurable lesions up to a maximum of 5 lesions total, and 2 lesions per organ, should be selected as target lesions. Paired organs (lungs, kidneys, adrenals, ovaries) are considered one organ. The lymph nodes collectively are considered one organ.
- **Non-nodal target lesions** are measured in the longest diameter in the axial plane (on CT or MR). Malignant lymph nodes are always measured in the short axis diameter (greatest dimension perpendicular to the longest diameter). The appropriate measurements for all

target lesions chosen at baseline will be added to produce the recorded sum of diameters, which will be recorded.
- Other disease present at baseline should be recorded as 'Non-target lesions'.

8.5 Assessment of Response

The overall response for each visit is a combination of target lesion response, non-target lesion response, and the presence or absence of new lesions. **Target lesions measurements** should be performed in the same manner as at baseline. The sum of diameters of all target lesions must be calculated and compared to the baseline value and to the nadir value (the smallest value previously seen during the trial, which may be the same as baseline). The following special rules apply to lesion measurements:

- If two target lesions coalesce the longest diameter measurement of the coalesced mass is used. If a large target lesion splits, the longest diameter of each fragment is measured, and the sum is used.
- Measurements for target lesions that become small should continue to be recorded, as long as the investigator is confident in the accuracy. If a target lesion is considered to have completely disappeared, 0 mm should be recorded. If it is too small to measure accurately, but is still present, a default value of 5 mm should be recorded.
- When nodal lesions decrease to < 10 mm (normal), the actual measurement should still be recorded.

Target lesion response categories are defined as follows:

- Complete response (CR): Disappearance of all non-nodal target lesions. Target lymph nodes must reduce to < 10 mm in short axis.
- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, compared to the sum at baseline.
- Progressive disease (PD): At least a 20% increase in the sum of target lesion measurements, compared to the smallest sum on study (including baseline). Also, the absolute increase in the sum has to be at least 5 mm.
- Stable disease (SD): If none of the above criteria meets.

Non-target lesion response assessment is qualitative. Categories are defined as follows:

- CR: Disappearance of all non-nodal non-target lesions. Non-target lymph nodes must reduce to < 10 mm in short axis. Note: If tumour markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- PD: Unequivocal progression of non-target lesions, evaluated as a whole, such that it is clear that treatment has failed, and disease is progressing, regardless of the status of the target lesions.
- Non-CR/Non-PD: Neither CR nor PD criteria are met.

New lesion response is classified as present or not ("Yes" or "No"). The response is "Yes" if there is at least one lesion that the investigator considers unequivocal new tumour.

- Lesions that are equivocal (for example, due to small size) should not be considered new until they are confirmed by later scanning. Once confirmed, they can be retrospectively called new lesions at the time they were first seen.
- A lesion identified in an area not previously scanned is considered a new lesion.
- New lesions seen on nuclear medicine bone scans should be confirmed using anatomical imaging, whenever possible. If bone lesions are confirmed on later CT or MRI scan, progression should be assigned to the visit in which new lesion(s) were first seen on bone scan (in a manner similar to other equivocal new lesions). In the absence of structural confirmation, the pattern of lesions must clearly indicate metastasis, usually with at least two new lesions present.

Overall response is determined by combining the target, non-target, and new lesion responses.

Table 9 : Response Assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Visit Response
CR	CR	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-CR/Non-PD or NE	No	PR
SD	Non-CR/Non-PD or NE	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

After all visits have been evaluated, the sequence of overall visit responses is used to derive best overall response (BOR).

- BOR is defined as the best visit response recorded from the start of the treatment until disease progression/recurrence.
- ORR: It is defined as sum of CR and PR rates
- Clinical Benefit Rates: It is defined as sum of CR, PR and SD rates
- PFS is measured from the time of first dose of study drug to radiographic (or tumour marker as applicable) documentation of disease progression or death due to any cause.

9 STATISTICAL METHOD AND CONSIDERATIONS

9.1 General 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. All statistical analyses will be performed using SAS 9.1 or higher. 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.

9.2 Determination of Sample Size

A sample size of 20 per group will provide a precision of 13% for a two-sided 90% confidence interval based on Exact (Clopper-Pearson) method assuming the percentage of patients without progression at the end of 6 month is 20%. Thus, total 40 patients (20 patients in each group) will be enrolled in the study.

9.3 Study Population

The following two analysis populations are planned for this study:

- Intent-to-Treat Population (ITT): The ITT is the primary analysis population and will include data from patients who have received at least 1 dose of study medication.
- Per-Protocol (PP) Population: The PP Population is a subset of the ITT population and will include patients without major protocol deviations.

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

9.4 Statistical Analysis

9.4.1 Demographic and Baseline Characteristics

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

9.4.2 Safety Analyses

The safety endpoints will include:

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

The safety endpoints will be listed and/or summarized by dose cohort. No inferential statistical analyses will be performed. The analyses of safety will be based on the frequency of adverse events and their severity for patients in each portion who received at least one dose of study treatment. Worst toxicity grades per patient will be tabulated for select adverse events and laboratory measurements by using NCI CTCAE criteria v5.0.

9.4.3 Efficacy analyses

The efficacy endpoints will include:

- The percentage of patients without disease progression at the end of 6 months
- ORR: The percentages of CR+PR will be calculated and presented along with 95% confidence intervals of these percentages.
- CBR: The percentages of CR+PR+SD will be calculated and presented along with 95% confidence intervals of these percentages.
- PFS: It is defined as time from the first dose of study drug to documented disease progression or death due to any cause. This variable will be analyzed via Kaplan-Meier methodology.

Additional efficacy parameters will be assessed depending on the emerging efficacy data. These analyses will be performed from time to time for presentation/publication purposes.

9.4.4 Exploratory Analyses

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

10 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This trial will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline, 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 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 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 national data protection laws, as applicable. The study participant will be informed on the following:

a. What protected health information 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 regulatory guidance, 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 eCRF 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 eCRF 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, 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 eCRFs are to be included on this document. All entries in the patient's eCRF 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 eCRF 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 eCRF 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 (eCRF). 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 entered 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 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: ECOG Performance Status Scale

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

Appendix B: Contraceptive Guidelines and Pregnancy

Women Not of Childbearing Potential are defined as Follows

Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or 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 30 days after the last dose of study drug. The highly effective contraception is defined as either:

1. True abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, 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 patients on the study, the vasectomized 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/pessary.

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

- Oral contraception, injected or implanted hormonal.
- 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.

Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to Rhizen Pharmaceuticals AG 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 AG. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational drugs to any pregnancy outcome will also be captured on the pregnancy form. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Appendix C: Cytokines/Chemokines and Tumour Biopsy

- Serum samples will be assessed for following cytokines/chemokines at the screening (baseline) and at Cycle 3 Day 1:

Assessment	Tissue sample	Exploratory marker
Cytokines/Chemokines	Serum	CCL2/JE/MCP-1, CCL3/MIP-1alpha, CCL4/MIP-1 beta, CCL11/Eotaxin,CCL13/MCP-4, CCL17/TARC, CCL22/MDC,CCL26/Eotaxin-3, CXCL9/MIG, CXCL10/IP-10/CRG-2, IL-8/CXCL8 IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8,IL-10, IL-12p70, IL-13, TNF-α
Gene expression by RNA sequencing	Tissue biopsy sample	Approx. 21,000 genes