PROTOCOL NO. RP6530-1901

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

Statistical Analysis Plan

Author and Designation:	[redacted]
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Signature Page

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Authoring Statistician	[redacted]		
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Signature above indicates approval of this plan, for the analysis and reporting of this study. Approval of the SAP and approval of any subsequent amendments is the responsibility of the Head of Statistics function or equivalent.

The approver serves as a single point of accountability for approval and must ensure that all relevant functions are in agreement with the final SAP.

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List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BID	Twice Daily
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DoR	Duration of Response
DRC	Data Review Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FAS	Full Analysis Set
IEC/IRB	Independent Ethics Committee/ Institutional Review Board
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NCI	National Cancer Institute
ND	Not Done
NE	Not Evaluable
ORR	Objective Response Rate
PFS	Progression-Free Survival
PP	Per-Protocol
PR	Partial Response
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
QTcF	QT interval with Fridericia's correction
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

1. Amendments from Previous Version(s)

Not Applicable.

2. Introduction

Note: [redacted]

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study RP6530-1901. This document may modify the plans outlined in the final protocol.

2.1 Rationale

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

Tenalisib is a highly specific and orally available dual PI3K δ/γ inhibitor with nano-molar inhibitory potency and several fold selectivity over α and β PI3K isoforms. Pre-clinical experiments demonstrated that Tenalisib is highly effective in killing primary CLL cells in vitro. The effect appeared to be equal to ibrutinib and higher than conventional chemotherapy agents. Tenalisib also demonstrated reduction in chemokine induced migration of Daudi cells, indicating its potential in modulating tumor microenvironment. Tenalisib has demonstrated clinical activity in patients with hematological malignancies with acceptable safety profile. Therefore, Tenalisib may offer a good treatment option for patient with relapsed/refractory CLL.

3. Study Objectives

3.1 Primary Objective

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

3.2 Secondary Objectives

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

4. Study Endpoints

4.1 Efficacy Endpoints

- *Overall response rate (ORR): ORR is defined as sum of CR and PR rates as defined by iwCLL guideline for CLL (Hallek et al. 2018)[2].*

- *Duration of response (DOR): DOR is defined as the interval from the first documentation of CR/PR to first documentation of definitive disease progression or death from any cause.*

- *Progression-free survival (PFS): PFS is defined as the interval from first dose to first documentation of definitive disease progression or death from any cause.*

4.2 Safety Endpoints

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

5. Study Design

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

Patients will be evaluated for efficacy response by CT at C3D1±7 days, C5D1±7 days and C8D1±7 days and/or at End of the treatment (EOT) visit. The study will end when all ongoing subjects have reached their third tumor assessment on Cycle 8/Day 1 (C8D1) or have discontinued from the study for any reason, whichever is earlier.

5.1 Study Stopping Rules

- ***Safety:*** *The* Data review Committee (*DRC*) *will continue to monitor safety of Tenalisib (or toxicity trends that may be of concern) at interval of approximately 3 months from initiation of study until the completion of the study. In the event of one (1) death attributed to the study drug, study accrual will be suspended pending further investigation, and will only be resumed at the recommendation of the DRC. In addition, the DRC may recommend for termination of the study in case of major safety concerns.*

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

In addition, Sponsor reserves the right to terminate the study in the interest of patient safety, for noncompliance with the protocol, lack of recruitment or any other administrative reasons. The sponsor and PIs will notify the regulatory authority and respective IRB/IEC respectively if the trial terminates early, with a justification for the early termination.

Notes:

- After reviewing the efficacy data, the study has been closed due to absence of clinically meaningful response to single agent Tenalisib in Stage 1 of the study. Therefore, Stage 2 will not be performed.
- The analysis proposed in this SAP is considering the available data at the time of completion of the study.

6. Sample Size Considerations

The sample size was derived based on Simon's two stage design to achieve 90% power at alpha of 0.05 for the null hypothesis of ORR≤40%, assuming 60% response rate. Up to 61 patients will be enrolled. In stage 1, 20 patients will be enrolled, if 08 or fewer responders are observed in this stage, the study will be terminated without rejecting the null hypothesis. Otherwise, 41 additional patients will be enrolled into stage 2. If 31 or more responders are observed in the study, the null hypothesis of ORR ≤40% will be rejected.

Stage 1: 21 patients with relapsed/refractory CLL is enrolled.

Stage 2 will not be initiated as the study is closed due to absence of clinically meaningful response to single agent Tenalisib.

7. Analysis Populations

7.1 Modified Intent-to-Treat Population (mITT) Analysis Set

The mITT is the primary efficacy analysis population set *and will include data from all patients who received at least 1 dose of study medication and provide at least 1 post-baseline efficacy assessment*.

7.2 Per-Protocol (PP) Population Analysis Set

The PP Population set *is a subset of the modified Intent-to-Treat Population* set *and will include patients without major protocol deviations.*

Major deviations shall include:

- Deviation from an IEC/IRB approved protocol which compromise the safety and welfare of participating subjects or the integrity of the study and /or the completeness, accuracy and reliability of study data. Examples of deviations included but not limited to:
    - Failure to obtain informed consent (e.g., there is no documentation of informed consent) for a subject;
    - Informed consent is obtained after initiation of study procedures;
    - Enrollment of subject who has failed to meet the inclusion/exclusion criteria.

The list of protocol deviations with categorization with respect to major and minor deviations will be generated prior to the study database lock. All deviations will be reviewed by the Medical monitor prior to database closure in order to decide whether to include the patient in a PP analysis population set. The PP population analysis set will also be used for efficacy assessment.

Note: If the patients qualifying for mITT set are same as the patients qualifying for PP set, the respective tables and figures proposed using PP set will not be produced to avoid the duplication of the results.

7.3 Safety Population Set

The Safety Population set *will include all subjects who receive at least 1 dose of the study drug.*

7.4 Full Analysis Set (FAS)

The FAS includes all the patients who sign the Informed Consent Document and are enrolled into the study. This set will be used for reporting patient demographic data and any available patient baseline characteristics as reported in the Case Report Form (CRF).

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

8. Randomization and Blinding

This is a non-randomized, open label study.

9. Method of Analysis

9.1 Statistical Hypotheses

The sample size was derived based on Simon's two stage design to achieve 90% power at alpha of 0.05 for the null hypothesis of ORR ≤ 40%, assuming 60% response rate. Up to 61 patients will be enrolled. In stage 1, 20 patients will be enrolled. If eight or fewer responders are observed in this stage, the study will be terminated without rejecting the null hypothesis. Else, 41 additional patients will be enrolled into stage 2. If 31 or more responders are observed in the study, the null hypothesis of ORR ≤ 40% will be rejected.

9.2 Interim Analysis

No formal interim analysis will be performed for this study; however, the study data will be reviewed periodically by DRC during the course of the study. Refer Section 5.1 for detailed information.

9.3 Handling of Missing Data

9.3.1 Missing Dates for Adverse Events and Concomitant Medications

Adverse events and concomitant medications with completely or partially missing assessment dates will have imputation performed as explained below for the purposes of calculation of durations or relativity to study medication.

For the end of a concomitant medication or adverse event:

- **If only Day of end date is missing**:

The last date of the month and year reported or the date of the final contact with the subject, whichever is earlier, will be used as the end date.

- **If Day and Month of end date are missing**:
  The last date of year i.e. December 31 of the year reported or the date of the last study contact with the subject, whichever is earlier, will be used as the end date.

- **If Year of end date or complete end date is missing**:
  If the year of end of medication/event is missing or end date is completely missing, then no end date will be imputed.

For the start of a concomitant medication or adverse event:

- **If only Day of start date is missing:**
  - If the start year and month of medication/event are the same as that for the first dose date, then following approach will be used:
    - If the end date of medication/event is NOT before the first dose date or end date of medication/event is completely missing, then impute the start day as the day of first dose date
    - Otherwise, impute the start day as 1.

  - If the start year and month of medication/event are NOT same as that for the first dose date, then
    - Impute the start day as 1.

- **If Day and Month of start date are missing:**

  - If start year of medication/event is same as first dose year, then following approach will be used:
    i. For medication, impute the start Month as January and the Day as 1
    ii. For adverse event,
    - If the end date of event is NOT before the first dose date or end date of event is completely missing, then impute the start Month and Day as the Month and Day of first dose date;
    - Otherwise, impute the start Month as January and the Day as 1.

  - If start year of medication/event is NOT same as first dose year, then
    - Impute start Month as January and the Day as 1.

- **If Year of start date or complete start date is missing:**

  If the year of start of medication/event is missing or start date is completely missing, then no start date will be imputed.

9.3.2 Missing Dates for Efficacy Endpoints

For time-to-event endpoints (Progression Free Survival, Overall Response and Duration of response), if the date is completely missing, no imputation will be performed.

However, the incomplete/partial dates will be handled following the general conventions as detailed in Section 9.3.1.

9.3.3 Missing dates for Primary Diagnosis/Prior therapy

Partial Primary diagnosis and prior therapy dates will have imputation performed as explained below for the purposes of calculation of relativity to study medication.

- If only Day is missing, impute the day 1
- If Day and Month are missing, impute the Month as January and the Day as 1.
- If the year of primary diagnosis is missing or the date of primary diagnosis is completely missing, then no date will be imputed.

10. Statistical Analysis

Due to early closure of the study, the analysis proposed in the SAP is based on the available data at the time of study closure.

The safety endpoints will be listed and/or summarized. No inferential statistical analyses will be performed.

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

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where necessary to account for dropouts and missing patients. Unless otherwise specified, the denominator for percentages will be the number of patients with a non-missing assessment in a given treatment group within the analysis population of interest.

All statistical analyses will be performed using SAS 9.4 or higher.

10.1 Patient Disposition

A tabular presentation of the patient disposition data will be provided. It will include the number of patients screened, enrolled, assigned treatment, completed the treatment, as well as the number of dropouts, with reasons for discontinuation, number in each population sets, number of patients with dose reductions or interruptions (if applicable), etc. All patients' data will be used for this report.

10.2 Demographic and Baseline Characteristics

Analysis set: FAS

Demographic and baseline characteristics data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, maximum) for continuous variables, and using frequencies and percentages for categorical variables.

Demographic characteristics will include age, race, gender, height, weight, etc.

Disease characteristics will include time from initial diagnosis to enrollment, chromosomal abnormalities, gene mutations, Rai staging at the time of screening, number of prior therapies, number of subject relapsed or refractory to the last therapy, time from date of last therapy to enrollment, ECOG performance status, etc.

10.3 Medical and Surgical History

Analysis set: FAS

This data will be summarized using frequencies and percentages by System Organ Class and Preferred Term. A listing will also be provided.

The medical history data will be coded using MedDRA dictionary [Version 23.0 (Hierarchy) or higher].

10.4 Prior and Concomitant Medications

Analysis set: FAS

Concomitant medications are those that were taken while on study drug. Also, the medications / non-drug treatments which start after study treatment will be termed as 'Concomitant'.

Prior medications are those that were taken prior to the initial dose of study drug.

The medication data will be coded using WHO-Drug dictionary (WHODRUG GLOBAL B3 March 1, 2020 or higher) and the non-drug treatments data will be coded using MedDRA dictionary [Version 23.0 (Hierarchy) or higher].

A summary of frequencies and percentages by ATC level 2 and Preferred Terms and the listing of the prior and concomitant treatments taken will be provided.

10.5 Efficacy Analysis

Analysis Set: mITT and PP

- These analyses will be done for overall population. }

Note: The analyses outlined below are subject to availability of adequate data. In absence of adequate data, some of the efficacy endpoints discussed below will be presented with basic summaries and/or plots and listings, as appropriate.

10.5.1 Objective Response Rate (ORR)

It is *defined as sum of CR and PR rates as defined by iwCLL guideline for CLL (Hallek et al. 2018)[2]. Only those patients who have had a pre-treatment baseline efficacy evaluation and at least one post-treatment efficacy evaluation (that includes confirmed disease progression) will be considered evaluable for response. Overall ORR will be calculated.*

Additionally, Disease Control Rate (DCR= CR+PR+SD) will be presented.

This data will be summarized using frequency, and percentage and the 95% CI (Using exact method based on binomial distribution, subject to availability of adequate data) for the Overall group.

The corresponding listing will also be provided.

10.5.2 Complete and Partial Response Rate

The investigator assessed response, which is done as per the iwCLL guideline for CLL will be used. Only those patients who have had a pre-treatment baseline efficacy evaluation and at least one post-treatment efficacy evaluation (that includes confirmed disease progression) will be considered evaluable for response.

This data will be summarized using frequency, and percentage. the 95% CI (Using exact method based on binomial distribution, subject to availability of adequate data) will be presented for the Overall only.

10.5.3 Duration of Response (DoR)

It *is defined as the time when the measurement criteria are first met for PR or CR (whichever is reported first) until the date of documented disease progression or death. For subjects who neither progress nor die, the duration of response will be censored at the date of their last disease assessment.*

This data will be summarized descriptively using n, mean, median, standard deviation, minimum and maximum values for overall subjects. The DoR data will be listed for each patient.

10.5.4 Best Overall Response

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

This data will be summarized using frequency and percentage for Complete Response (CR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (PD), as reported in the CRFs for overall subjects.. This data will also be listed.

10.5.5 Progression Free Survival (PFS)

It is defined as time of the first dose of Tenalisib to disease progression or death. Subjects who die without a reported prior progression will be considered to have progressed on the date of

their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment that will be assessed at End of Treatment visit for this study. End of treatment visit will be considered as the cut-off visit for the calculation of PFS.

This data will be summarized using the Kaplan-Meier method and displayed graphically for overall subjects. The following reports will be generated:

- The Q1, median and Q3 PFS time will be provided along with95% CI for the Q1, median, and Q3 PFS time will be presented for the Overall subjects using Brookmeyer-Crowley method, subjected to availability of adequate data.
- The number and % of patients with disease progression (further divided into disease progression or death) will be provided.
- The number and % of patients censored (further divided by reasons for censoring) will be provided.
- Kaplan-Meier curves will be produced.
- A listing of PFS data will be provided.

10.6 Safety Analysis

Analysis Set: Safety

The safety analyses will be reported for Overall patient data only.

10.6.1 Treatment Exposure and Compliance

Analysis set: Safety

Treatment compliance and the treatment exposure will be summarized descriptively (n, mean, median, standard deviation, minimum and maximum values) and will also be listed.

- The treatment exposure to the study medication for subject will be calculated as:

  Exposure (day) = Last day of dosing – First Day of dosing + 1

  - A summary of duration of treatment (days) will be provided. In addition, a plot for duration on treatment will be provided per patient.

- The treatment compliance percentage (per patient), which is reported in the eCRF, will be summarized descriptively per Cycle. This data will be listed for individual patient.

10.6.2 Adverse Events

Analysis set: Safety

Note: If needed, adverse event data may be presented for all screened patients.

The frequency of adverse events (AEs) will be computed by counting each patient only once per MedDRA [Version 23.0 (Hierarchy) or higher] preferred term and according to the maximum NCI CTCAE v.5.0 grade attained by the patient over the specified period. The percentage of

patients with an event will be calculated using the number of patients in the safety analysis set as the denominator.

Standard Summaries of Adverse Events

Treatment Emergent Adverse Events (TEAEs) are those that start on or after the date of first dose of study medication.

An overall summary of TEAEs (number and percentage of patients along with the number of events) will be presented with the following:

- Any non-TEAE
- Any TEAE
- Treatment Related TEAEs
- Serious non-TEAEs
- Serious TEAEs
- Treatment Related Serious TEAEs
- Grade 3 or 4 TEAEs
- Treatment Related Grade 3 or 4 TEAEs
- TEAEs leading to discontinuation
- Treatment Related TEAEs leading to discontinuation
- Serious TEAEs leading to discontinuation
- Treatment Related Serious TEAEs leading to discontinuation
- TEAEs leading to dose interruptions/dose reductions
- Fatal TEAEs
- Treatment Related Fatal TEAEs
- Protocol-Defined Adverse Events of Special Interest:
  - Pregnancy, abortion, birth defects/congenital anomalies
  - Overdose

Summaries showing the number of patients (n, %) along with number of events by SOC and PT will be provided for the following:

- TEAEs (Related/ Not Related/ Total)
- Grade 3, 4 and 5 TEAEs (Related/ Not Related/ Total)
- Treatment-Emergent SAEs (Related/ Not Related/ Total)
- TEAE with maximum CTCAE grade
- Treatment-Related TEAEs with maximum CTCAE grade
- Deaths

The adverse events data will also be listed for individual patients.

- Any non-TEAE
- AEs
- Related TEAEs
- Treatment Emergent Grade 3, 4 and 5 AEs
- Treatment Related Grade 3, 4 and 5 AEs
- SAEs

- Treatment Related SAEs
- TEAE leading to discontinuation

10.6.3 Clinical Laboratory Tests

Analysis Set: Safety

Laboratory data will be presented per cycle.

The baseline measurement is the last pre-treatment measurement taken on or before Cycle1 Day1.

Absolute values of Laboratory parameters will be presented using descriptive statistics (n, mean, median, standard deviation, minimum and maximum values) as appropriate.

The laboratory data will also be listed.

A separate listing of patients with abnormal laboratory test values will also be presented.

Hematology	***Chemistry Panel I***	***Chemistry Panel II***	***Urinalysis***	***Other***
Hematocrit	*Total bilirubin*	*Blood glucose*	*Blood*	*PT*
Hemoglobin	*Alkaline phosphatase*	*LDH*	*Glucose*	*INR*
Platelet count	*Alanine aminotransferase*	*Albumin*	*Protein*	
White blood cell count	*Aspartate aminotransferase*	*Total protein*	*Specific gravity*	
WBC (Total and differentials)	*Urea or blood urea nitrogen*	*Total Cholesterol*	*Microscopic exam*	
Red blood cell count	*Creatinine*	*Triglyceride (TG)*		
Absolute neutrophil count	*Gamma-glutamyl transferase*	*LDL*		
Absolute lymphocyte count	*Sodium*	*HDL*		
	Potassium	*TSH*		
	Calcium	*T3 (Total or Free)*		
	Phosphorous	*T4 (free)*		
	Carbon Dioxide (CO2) or bicarbonate			
	Chloride			
	Magnesium			

10.6.4 Physical Examinations

Analysis Set: Safety

Physical examination data will be listed for Screening visit.

A separate listing of patients with abnormal findings will also be presented.

10.6.5 Vital Signs

Analysis Set: Safety

Vital signs will include pulse rate, respiratory rate, blood pressure, and temperature (oral/axillary/tympanic). Weight will also be included here.

The baseline measurement is the last pre-treatment measurement taken on or before Cycle1 Day1.

Absolute values of Vital Signs data will be summarized descriptively (n, mean, median, standard deviation, minimum and maximum) per cycle. A listing will also be provided.

A separate listing of patients with abnormal vital signs findings will also be presented.

10.6.6 Electrocardiogram

Analysis Set: Safety

- The baseline measurement is the last pre-treatment measurement taken on or before Cycle1 Day1.
- Absolute values of ECG parameters [PR Interval, HR (heart rate), QT interval, QTcF (QT interval with Fridericia's correction), QRS Duration] as collected on CRF will be presented through n, mean, median, standard deviation, minimum, and maximum per cycle.
- A summary of abnormal ECG results will also be provided per cycle including baseline visit using frequencies and percentages.
- A listing of this data will also be provided.
- A separate listing for the abnormal ECG values will also be presented.

10.6.7 ECOG

Analysis Set: Safety

ECOG performance status, as reported in the eCRF, will be summarized per cycle with number and percentage for each status category. This data will also be listed.

The baseline measurement is the last pre-treatment measurement taken on or before Cycle1 Day1.

11. Protocol Deviations

Analysis set: FAS

A full list of protocol deviations for the study report will be compiled prior to database closure. All deviations will be reviewed by the Medical monitor prior to database closure. Each deviation

will be categorized as major and minor and a decision will be taken by the medical monitor whether to include the subject in a PP analysis population set.

Protocol deviations will be presented as number and percentage of patients with minor and major deviations in the study. This data will also be listed as appropriate.

12. Listings

In addition to all the listings mentioned above, separate listings will be presented for the following:

- Screened patients
- Eligibility review
- Study completion/Reasons for withdrawal of patient from the study
- Analysis populations
- Prior therapy
- Baseline Serology assessment
- Cancer diagnosis
- Disease assessment at Screening visit
- Follow-Up Cancer Overall Assessment
- Study drug exposure
- Study drug accountability
- Target lesion assessment
- Non-target lesion assessment
- Disease Response assessment
- Overall tumor assessment
- Pregnancy test
- Investigator Comments
- Patient visits

13. References

1. Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. Biometrics. 38: 29-41, 1982.
2. Hallek, M. *et al.* iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018;131(25):2745-2760