Protocol Number: RP6530-1901

A Phase 2, Open label Study to Assess the Efficacy and Safety of Tenalisib (RP6530), a Novel PI3K Dual δ/γ Inhibitor, in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)

SUMMARY CLINICAL REPORT

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Version and Date of Summary Clinical Report: 1.0 Dated 22 April 2021

PROTOCOL IDENTIFIER	RP6530-1901
PROTOCOL VERSION	Version 1.0, Dated 29 August 2019
STUDY TITLE	A Phase 2, Open label Study to Assess the Efficacy and Safety of Tenalisib (RP6530), a Novel PI3K Dual δ/γ Inhibitor, in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)
PHASE OF DEVELOPMENT	Phase II
INVESTIGATIONAL MEDICINAL PRODUCT	RP6530 (Tenalisib)
IND NUMBER	124584
INDICATION STUDIED	Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)
TRIAL CONDUCTED IN COUNTRIES	Bulgaria, Georgia and Poland
DATE OF FIRST SUBJECT FIRST VISIT **DATE OF FIRST SUBJECT DOSED**	28 Nov 2019 12 Dec 2019
DATE OF LAST SUBJECT FIRST VISIT **DATE OF LAST SUBJECT LAST VISIT**	09 Mar 2020 02 Oct 2020
SPONSOR	Rhizen Pharmaceuticals AG
SPONSOR SIGNATORY	**Prajak Barde, MD.** Senior Medical Director, Clinical Research and Development Rhizen Pharmaceuticals AG, Steinentorstrasse 23, 4051 Basel, Switzerland. Tel: +1 (301) 250-5591; Fax +41 32 580 0175 Email: pjb@rhizen.com
GCP COMPLIANCE	This clinical study was conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements including but not 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)
VERSION AND DATE OF REPORT	1.0; Dated 22 April 2021

List of Abbreviations:

AE	Adverse events
ALP	Alkaline Phosphatase
ALT (SGOT)	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST (SGPT)	Aspartate Aminotransferase
BID	Twice daily
CLL	Chronic lymphocytic leukemia
CR	Complete Response
CRF	Case Report Form
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
DoR	Duration of Response
DRC	Data Review Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group Performance Status
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
FSH	Follicular Stimulating Hormone
GCP	Good Clinical Practices
GGT	Gamma- glutamyl transferase
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immuno Deficiency Virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent to treat
LDL	Low-density Lipoprotein
NCS	Not Clinically Significant
ORR	Overall Response Rate
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI3K	Phosphoinositide-3-kinase
PK	Pharmacokinetics
PP	Per Protocol
PR	Partial Response
PT	Preferred Term
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class

SLL	Small Lymphocytic Lymphoma
TEAE	Treatment Emergent Adverse Events
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal

1. BACKGROUND AND RATIONALE

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

Chronic Lymphocytic Leukemia (CLL) is a lymphoproliferative neoplasm characterized by an accumulation of monoclonal mature B-cells (CD5+CD23+) in the blood, bone marrow, and secondary lymphatic organs. CLL is the most common form of adulthood leukemia. The clinical course of CLL varies but it is typically a slowly progressing disease. The approximate 5-year survival rate for patients with CLL is 81.7% [**2**]. Due to infiltration of the bone marrow by lymphocytes, the principal complication of CLL is immunodeficiency related to myelosuppression and as a result, infection is the major cause of death in these patients [**3**].

Despite high response rates to initial treatment, relapse is common in CLL and relapsed/ refractory disease is often characterized by resistance to chemotherapy. Among patients who either relapse or are refractory to first line treatment, the choice of subsequent therapy depends on age, duration of response to prior therapy, ability to tolerate treatment, disease related manifestations, and the presence of molecular poor-risk features. The majority of CLL patients receive intermittent treatment with periods of remission or stable disease. With each successive treatment regimen, many patients become refractory to treatment with diminished response rates and shorter response durations. Although newer agents ibrutinib (BTK inhibitor), venetoclax (BCL-2 inhibitor), idelalisib (PI3K δ inhibitor), duvelisib (PI3K δ/γ inhibitor) have become available for the treatment of CLL recently [**4**], CLL still remains an incurable disease and an unmet medical need.

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

Pre-clinical experiments demonstrated that Tenalisib is highly effective at killing primary CLL cells *in vitro*. The effect appeared to be equal to the bruton tyrosine kinase (BTK) inhibitor-ibrutinib (362 nM, versus 567 nM). In comparison, the IC_{50} for Tenalisib was lower than IC_{50} for the conventional chemotherapy agents fludarabine (14.8 μM), bendamustine (382 μM), and chlorambucil (152 μM). Tenalisib also induced 50-60% reduction in chemokine induced migration of Daudi cells, indicating the potential of the molecule in modulating tumor microenvironment. *In vivo* efficacy of Tenalisib was confirmed in a subcutaneous mouse MOLT-4 xenograft model representative of human T-cell acute lymphoblastic leukemia. Oral

administration of 50 mg/kg/BID over an 18-day period resulted in a significant delay in tumor growth.

In prior clinical settings, Tenalisib has demonstrated clinical activity in patients with hematological malignancies with acceptable safety profile. Therefore, Tenalisib may offer a good treatment option for patient with relapsed/refractory CLL.

2. STUDY OBJECTIVES

Primary Objective

- To assess the anti-tumor activity of Tenalisib as determined by the overall response rate (ORR) and duration of response (DoR)

Secondary Objective:

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

3. STUDY DESIGN

This was a Phase II, open label, Simon's two stage study design to evaluate the efficacy and safety of Tenalisib in 61 patients with CLL who had relapsed or were refractory after at least one prior therapy. Stage 1 of the study was to assess the efficacy and safety in 20 patients with R/R CLL. If eight fewer responders were to be observed at this stage, the study would be terminated. Else, 41 additional patients would be enrolled into stage 2.

The study treatment Tenalisib (800 mg BID) was administered orally in 28-days of cycle over a period of 7 months (C1D1 to C8D1) in the absence of definitive disease progression or unacceptable toxicity. The study had to end when all ongoing subjects would have reached their third tumor assessment on Cycle 8/Day 1 (C8D1) or would have discontinued from the study for any reason, whichever was earlier.

At the end of the study, all ongoing patients with no evident disease progression had an opportunity to enroll in an open-label compassionate medication use study [Protocol:RP6530-1803; NCT03711604] and these patients were followed up in compassionate study.

Anti-infective prophylaxis (e.g., for herpes simplex virus (HSV), pneumocystis Jirovecii pneumonia (PJP), hepatitis B, cytomegalovirus (CMV)) were recommended and were given at the discretion of study investigator. All safety laboratory assessments, electrocardiogram (ECG) and radiological assessments (e.g., CT) were performed at the respective sites.

4. SELECTION OF STUDY SUBJECTS

4.1. Eligibility Criteria

4.1.1. Inclusion Criteria

1. Patients with diagnosis of B-cell CLL as confirmed by histopathology or flow cytometry.

2. Disease status defined as refractory to or relapsed after at least one prior therapy.
3. Presence of measurable lymphadenopathy, defined as the presence of > 1 nodal lesion that measures ≥ 1.5 cm in the longest diameter (LD) as assessed by computed tomography (CT).
4. ECOG performance status ≤ 2.
5. Male or female ≥ 18 years of age.
6. Life expectancy of at least 3 months.
7. Adequate bone marrow (BM), liver, and renal function as assessed by the following laboratory requirements conducted within 14 calendar days before starting study treatment.
   a. Adequate bone marrow function:
      I. Hemoglobin ≥ 9 g/dl
      II. Absolute neutrophil count (ANC) ≥ 1 x 10^9/L
      III. Platelets ≥50 x 10^9/L
      Patients with hemoglobin, neutrophil and platelet counts below the above specified values were eligible if it is due to tumor dissemination or infiltration to bone marrow and as per physician's discretion. Hemoglobin and platelet requirements should not be met by use of recent transfusion or growth factor support (G-CSF or erythropoietin) within 3 weeks prior to assessment.
   b. Adequate liver function:
      I. Total bilirubin ≤1.5 times the upper limit of normal (ULN)
      II. ALT and AST should be ≤ 3 x ULN. ALT and AST ≤ 5 x ULN if known liver involvement.
   c. Adequate renal function: Calculated creatinine clearance ≥ 50 mL/min (as calculated by the Cockcroft-Gault method) or Creatinine ≤ 1.5 mg/dl.
8. Ability to swallow and retain oral medication.
9. Female patients who were not of child-bearing potential, and female patients of child-bearing potential who have a negative serum pregnancy test within 3 days prior to Cycle 1 Day 1 (C1D1). Female patients of child-bearing potential who consented to use a medically acceptable method of contraception, throughout the study period and for 30 days after the last dose of study drug.
10. Male patients who consented to use adequate contraceptive measures throughout the study period and for 12 weeks after the last dose of Tenalisib.
11. Willingness and ability to comply with trial and follow-up procedures, who given informed consent.

4.1.2. Exclusion Criteria

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

1. Patient with Richter's (large cell) Transformation, or prolymphocytic leukemia (PLL) transformation.
2. Patients who received cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) or any cancer investigational drug within *3 weeks (21 days)* or *5 half-lives* (whichever is shorter) prior to C1D1.
3. Prior exposure to drug that specifically inhibits PI3K (e.g. idelalisib, copanlisib, duvelisib, umbralisib)
4. Patient with autologous / allogeneic stem cell transplant (ASCT/Allo-SCT) received treatment for active graft versus-host disease (GVHD).
5. Evidence of ongoing severe systemic bacterial, fungal or viral infection as assessed by the investigator.
6. Central nervous system (CNS) involvement of leukemia or lymphoma
7. Ongoing immunosuppressive therapy including systemic corticosteroids except as allowed per concomitant medication.
8. Known history of severe drug-induced liver injury (e.g. alcoholic liver disease, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver or portal hypertension) as judge by investigator.
9. Any severe and/or uncontrolled medical conditions or other conditions that could affect patient participation in the study, as judge by investigator, such as:

    a. Symptomatic or history of documented congestive heart failure (New York heart association (NYHA) functional classification III-IV)

    b. Myocardial infarction within 6 months of C1D1

    c. QTcF >470 msec.

    d. Angina not well-controlled by medication.

    e. Poorly controlled atherosclerotic vascular disease (e.g. cerebrovascular accident, transient ischemic attack, angioplasty, cardiac/vascular stenting).

10. Patient treated for other malignancy in last 3 years of study enrollment except for adequately treated basal, squamous cell carcinoma or non-melanomatous skin cancer, carcinoma in situ of the cervix, superficial bladder cancer not treated with intravesical chemotherapy or BCG within 6 months; and localized prostate cancer with PSA <1.0 mg/dL within 4 weeks of C1D1.
11. Pregnant or lactating women

12. Known seropositive requiring anti-viral therapy for human immunodeficiency virus (HIV) infection.
13. Known seropositive requiring anti-viral therapy for hepatitis B virus (HBV) infection OR evidence of active hepatitis B infection as defined by detectable viral load if the antibody tests were positive.

    [Note: Subject with a positive HBcAb with an undetectable/negative hepatitis B DNA test (e.g., polymerase chain reaction [PCR] test) can be enrolled].
14. Known seropositive requiring anti-viral therapy for hepatitis c virus (HCV) infection OR patients with positive hepatitis C virus Ab with detectable viral load. [Note: Subject with a positive HCV with an undetectable/negative hepatitis C RNA test (e.g., PCR) can be enrolled].
15. Known seropositive requiring anti-viral therapy for active CMV infection (Note: A serology positive CMV subject with negative CMV PCR test will be enrolled).
16. Unresolved NCI-CTCAE grade 2 and above toxicity (except as mentioned in adequate organ function) attributed to any prior therapy/procedure excluding alopecia.
17. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol.
18. Concurrent condition that in the investigator's opinion would jeopardize compliance with the protocol.

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

4.1.3. Discontinuation from Trial Treatment

The following events were considered for discontinuation of the study drug.

- NCI CTCAE v5.0 Grade 3/4 non-hematological toxicity related to study drug that necessitated withdrawal in the opinion of investigator.
- Withhold of study drug for > 28 days due to adverse event, unless approved by medical monitor.
- Development of an intercurrent illness, condition or procedural complication, which could interfere with the patient's continued participation.
- Voluntary patient withdrawal from study treatment (all patients were free to withdraw from participation in this study at any time, for any reasons, specified or unspecified, and without prejudice).
- Any other situation where, in the opinion of the investigator, continued participation in the study would not have been in the best interest of the patient
- Confirmed disease progression
- Lack of protocol compliance in the opinion of study investigator
- Study completion.

4.2. Study Treatment:

Tenalisib was administered continuously twice a day in 28-days cycle up to 7 months (C1D1 to C8D1) unless progression of disease or toxicity warranted discontinuation of therapy. Post completion of 7 months, if the patient showed clinical benefit, patient was enrolled into a compassionate medication use study [Protocol:RP6530-1803] to receive further treatment with Tenalisib.

4.3. Identity of Investigational Medicinal Product

Chemically Tenalisib is an isoflavone substituted adenine, ((S)-2-(1-(9H-purin-6-ylamino) propyl)-3-(3-fluorophenyl)-4H-chromen-4-one).

Formulation and Composition

Tenalisib was available as 200 mg and 400 mg, mustard coloured, oval shaped, film-coated tablets, plain on both sides (Table 1).

Table 1: Composition of Tenalisib tablets

Ingredient	% w/w
RP6530	50.00
Microcrystalline cellulose (Avicel PH102)	40.25
Hydroxypropyl cellulose (Klucel LF)	2.00
Purified Water	-
Croscarmellose Sodium (AC-DI-SOL)	6.00
Talc	1.00
Colloidal silicon dioxide (Aerosil-200)	0.25
Magnesium stearate	0.50
Opadry 03F520226 Yellow	3.00

Labelling, Packaging and Supply

Tenalisib tablets were manufactured by Shanghai STA Pharmaceutical Co., Ltd., (A Subsidiary of WuXi AppTec Co., Ltd.,) and supplied through Rhizen Pharmaceuticals SA to the study site. The primary packaging was in high density polyethylene (HDPE) bottles with 30 tablets of 200 mg and 400 mg in each bottle. Recommended storage condition for the drug substance was between 20°C and 25°C with excursions permitted between 15°C and 30°C.

Stability studies on several clinical batches were ongoing. The drug product had remained stable for the duration of these stability studies. An expiry date for the drug product was defined based on real time stability of individual batches. If the drug product continued to meet its specification, a shelf-life would be ascertained based on real time stability (Table 2).

Table 2: Following Batches of Tenalisib were used for the study

IMP Name	Strength	Batch #	Manufacturer
Tenalisib	400 mg	1608FP1921-01	Shanghai STA Pharmaceutical Product Co., Ltd. (A Subsidiary of WuXi AppTec Co., Ltd.)
Tenalisib	400 mg	1704FP1921-01	
Tenalisib	400 mg	1711FP1921-01	
Tenalisib	400 mg	AMO00120N	VerGo Pharma Research Lab. Pvt. Ltd. Goa, India

Accountability of Investigational Medicinal Product

The Investigator/designee was responsible for accountability of all used and unused trial drug supplies at the site. The study monitors verified receipt of investigational medicinal product at the site during monitoring visit(s) and conducted an inventory of remaining clinical trial supplies at the site close-out visit.

Returned or expired drugs were destroyed according to local institutional policy with Sponsor pre-approval of a site-specific destruction policy. Certificate(s) of destruction were filed at the site and in Trial Master File.

4.4. Concomitant Medications

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

- Antimicrobial and/or anti-viral prophylaxis according to local standard practice; PCP and herpes zoster prophylaxis was strongly recommended. CMV carriers were monitored per institutional guidelines and/or were given anti-CMV therapy (e.g., ganciclovir, valganciclovir). Similarly, chronic carriers of HBV received prophylactic anti-viral therapy.
- G-CSF and other hematopoietic growth factors for the management of acute toxicity (such as febrile neutropenia) when clinically indicated.
- Transfusions (blood/platelets) based on standard criteria and clinical judgment.
- No routine prophylactic anti-emetics or pre-medications were given outside of protocol requirements. However, these medications were administered for the treatment of symptoms.
- Prophylactic allopurinol, in case the risk of tumor lysis syndrome.
- Low doses of steroids if it was administered at dose ≤ 20 mg per day of prednisone or equivalent. The dose should have been stabilized for at least 1 week or *5 half-lives* (whichever was shorter) prior to C1D1.
- Topical, ocular, intra-articular, intranasal, and inhaled corticosteroids (with minimal systemic absorption).
- Inactivated seasonal influenza vaccine

- Drugs metabolized by CYP3A4/CYP2C9 enzymes if clinically warranted.
- Low molecular weight heparin (LMWH), dabigatran or edoxaban for prophylaxis and/or treatment of venous thrombosis.

4.5. Prohibited Medications

The following treatments were prohibited while on the clinical trial and were discontinued:

- Any other anti- leukemia/lymphoma therapy
- Herbal medications. Patients had to stop using herbal medications at least 7 days prior to C1D1.
- Strong inhibitors or inducers of CYP3A4. Patients had to stop using these medications at least 7 days or 5 half-lives (whichever is shorter) prior to C1D1.
- Strong inhibitors or inducers of CYP2C9. Patients had to stop using these medications at least 7 days or 5 half-lives (whichever is shorter) prior to C1D1.
- Substrates of CYP3A4 enzyme with a narrow therapeutic range. Patients had to stop using these medications at least 7 days or 5 half-lives (whichever is shorter) prior to C1D1.
- Use of heparin, warfarin, apixaban or rivaroxaban for prophylaxis and/or treatment of venous thrombosis was prohibited. These drugs had to be stopped at least 7 days or 5 half-lives (whichever was shorter) prior to C1D1.
- Live attenuated vaccine (e.g., Flu vaccine, pneumovax, varicella).
- Steroids > 20 mg unless it was required for management of toxicity (e.g., transaminitis) during the study.

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

4.6. Procedures for Monitoring Subject Compliance.

The following measures were employed to ensure treatment compliance.
Subjects were asked to bring unused study drug to the research center at their next visit. Research personnel counted and recorded the number of used and unused study drug tablets at each visit. The study coordinator questioned the patient regarding adherence to the dosing regimen, recorded the number of tablets and strengths returned, the date returned and determined treatment compliance before dispensing new medication to the study patient. Patients with compliance below 80% were counseled by the study site personnel.

4.7. Data review Committee (DRC)

The DRC was constituted by the sponsor to review the safety and efficacy data. The committee consisted of PI of respective sites, sponsor representative, sponsor's medical expert, and a statistician. The DRC reviewed the efficacy and safety data at regular intervals to assess the safety and efficacy of study drug and provided the recommendations.

4.8. Assessment of Efficacy

Initial disease assessment of relapsed/refractory CLL patient was performed within 28 days prior to the first dose of study drug using CT scan of chest/abdomen/pelvis, as applicable (This scan was considered as the baseline scan). The PI reviewed baseline scan images to confirm the subject had measurable disease as defined in the inclusion criteria. Scan performed as part of routine clinical management was acceptable for use as the baseline scan if it was of diagnostic quality and performed within 28 days prior to the C1D1 or as approved by the medical monitor if it was out of window period. Subsequently, CT scan was done throughout the study at time-points designated in Study Assessments and Treatment Schedule (Table 3**).** Other radiological evaluations (e.g., MRI/USG) were performed if warranted.

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

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

Efficacy parameters included ORR, CR rate, DOR and PFS. ORR was defined as sum of CR and PR rates, as assessed by the site investigator according to iwCLL guideline for CLL (Hallek *et al.* 2018) [**5**]. Only those patients who had a pre-treatment baseline efficacy evaluation and at least one post-treatment efficacy evaluation (that included confirmed disease progression) were considered evaluable for response.

CR rate was assessed by the investigator according to the iwCLL guideline for CLL. Only those patients who had a pre-treatment baseline efficacy evaluation and at least one post-treatment efficacy evaluation (that included confirmed disease progression) were considered evaluable for response.

PFS was defined as time of the first dose of Tenalisib to disease progression or death. Subjects who died without a reported prior progression were considered to have progressed on the date of their death. Subjects who did not progress or die were censored on the date of their last tumor assessment.

DoR was defined as the time when the measurement criteria were first met for PR or CR (whichever was reported first) until the date of documented disease progression or death. For subjects who neither progressed nor died, the duration of response was censored at the date of their last disease assessment.

The **best overall response** was the best response, as assessed and confirmed by site PI, from the start of the treatment until disease progression or discontinuation from the study.

Criteria for evaluable subjects for stage 2 had to be re-defined based on the results of stage 1.

5. TRIAL ASSESSMENT AND PROCEDURE

Schedule of Event summarizes the trial procedures which were performed at each visit and were divided into following.

1. Screening (Day -28 day to Day 0)
2. On treatment procedures (C1D1 to C8D1)
3. End of Treatment (Day +7 from last dose)
4. End of Study (Day +30 from last dose)

Individual trial procedures were described as detailed below (Table 3). At times, these procedures were performed at unscheduled time points if deemed clinically necessary by the investigator.

Table 3: Study Assessments and Treatment Schedule

Day	**Screening**	**C1**		**C2**		**C3**	**C4**	**C5**	**C6**	**C7**	**C8/ EOT[18]**	**EOS[19]**
Day		**D1**	**D15**	**D1**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	-
Window period	**-28**	0	±1	±1	±1	±3	±3	±3	±3	±3	+7	+30
Study Days	**D-28 to 0**	1	15	29	43	57	85	113	141	169	197	227
Informed consent[1]	X	-	-	-	-	-	-	-	-	-	-	-
Demographics[2]	X	-	-	-	-	-	-	-	-	-	-	-
Medical history[3]	X	-	-	-	-	-	-	-	-	-	-	
Vitals[4]	X	X	X	X	X	X	X	X	X	X	X	-
Height and weight[5]	X	X	X	X	X	X	X	X	X	X	X	-
Complete physical exam[6]	X	-	-	-	-	-	-	-	-	-	X	-
Abbreviated physical exam[6]	-	X	X	X	X	X	X	X	X	X	-	-
ECOG Performance Status	X	X	-	-	-	X	-	X	-	-	X	-
Rai Staging	X	-	-	-	-	-	-	-	-	-	-	-
Laboratory assessment												
Complete blood count[7]	X	X	X	X	X	X	X	X	X	X	X	-
Chemistry panel I[8]	X	X	X	X	X	X	X	X	X	X	X	-
Chemistry panel II[9]	X	X	-	-	-	X	-	X	-	-	X	-
Serology[10]	X	-	-	-	-	-	-	-	-	-	-	-
PT and INR[11]	X	X	X	X	X	X	X	X	X	X	X	-
Urinalysis (routine)	X	X	X	X	X	X	X	X	X	X	X	-
Pregnancy test[12]	X	X	-	-	-	-	-	-	-	-	-	-
12-lead ECGs[13]	X	X	-	X	-	X	-	X	-	-	X	-
Bone marrow biopsy/ aspirate[14]	X	-	-	-	-	-	-	-	-	-	-	-
Disease assessment												
Radiological scan/imaging[15]	X	-	-	-	-	X	-	X	-	-	X	-
Treatment administration												
Tenalisib[16]	-	X	X	X	X	X	X	X	X	X	X	-
Drug compliance	-	X	X	X	X	X	X	X	X	X	X	-
Safety evaluation												
AE evaluation[17]	X	X	X	X	X	X	X	X	X	X	X	X
SAE evaluation	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X

Foot notes:

1. Patient was to be re-consented, if informed consent was obtained >30 days prior to the initiation of study drug.
2. Demographic profile included age, sex and race.
3. Detailed history to be taken at screening that includes history of cancer, past history, no of prior therapies; prior medication (in last 4 weeks); and other medical history (history of transfusions). Any medical significant history at subsequent visit was captured as adverse event.
4. Vitals to be done prior to the administration of study drug (Pre-dose) at the days specified above.

5. Weight to be measured at all visits. Height to be recorded at screening only; historical data is acceptable.
6. Physical examination included lymph node and systemic examination. Complete physical examination to be done at screening and EOT visits. At other visits, abbreviated examination (directed physical examination) to be done depending on the assessment of tumor.
7. Complete blood count: hemoglobin, complete blood count including hematocrit, total leucocyte and differential count and platelet count. Additional investigations were to be performed if clinically indicated. Hematology should be done ≤ 14 days prior to C1D1. However, if screening assessments were performed within 72 hours of C1D1; these tests need not be repeated on C1D1.
8. Chemistry Panel I included total bilirubin, ALP, AST, ALT, GGT, urea/ blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, phosphorus, CO2/bicarbonate and magnesium. The tests should be done ≤ 14 days prior to C1D1. However, if screening assessments are performed within 72 hours of C1D1; these tests need not be repeated on C1D1. These tests were to be performed at supplementary (unscheduled) visits if clinically indicated.
9. Chemistry Panel II included blood glucose, LDH, albumin, total protein, TSH, T3 (total/free), T4 (free), total Cholesterol, TG, LDL and HDL. These tests were to be performed at unscheduled visits if clinically indicated.
10. Serology included HIV, HBV, HCV and CMV. Historical results in last 12 weeks were acceptable.
11. PT and INR. In case of abnormality, additional tests including aPTT were to be done as per investigator discretion. These tests were to be performed at supplementary visits if clinically indicated.
12. Pregnancy test was required for women of childbearing potential. A serum pregnancy test was to be performed at screening; and serum/urine pregnancy test at C1D1 (within 72 hours) of dosing. Urine pregnancy test were to be performed at other visits as indicated.
13. 12-lead ECG: ECG was to be done at Pre-dose on scheduled timepoints on the day of drug administration. Additional ECGs were to be obtained if clinically indicated. Triplicate ECGs will be performed to confirm the significant changes of single ECG.
14. A bone marrow biopsy/aspirate: Unilateral bone marrow aspiration and/or biopsy will be performed at investigator discretion in patients for whom assessment of extent of CLL involvement and bone marrow cellularity is important in determining eligibility. However, post initiation of treatment, bone marrow biopsy was to be done to confirm potential CR.
    Radiological assessment: "Diagnostic quality" CT scan of chest/abdomen/pelvis was to be done at the time of screening within 28 days of C1D1. The scan and other investigations to document measurable or evaluable disease was to be performed ≤28 days prior to initiation of treatment or as approved by the medical monitor if it is out of 28-days window period. Following screening, CT scans was to be repeated at C3D1 (± 7 days), C5D1 (± 7 days) and C8D1 (± 7 days) or at end of the treatment (EOT) visit. Tenalisib was to be administered orally twice a day in 28-days of cycle for 7 cycles (C1D1 to C8D1) in absence of disease progression or toxicity warranting discontinuation of therapy.
15. All AEs regardless of seriousness or relationship to study drug was to be recorded spanning from the informed consent drug until 30 calendar days after the last dose of study drug.
16. Post C8D1, patient experiencing clinical benefit with no evident disease progression was to be given the opportunity to enroll in an open-label compassionate medication use study and have to be followed up. Excluding patients who participate in compassionate medication use study [Protocol:RP6530-1803], all other patients will undergo the end-of-treatment (EOT) assessments within 7 days after the last dose of study drug or discontinuation from the study.
17. Patients should be followed for AEs for 30 calendar days after the last dose of study treatment. Telephonic follow up during this period is acceptable. All new AEs occurring during this period should be reported and followed until resolution unless, in the opinion of the investigator, the adverse event or laboratory abnormality/ies are not likely to improve because of the underlying disease.

6. STUDY RESULTS

This was a multi-centre study conducted across six sites in three countries. Two sites each, from Bulgaria, Georgia and Poland enrolled the study patients. **(**Table 4**).** Below is a list of the study Investigators and number of patients enrolled at each site.

Table 4: Details of the study sites and no. of patient enrolled at each site.

Site No.	Name of Site	Name or Investigator	No. of patient enrolled
CB01	University Multiprofile "Dr Georgi Stranski"	Dr. Nikolay Tzvetkov	02
CB02	University Multiprofile "Sv Ivan Rilski"	Dr. Atanas Radinoff	01
CG01	Medinvest-Institute of Hematology and Transfusiology	Dr. Genadi Iosava	06
CG02	Zodelava Hematology Centre	Dr. Mamia Zodelava	03
CP01	Wojewódzkie Wielospecjalistyczne Centrum Onkologii	Dr. Tadeusz Robak	02
CP02	Silesian Healthy Blood Clinic	Dr. Sebastian Grosicki	07

6.1. Disposition of Subjects

A total of 27 patients were screened in the study, of which 21 patients were eligible and received at least one dose of Tenalisib. All patients completed Cycle 2 and Cycle 4 and 15 (71.4%) patients completed 7 cycles (C8D1). Six patients discontinued from the study before C8D1. Out of these six patients, three (50%) discontinued due to disease progression and another three (50%) discontinued due to adverse event. (Table 5). Seven patients out 15 who completed the study (C8D1) were moved to compassionate use study (RP6530-1803 study).

Table 5: Summary of Subject Disposition and reason for discontinuation

Summary	
No of patients screened, n	27
No of patients eligible and received the study drug, n	21
Number cycles completed, [n (%)]	
Completed Cycle 2 (C3D1)	21 (100.0%)
Completed Cycle 4 (C5D1)	21 (100.0%)
Completed Cycle 7 (C8D1)	15 (71.4%)
No of Patients rolled over to compassionate study	07 (33.3%)
Number of subject discontinued #[n (%)]	06 (28.6%)
Primary reason for discontinuation	
Adverse Event	03 (50.0%)
Disease Progression	03 (50.0%)

N: Number of patients; % are based on the number of patients who received the study drug.; # Number of patients discontinued by the end of the study. Percentages for reason of discontinuation are based on the total number of patients discontinued.
Source: Listing 16.2.7.8.and Table 14.1.1.1.

6.2. Protocol Deviations

A total of 56 protocol deviations were reported in 15 (71.4%) subjects. Two deviations were major and observed in two subjects. The most commonly reported deviations included missed laboratory assessments / procedures. The major deviations reported were missed study efficacy assessments at C3D1/ C5D1 due to COVID-19 outbreak. In both cases, the patients were in quarantine due to Covid-19 and could not visit the clinical sites. Since both deviations were due to COVID-19 outbreak and didn't relate to patient compliance, these subjects were included in the PP population. (Table 6).

Table 6: Summary of Protocol deviation

Deviation type	**Tenalisib N=21 n (%), E**
All Protocol Deviations [n (%) E],	15 (71.4), 56
Major Protocol Deviations	2 (9.5), 2
Minor Protocol Deviations	14 (66.7), 54
Patients with at least one protocol deviation [n (%), E]	
• Inclusion / Exclusion Criteria	2 (9.5), 2
• Laboratory assessments / procedures	9 (42.9), 37
• Procedures out of timeframe, Visit Schedule / Interval	1 (4.8), 1
• Study Procedures	2 (9.5), 2
• Study Procedures, Laboratory assessments / procedures	5 (23.8), 8
• Study medication therapy	2 (9.5), 2
• Visit schedule / Interval	4 (19.0), 4

Percentages are based on the total number of patients (N); n: Number of patients with protocol deviation, E: Number of protocol deviations

Source: Table 14.1.2.1, Listing 16.2.2.

6.3. Demographic and other baseline characteristics

The median age of the patients was 64.5 years. There was higher male preponderance (males: 85.7%, females: 14.3%). All patients were White/Caucasian (Table 7). All patients (100%) had received at least prior systemic cancer therapy with 33.3% patients receiving ≥ 3 prior therapies. The patients were either refractory [6 (28.6%)] to the last therapy or had relapsed [15 (71.4%)] following the last therapy. Majority of the patients (90.5%) had an ECOG status 0 or 1 while only 2 (9.5%) patients had an ECOG 2.

Table 7: Demography and baseline characteristics

Demography and Baseline Characteristics	**Tenalisib, N=21**
Age (years)	
Mean	64.5
SD	8.7
Median	66.0
Min, Max	44.9, 79.2
Gender [n (%)]	

Demography and Baseline Characteristics	Tenalisib, N=21
Male	18 (85.7%)
Female	3 (14.3%)
Race [n (%)]	
American Indian or Alaska Native	0
White	21 (100.0%)
Asian	0
Black or African American	0
Native Hawaiian or Other Pacific Islander	0
Number of patients with Chromosomal abnormalities [n (%)]	
11q deletion	1 (4.8%)
13q deletion	1 (4.8%)
17p deletion	2 (9.5%)
Not known	17 (81.0%)
Number of patients with Gene mutations [n (%)]	
TP53	1 (4.8%)
NOTCH1	0
SF3B1	0
BIRC3	0
IGHV (unmutated)	0
ZAP	1 (4.8%)
Not known	19 (90.5%)
Rai Staging at Screening visit [n (%)]	
I	7 (33.3%)
II	6 (28.6%)
III	2 (9.5%)
IV	6 (28.6%)
Number of patients with prior therapies [n (%)]	
Systemic therapies	21 (100.0%)
Transplantation	0
Outcome of the last prior therapy [n (%)]	
Relapse	15 (71.4%)
Refractory	6 (28.6%)
Number of Prior therapies	
Mean	2.0
Median	2.0
Min, Max	1, 4
Number of prior therapies [n (%)]	
Therapy < 3	14 (66.7%)
Therapy ≥ 3	7 (33.3%)
ECOG Performance Status [n (%)]	
0	5 (23.8%)
1	14 (66.7%)
2	2 (9.5%)

Source: Table 14.1.3.1, Listing 16.2.4.1

6.4. Data Sets Analysed

The safety population, defined as patients who received at least one dose of study medication, included all 21 patients and was used for safety analysis. mITT population, defined as patients who received at least 1 dose of study medication and provided at least 1 post-baseline efficacy assessment, were used for efficacy assessment. Since all 21 patients had at least one post baseline efficacy assessment as defined in the protocol, all patients were considered as mITT population (Table 8).

There were two major deviations reported due to COVID-19 outbreak which didn't relate to patient compliance; hence all subjects including two patients with major protocol deviation were included in PP population. The efficacy results were summarized using only mITT population as mITT and PP populations were same. Table below summarizes the final populations analyzed in the study.

Table 8: Study Population

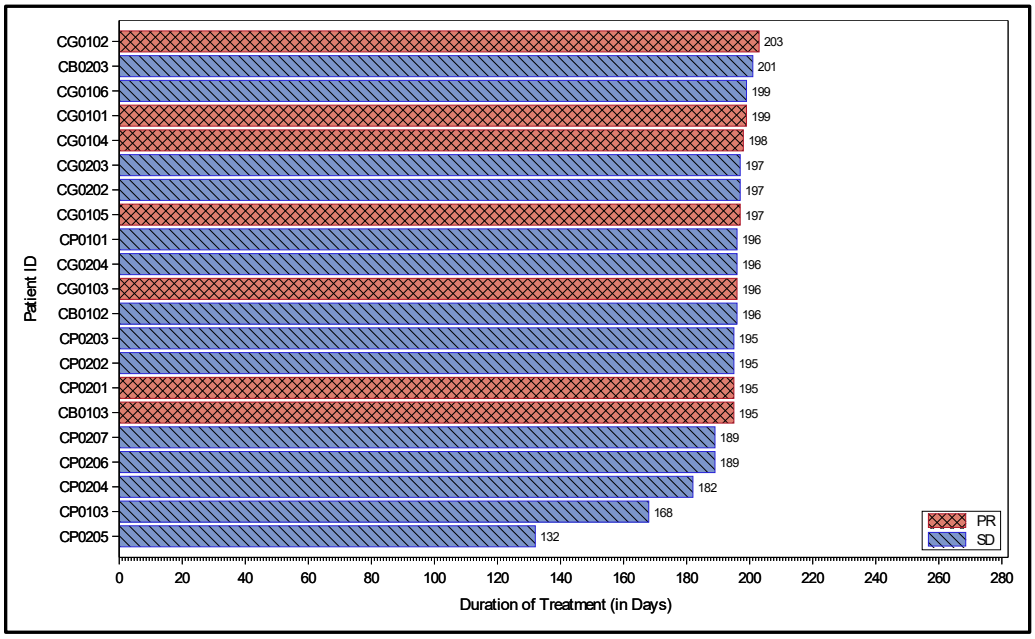
Analysis Populations	
Number of Patients enrolled and taken at least one dose of Tenalisib [n]	21
Full Analysis Set [n (%)]	21 (100.0%)
Safety Analysis Set [n (%)]	21 (100.0%)
Modified Intent-To-Treat Analysis Set [n (%)]	21 (100.0%)
Per Protocol Analysis Set [n (%)]	21 (100.0%)

Source: Listing 16.2.3.

6.5. Extent of Exposure

A total of 21 patients received at least one dose of Tenalisib. All patients (100%) received at least 4 cycles of Tenalisib of which 15 patients (71.5%) went on to receive at least 7 cycles of Tenalisib. (Figure 1). The median duration of exposure to study drug in the study was 196 (range 132-203) days.

Figure 1: Duration of treatment in study population



Source: Figure 14.1.6.2.and Table 14.3.6.1.

6.6. Measurement of Treatment Compliance

Compliance to study treatment was calculated on the basis of total planned doses of Tenalisib dispensed at each cycle and total dose consumed in that cycle. Compliance at each cycle was derived based on calculation at each cycle. All patients had overall drug compliance between 80 to 120%.

6.7. SAFETY ASSESSMENT

6.7.1. Overview Adverse Events

Overall, 15 (71.5%) patients reported at least one TEAE during the study of which 4 (19.1%) patients reported at least one related TEAE. Severe TEAEs (Grade 3 and 4) were reported in 7 (33.3%) patients, of which 3 (14.6%) patients reported at least one related Grade 3 or 4 TEAE (Table 9).

Four serious TEAEs were reported during the study; none of them was attributed to Tenalisib. Three (14.3%) patients were discontinued due to TEAEs, of which 1 (4.7%) patient had related TEAE. No protocol defined AEs of interest which included pregnancy/pregnancy complications and overdose were reported during the study. Two patients experienced TEAEs leading to death and none of them was related to Tenalisib. Below is an overview of TEAEs reported during the study.

Table 9: Overview of Non-Treatment and Treatment Emergent Adverse Events

Adverse Events	Tenalisib (N=21) n (%), E
Any non-TEAE	2 (9.5%), 2
Any TEAE	15 (71.4%), 65
Related TEAEs	4 (19.1%), 20
Serious non-TEAEs	1 (4.7%), 1
Serious TEAEs	3 (14.3%), 4
Related Serious TEAEs	0
Grade 3 or 4 TEAEs	7 (33.3%), 12
Related Grade 3 or 4 TEAEs	3 (14.3%), 6
TEAEs leading to discontinuation	3 (14.3%), 3
Related TEAEs leading to discontinuation	1 (4.8%), 1
Serious TEAEs leading to discontinuation	2 (9.5%), 2
Related Serious TEAEs leading to discontinuation	0
TEAEs leading to dose interruptions/dose reductions	4 (19.1%), 6
Fatal TEAEs	2 (9.5%), 2
Related Fatal TEAEs	0
Protocol-Defined Adverse Events of Special Interest	
Pregnancy	0
Abortion	0
Birth defects/congenital anomalies	0
Overdose	0

Percentages are based on the total number of patients (N). n: Number of patients with any event, E: Number of events, TEAE: Treatment-Emergent Adverse Event. TEAE are those that start on or after the date of first dose of study drug. Discontinuation refers to discontinuation of study drug.
Source: Listing 16.2.7.1. Table 14.3.1.1

6.7.2. Brief Summary of Adverse Events: Overall study

A total of 65 TEAEs were reported in 15 (71.5%) patients, of which 3 TEAEs [3 (14.3%) patients] were assessed as serious. Among the TEAEs, 20 [04 (19.1%) patients] were assessed as related to Tenalisib; none of them was assessed as serious. Twelve (12) TEAEs [7 (33.3%) patients] were of Grade 3/4 intensity; of which 6 TEAEs in 3 (14.3%) patients was assessed as related to study drug. Three (14.3%) patients were discontinued due to AEs. Two of the TEAEs resulted in death; both were not related to the study drug.

6.7.3. Most Frequently Reported Adverse Events

The most frequently affected system organ class (SOC) in the study were Blood and lymphatic system disorders and Investigations (33.3% each) and followed by Metabolism and nutrition disorders (14.3%).

Other than the above systems, the other affected SOC included Gastrointestinal disorders, Infections and infestations and Nervous system disorders in 9.5% patients each.

Among individual TEAEs, the most frequently reported TEAE was anemia in 28.6% patients. This was followed by neutropenia (23.8%), alanine aminotransferase increased, and aspartate aminotransferase increased (19.0% each).

Among related TEAEs, the most frequently reported TEAEs were neutropenia, alanine aminotransferase increased, and aspartate aminotransferase increased (9.5% each). This was followed by blood alkaline phosphatase increased, gamma-glutamyl transferase (GGT) increased and tremor (4.8% each).

Table below provides the frequently reported TEAEs categorized both by SOC and PT (Table 10 and Table 11).

Table 10 : Summary of TEAEs by System Organ Class and Preferred Term (Causality-All)

System Organ Class Preferred Term	AE-All n (%), E
At Least one TEAE	15 (71.4), 65
Blood and lymphatic system disorders	7 (33.3), 31
Anemia	6 (28.6), 10
Neutropenia	5 (23.8), 18
Thrombocytopenia	2 (9.5), 3
Gastrointestinal disorders	2 (9.5), 2
Diarrhoea	2 (9.5), 2
Infections and infestations	2 (9.5), 3
Pneumonia	2 (9.5), 3
Investigations	7 (33.3), 21
Alanine aminotransferase increased	4 (19.0), 7
Aspartate aminotransferase increased	4 (19.0), 6
Blood alkaline phosphatase increased	2 (9.5), 3
Gamma-glutamyl transferase increased	1 (4.8), 3
Blood lactate dehydrogenase increased	1 (4.8), 1
Blood thyroid stimulating hormone increased	1 (4.8), 1
Metabolism and nutrition disorders	3 (14.3), 3
Hyperglycemia	1 (4.8), 1
Hypocalcemia	1 (4.8), 1
Hypokalemia	1 (4.8), 1
Musculoskeletal and connective tissue disorders	1 (4.8), 1
Arthralgia	1 (4.8), 1
Nervous system disorders	2 (9.5), 3
Tremor	1 (4.8), 2
Neuritis cranial	1 (4.8), 1
Renal and urinary disorders	1 (4.8), 1
Glycosuria	1 (4.8), 1

Source: Table 14.3.1.3 and Listing 16.2.7.1

Table 11: Summary of TEAEs by System Organ Class and Preferred Term (Causality-Related)

System Organ Class Preferred Term	AE-Related n (%), E
At Least one TEAE	4 (19.0), 20
Blood and lymphatic system disorders	2 (9.5), 5
Neutropenia	2 (9.5), 5
Investigations	2 (9.5), 13
Alanine aminotransferase increased	2 (9.5), 4
Aspartate aminotransferase increased	2 (9.5), 4
Blood alkaline phosphatase increased	1 (4.8), 2
Gamma-glutamyl transferase increased	1 (4.8), 3
Nervous system disorders	1 (4.8), 2
Tremor	1 (4.8), 2

Source: Table 14.3.1.3 and Listing 16.2.7.4

6.7.4. Adverse Events Leading to Discontinuation

Three TEAEs led to discontinuation of 3 (14.3%) patients. The first patient was withdrawn due to an important medical event -pneumonia leading to death, assessed as not related to Tenalisib. The second patient was withdrawn due to GGT increased which was considered Tenalisib related (Table 12). The event was ongoing at the time of discontinuation. The third patient was withdrawn due to anemia, assessed as not related to Tenalisib. The event recovered later.

Table 12 : Adverse events leading to discontinuations

Subject ID	Event Term (PT term)	Relationship to Tenalisib	CTCAE Grade	SAE	Outcome
CG0102	Pneumonia	Not Related	Grade 5	Yes	Fatal
CP0103	Gamma- glutamyl transferase increased	Related	Grade 3	No	Not Resolved
CP0205	Anemia	Not Related	Grade 4	Yes	Resolved

Source: Listing 16.2.7.8

6.7.5. Deaths, Other Serious Adverse Events and Other Significant Adverse Events

6.7.5.1. Deaths

Two TEAEs (pneumonias) led to death of 2 (9.5%) patients. Both these events of pneumonia were important medical events. They were assessed as not related to Tenalisib and were considered related to suspected Covid infection. (Table 13).

Table 13: Adverse Events leading to Death

Subject ID	Event Term (PT term)	Relationship to Tenalisib	CTCAE Grade	SAE	Outcome
CB0203	Pneumonia	Not Related	Grade 5	Yes	Fatal
CG0102	Pneumonia	Not Related	Grade 5	Yes	Fatal

Source: Table 14.3.1.8 and Listing 16.2.7.5

6.7.5.2. Other Serious Adverse Events

A total of 5 SAEs were reported in 4 (19.0%) patients during the study, one of which (death-unknown reason) was reported in a screen-failure patient and hence the event was considered as a non-TEAE. Four SAEs were reported in 3 (14.3%) patients during the study (Table 14).

Table 14: Serious Adverse Events

Sub ID	Event Term (PT term)	Relationship to Tenalisib	CTCAE Grade	Outcome
CB0203	Pneumonia	Not Related	Grade 5	Fatal
CG0102	Pneumonia	Not Related	Grade 3	Resolved
CG0102	Pneumonia	Not Related	Grade 5	Fatal
CP0205	Anemia	Not Related	Grade 4	Resolved

Source: Table 14.3.1.5. and Listing 16.2.7.3

Narrative:

SAE Term: Pneumonia (CB0203; Grade 5)

This clinical trial case report refers to a 74-year-old, male, patient (Patient ID: CB0203) who started treatment with tenalisib 800 mg twice daily (bid) orally on 06-Feb-2020 for CLL. Patient received study drugs from 06-Feb-2020 until 24-Aug-2020 for 7 cycles and completed the study. On 24-Aug-2020, the patient received the last dose of tenalisib and completed the study as per the protocol.

Post completion of treatment, on an unknown date, the patient developed fatigue, cough and shortness of breath. After 25 days of the last dose of Tenalisib (18-Sep-2020), the patient was hospitalized with pneumonia. On auscultation, weakened vesicular respiration with small moist rales mainly in the right base of the lung was noted. X-ray revealed diffusely dispersed shadows in the base of the right chest. Polymerase chain reaction (PCR) test for Covid-19 was negative. Laboratory data included leukocytes 154.5 x10^9/l, lymphocytes 122x10^9/l, hemoglobin 114 g/l, platelet 147x10^9/l, glucose 6.8 mmol/l, creatinine 91 mmol/l, AST 35 U/l, ALT-23 U/l, GGT 50 U/l. The patient was diagnosed with bacterial pneumonia. The patient was treated with levofloxacin 500 mg/d intravenous (IV), aminophylline

(Novphyllin) 0.24 mg/d IV, nadroparin (Fraxiparine) 0.4 subcutaneous and bromhexine 2 teaspoon orally and oxygen. On the same day, the patient died due to complications. Cause of the death was reported as cardiac arrest and pneumonia. No additional information was available as the investigators became aware of the event 15 days after the occurrence of the event. Autopsy was not performed. Outcome of the event pneumonia was fatal. The investigator assessed the event of pneumonia as not related to the study drug Tenalisib as there was no temporal relationship with the study drug.

SAE term: Pneumonia (CG0102; Grade 3)

This clinical trial case report refers to a 53-year-old male patient (patient ID: CG0102), who started Tenalisib at 800 mg oral twice daily on 14-Jan-2020 for CLL. Patient's medical history included hypokalemia, elevation of AST and ALT, diarrhea and hypothyroidism. Concomitant medications included levothyroxine, acyclovir, co-trimaxazole (sulfamethoxazole, trimethoprim), magnesium aspartate and potassium aspartate.

On 21-Jun-2020, the patient had temperature and cough. On the same day, study drug was temporarily withheld. On 24-Jun-2020, the patient was hospitalized due to worsening of condition. X-ray revealed bilateral pneumonia. C-reactive protein (CRP) was 308 mg/dL. The Covid-19 test was negative. The patient received meropenem 1 g tid, levofloxacin 500 mg bid, metamizole sodium 50% 2 ml as needed, hydroxyzine 25 mg once a day, diphenhydramine 1%, paracetamol 0.5 g, simeticone 40 mg as needed, omeprazole 20 mg once a day, nadroparin and calcium 9500 IU once a day as treatment. With antibiotic therapy, patient's condition improved, and temperature was normalized. On 02-Jul-2020, the patient was treated with ceftriaxone 1gm BID and fluconazole 150 mg every third day. Bilateral pneumonia resolved and the patient was discharged from hospital on 2 July.

On 03-Jul-2020, the patient restarted Tenalisib. The investigator assessed that the event of bilateral pneumonia was not related to the study drug Tenalisib. Though the culture was not done, there was positive response to antibiotic therapy and thus the cause of pneumonia was considered as bacterial infection.

SAE Term: Pneumonia (CG0102; Grade 5)

This clinical trial case report refers to a 53-year-old male patient (patient ID: CG0102), who started Tenalisib at 800 mg oral twice daily for CLL.

Medical history included bilateral pneumonia, hypokalemia, elevation of AST and ALT, diarrhea and hypothyroidism. Previously reported SAEs for this subject included bilateral pneumonia on 24-Jun-2020. Concomitant medications included levothyroxine, acyclovir and Co-trimoxazole (trimethoprim/sulfamethoxazole). Historical drug included magnesium aspartate; potassium aspartate, metamizole sodium, diphenhydramine, paracetamol, simethicone, omeprazole, nadroparin calcium and fluconazole.

On 04-Aug-2020, the patient had fever 38.5 °C in the morning. After a few hours the patient had mild abdominal pain, hyperthermia and few episodes of vomiting. Later hypotonia was noted and the patient was hospitalized due to worsening of condition including arterial hypotension. Chest X-ray revealed bilateral pneumonia. Complete blood count showed hyperleukocytosis with lymphocytes 99%. Electrocardiogram (ECG) was without acute focal injury. Covid-19 testing was not reportedly performed. On the same day, Tenalisib was interrupted. Treatment included meropenem, levofloxacin, ceftriaxone, allopurinol, metamizole sodium,

pipecuronium bromide, acetylsalicylic acid, metoprolol, dexamethasone, potassium chloride, calcium gluconate, norepinephrine, ketamine, phenylephrine, budesonide, pantoprazole and nadroparin calcium.

On 05-Aug-2020, the patient's condition worsened with shock and cardiac arrest and at 18:00, the patient passed away. Autopsy was not done.

The investigator assessed event of bilateral pneumonia was not related to Tenalisib. Based on the limited information it was difficult to assess the causes of the complications. Investigator confirmed that the primary event was a bilateral pneumonia. Shock and cardiac arrest are the complications and death were the outcome.

SAE term: Anemia (CP0205; Grade 4)

This clinical trial case report refers to a 56-year-old male patient (patient ID: CP0205), who developed serious adverse event recurrent anemia (PT: Anemia) on 05-Jul-2020.

On 05-Jul-2020, patient was hospitalized due to anemia. On the same day, the study drug tenalisib was temporarily withheld. The patient received blood transfusion. On 06-Jul-2020, hemoglobin was 3.3 g/dl (Normal range: 12.4-17.2), life threatening in severity (Grade 4). The patient had received total of 4 units of RBCs. On 08-Jul-2020, hemoglobin was 5.8 g/dl (Normal range: 12.4-17.2), severe (Grade 3) in intensity. The patient was discharged from hospital with improvement. Tenalisib was continued to be on hold. On 12-Jul-2020, the patient was re-admitted to hospital due to of anemia. Tenalisib treatment was on hold since 5-Jul-2020 and therefore patient was not on tenalisib treatment at the time of admission. Hemoglobin was 2.7 g/dl. Life threatening in severity (Grade 4). The patient received RBCs transfusion and prednisolone (Encorton) 80 mg once daily as treatment. On 15-Jul-2020, the patient was hospitalized in the department of hematology unit due to anemia (hemoglobin 2.7 g/dl and RBC count 0.75 T/L) with features of hemolysis (bilirubin was 6-8 time the normal value, jaundice and splenomegaly). The patient had no signs of infection. The test for SARS-COV-2 was negative. It was concluded that the patient had developed hemolysis, which might be the symptom of disease progression. On the same day the patient was excluded from the study.

On 16-Jul-2020, the patient received alternative treatment Rituximab, Cyclophosphamide, Vincristine and Prednisolone (R-CVP) to stop the hemolysis mechanism. On the same day Encorton (prednisolone) was stopped. On 21-Jul-2020, hemoglobin was 7.8 g/dl (Normal range: 13.7-16.5). The patient had received total of 14 units of RBCs during this period. On 22-Jul-2020, as anemia resolved, the patient was discharged from hospital with improvement.

On 28-Jul-2020, the patient was re-admitted to hospital due to recurrent anemia. The patient's hemoglobin (Hgb) was 5.2 g/dL (Reference Range: 13.7-16.5 g/dL), life threatening in severity (Grade 4) and received transfusion of 1 unit RBC. The patient received two cycles of R-CVP due to progressive disease. On 29-Jul-2020, the patient received 1 unit RBC transfusion. On 06-Aug-2020, the patient received 2 units RBC transfusion.

On 07-Aug-2020, the patient's hemoglobin (Hgb) was 7.4 g/dl, (Grade 3). On Same day, the patient recovered from the event of recurrent anemia and discharged from hospital. The outcome of the event recurrent anemia was reported as resolved. Action taken with the study drug tenalisib was drug discontinued.

The investigator assessed that the event of recurrent anemia was not related to tenalisib but due to the underlying disease condition (hemolytic anemia). Considering the immune basis of anemia, steroids were started.

6.7.5.3. Other Significant Adverse Events (Grade ≥ 3 AE)

Overall, 14 Grade ≥ 3 TEAEs were reported.12 Grade 3/Grade 4 TEAEs were reported during the study in 7 (35.0%) patients. Six (6) TEAEs related Tenalisib were reported in 3 (15.0%) patients and included events of neutropenia (3 events), and GGT elevation (3 event). Two TEAEs (pneumonias) led to death of 2 (9.5%) patients. All related events resolved with or without dose interruptions except one event (GGT increased) which led to permanent drug discontinuation. (Table 15).

Table 15 : Treatment-Emergent Grade 3, 4 and 5 TEAEs

Patient	Preferred Term,	CTCAE Grade	SAE (yes /no)	Action Taken with Study Drug	Relationship to Study Drug	Outcome
CB0203	Pneumonia	Grade 5	Yes	Not Applicable	Not Related	Fatal
CG0102	Pneumonia	Grade 3	Yes	Drug Interruption	Not Related	Resolved
CG0102	Pneumonia	Grade 5	Yes	Drug Withdrawn permanently	Not Related	Fatal
CP0101	Neutropenia	Grade 4	No	Drug Interruption	Related	Resolved
CP0103	Gamma-glutamyl transferase increased	Grade 3	No	Drug Interruption	Related	Resolved
CP0103	Neutropenia	Grade 3	No	No action taken	Not Related	Resolved
CP0103	Gamma-glutamyl transferase increased	Grade 3	No	Drug Interruption	Related	Resolved
CP0103	Gamma-glutamyl transferase increased	Grade 3	No	Drug Withdrawn permanently	Related	Not resolved
CP0203	Neutropenia	Grade 3	No	No action taken,	Not Related	Resolved
CP0205	Anemia	Grade 4	Yes	Drug Withdrawn permanently	Not Related	Resolved
CP0206	Neutropenia	Grade 3	No	No action taken	Not Related	Resolved
CP0207	Neutropenia	Grade 3	No	No action taken	Related	Resolved
CP0207	Neutropenia	Grade 4	No	Drug Interruption	Related	Resolved
CP0207	Thrombocytopenia	Grade 3	No	No action taken	Not Related	Not resolved

Source: Table 14.3.1.4. Listing 16.2.7.5.

6.7.6. Safety Results Summary

Tenalisib administered as single agent at a dose of 800 mg BID, demonstrated acceptable and manageable safety profile in patients with relapsed/ refractory CLL. Most of the TEAEs were

Grade 1/2 in severity. Grade 3/4 TEAEs were minimal and were managed with drug interruption of Tenalisib. Treatment discontinuations due to related TEAEs were minimal.

6.8. ANALYSIS OF EFFICACY

6.8.1. Analysis of Efficacy

Assessments of efficacy parameters such as the ORR and DoR were primary endpoints in the study. Response assessments were assessed as per iwCLL guideline for CLL (Hallek *et al.* 2018) at C3D1, C5D1 and approximately every 12 weeks thereafter, and/ or at the EOT.

6.8.2. Summary of Best Overall Response (BOR)

Out of 21 patients evaluated for efficacy assessment, 7 (33.3%) patient showed partial response (PR), 14 (66.7%) patients showed stable disease (SD) as the best overall response.

6.8.3. Summary of Overall Response Rate

Overall, ORR, as defined as percentage of patients with CR or PR at any time point during the study, was 33.3% for both mITT and PP populations (Table 16). Based on PR and SD, Disease Control Rate (DCR) was 100% for both mITT and PP populations.

Table 16 : Overall Response Rate in Study Population

	Overall N=21	**95% CI***
Number of patients, n (%)		
Complete Response (CR)	0	(0.00, 16.11)
Partial Response (PR)	7 (33.3%)	(14.59, 56.97)
Stable Disease (SD)	14 (66.7%)	(43.03, 85.41)
Progressive Disease (PD)	0	(0.00, 16.11)
ORR (CR+PR)	7 (33.3%)	(14.59, 56.97)
DCR (CR+PR+SD)	21(100.0%)	(83.89, 100.00)

** Due to low number of patients in each disease subtype, 95% CIs are reported only for the Overall group using clopper pearson exact method based on binomial distribution.*
Source: Table 14.2.1.1

6.8.4. Summary of Duration of Response

Duration of Response (DoR) was defined as time from the first documented assessment of CR or PR until documented tumour disease progression. The DoR was calculated up-to a predefined cut-off date (i.e., up-to LPLV which was on 02 Oct 2020). Median DoR in the study was 143 days (with range 87, 148) (Table 17). Out of 7 responded patients, four patients were rolled over to compassionate protocol and are being followed up.

Table 17: Duration of Response in Study Population

	Tenalisib (N=21)
Number of patients with	
Objective response (CR or PR) [(n (%)]	7 (33.3%)
CR	0
PR	7 (33.3%)
Duration of response (days)	
N	7
Mean	135.3
SD	21.54
Median	143
Q1, Q3	138.0, 146.0
Min, Max	87, 148

Source: Table 14.2.3.1

6.8.5. Summary of Progression Free survival (PFS)

PFS was defined as time of the first dose of Tenalisib to disease progression or death. Median PFS in the study was 205 days (Table 18 and Figure 2). Out of 21 subjects, 13 patient's data was censored for PFS calculation as the patients neither progressed nor died at the time of study completion. Of these, 7 patients were rolled over to compassionate protocol and are being followed up.

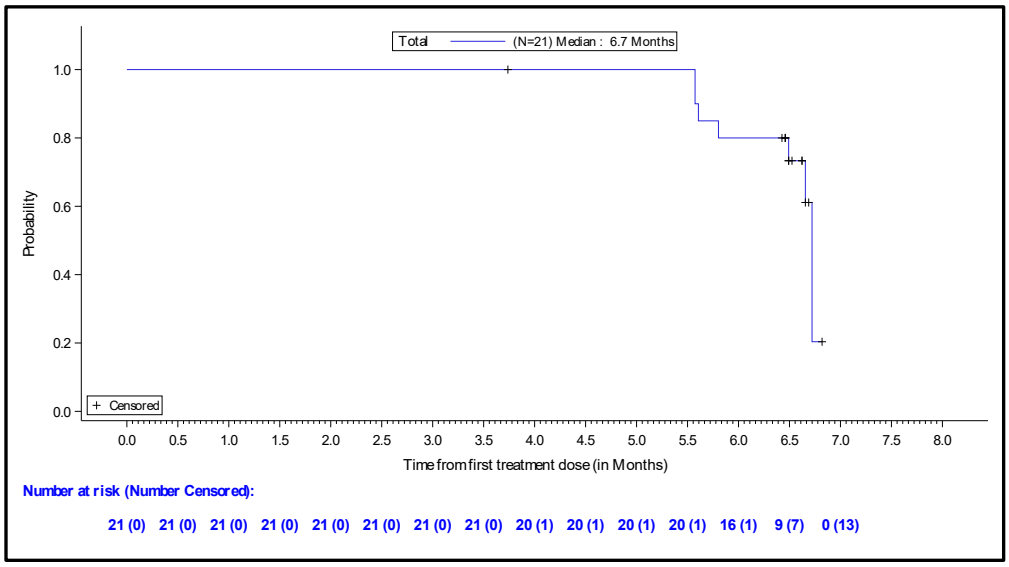
Table 18 :Progression Free Survival in Study Population

	Tenalisib (N=21)
Number of patients with Progressive Disease/Death [(n (%)]	8 (38.1%)
Progressive Disease, n (%)	7 (33.3%)
Death, n (%)	1 (4.8%)
Number of censored patients [(n (%)]	13 (61.9%)
Reason for Censoring, n (%)	
Last tumor assessment	13 (61.9%)
Time to Progressive Disease/ Death (days)	
Quartiles (95% CI)*	
Q1	198.0 (170.00, 203.00)
Median	205.0 (198.00, NE)
Q3	205.0 (NE, NE)

**Quartiles are calculated using Kaplan-Meier Estimate method. Due to low number of patients in each disease subtype, 95% confidence intervals are displayed only for the Overall group using Brookmeyer and Crowley Method.*

Source: Table 14.2.2.1

Figure 2: Progression Free Survival in Study Population



Source: Figure 14.2.2.3

6.8.6. Efficacy Results Summary

Overall, seven out of 21 enrolled patients in the study responded to Tenalisib with ORR of 33.3%, a median PFS of 205 days and median DoR of 143 days.

7. CONCLUSION

Tenalisib administered as single agent at a dose of 800 mg BID demonstrated an acceptable safety profile in patients with relapsed / refractory CLL.

After all the 21 patients were evaluated in stage 1 of the study, the DRC assessed the anti-tumor activity for all subjects. The committee arrived at a conclusion that since there were fewer than 8 responses seen in stage 1 of the study, as per the Simon two stage design of the study protocol, the study would be discontinued by accepting the null hypothesis of ORR$\leq$ 40%. Hence stage 2 of the study was not initiated.

8. REFERENCES

1. Tenalisib (RP6530) Investigator's brochure. Version 11.0 Dated 19 October 2020.
2. Gunawardana C., et al. South Asian chronic lymphocytic leukemia patients have more rapid disease progression in comparison to White patients. Br J Haematol. 2008; 142:606–9.
3. Howlader N, *et al.*, SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD, *http://seer.cancer.gov/csr/1975_2012.*
4. Stilgenbauer, S. and T. Zenz, Understanding and managing ultra-high-risk chronic lymphocytic leukemia. *Hematology Am Soc Hematol Educ Program*, 2010:481-8.
5. Hallek, M. *et al.* iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-60