PROTOCOL NO. RP6530+Romidepsin-1805

An Open label, Phase I/II study to evaluate the safety and efficacy of Tenalisib (RP6530), a novel PI3K δ/γ dual inhibitor given in combination with a histone deacetylase (HDAC) inhibitor, Romidepsin in adult patients with relapsed/refractory T-cell Lymphoma

Statistical Analysis Plan

[redacted]	[redacted]
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Revision History:

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FINAL 1.0	Not Applicable	[redacted]	09AUG2021

Signature Page

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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
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T cell lymphoma
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DoR	Duration of Response
DRC	Data Review Committee
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
HDAC	histone deacetylases
IEC/IRB	Independent Ethics Committee/ Institutional Review Board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
mSWAT	Modified Severity-Weighted Assessment Tool
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ND	Not Done
NE	Not Evaluable
ORR	Objective Response Rate
P13K	phosphoinositide-3-kinase
PK	Pharmacokinetics
PP	Per-Protocol
PR	Partial Response
PT	Preferred Term
PTCL	Peripheral T-cell lymphoma
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
SRC	Scientific Review Committee
TCL	T-cell lymphoma
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

1. Amendments from Previous Version(s)

Not Applicable.

2. Introduction

Note: In this document, any text taken directly from the protocol (Number: RP6530+Romidepsin -1805, Amendment 1 to Version 1.0 Dated 16 August 2018, Amendment version dated 30 November 2018) is *italicized*.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study RP6530+Romidepsin-1805. This document may modify the plans outlined in the final protocol.

2.1 Rationale

Tenalisib is a highly specific and orally available dual kinase PI3K (phosphoinositide-3-kinase) *δ/γ inhibitor with nano-molar inhibitory potency and several fold selectivity over α and β PI3K isoforms. The specificity of Tenalisib towards PI3K δ and γ is evidenced by >1000 and >100-fold selectivity over α and β isoforms in an enzyme-based assay. Chemically, Tenalisib is an iso-flavone substituted adenine.*

Romidepsin is a histone deacetylases (HDAC) inhibitor and was approved by FDA for the treatment of CTCL and PTCL in 2009 and 2011 respectively for the patients who have received at least one prior systemic therapy.

Given the fact that both Romidepsin and Tenalisib have non-overlapping toxicity profiles, half of the optimal dose of Tenalisib (400 mg BID) and one dose below the approved dose of Romidepsin (12 mg/m2) are considered reasonable as starting doses of the combination from safety point of view. It is expected that proposed combination of Tenalisib with Romidepsin has the potential to improve response rates and increase the durability of response.

3. Study Objectives

3.1 Primary Objective

- *To characterize safety, tolerability and to establish the maximum tolerated dose (MTD) of Tenalisib in combination with Romidepsin in patients with R/R T-cell lymphoma.*

3.2 Secondary Objectives

- *To assess the preliminary anti-tumor activity of various dose levels of Tenalisib in combination with Romidepsin as determined by the Objective Response Rate (ORR) and Duration of Response (DoR).*

- *To characterize the Pharmacokinetics (PK) of Tenalisib and Romidepsin when given in combination.*

3.3 Exploratory Objective

- *To correlate clinical efficacy with markers that include but are not limited to quantitative and qualitative measurements of malignant cells, cytokines, and chemokines in blood/serum.*

4. Study Endpoints

4.1 Primary Endpoint

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

4.2 Secondary Endpoints

- **Efficacy**
  - *Objective Response Rate (ORR), defined as sum of CR and PR rates, assessed according to the Lugano Classification for initial evaluation, staging, and response assessment of Hodgkin/non-Hodgkin lymphoma in PTCL patients; and according to the modified Severity Weighted Assessment Tool (mSWAT) in CTCL patients.*
  - *Duration of Response (DoR), calculated as time from the initial response to documented disease progression.*
- **Pharmacokinetics**
  - *PK Parameters [$AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, t_{max}, Kel, and $t_{½}$] of Tenalisib and Romidepsin.*

4.3 Correlative/ Exploratory Endpoints

- *Correlative markers include baseline and on-treatment serum levels of chemokines, cytokines, antibodies to tumor antigens, and other immune mediators (e.g. sIL2R and CTACK for PTCL; CD30, IL-31 and IL-32 for CTCL) as deemed relevant by the sponsor.*

5. Study Design

This is a multi-center, open label, non-randomized, two-part Phase I/II study of Tenalisib in combination with Romidepsin in adult patients with relapsed/refractory TCL. The first part is an open-label, 3+3 dose escalation, Phase I study for MTD determination. The second part is a Phase II, dose expansion to delineate the safety and anti-tumor activity of the combination at the MTD/optimal dose.

In dose escalation, a minimum of 2 and maximum 18 patients will be enrolled in three dose levels unless additional dose levels are required to reach MTD/ optimal dose. In dose expansion,

up to 24 TCL patients will be enrolled (Group 1= 12 PTCL patients and Group 2= 12 CTCL patients).

The study will end when all ongoing subjects have reached their third tumor assessment on Cycle 8/Day 1 (C8D1) or have discontinued from the study for any reason, whichever is earlier. At the end of the study, all ongoing patients with no evident disease progression will be given the opportunity to enroll in an open-label compassionate use study protocol and will be followed up.

5.1 Phase I: Dose escalation

Sequential dose escalation will begin with Cohort 1. A minimum of three patients will be enrolled at each dose level. Dose levels will be increased in successive increments according to the dose escalation cohorts mentioned in the table below. Escalation to the next cohort will occur if no patient within a three-patient cohort or one in six patients experiences a dose limiting toxicity (DLT). De-escalation to different lower doses in case DLT criteria is met, will be done as per the discretion of Safety Review Committee (SRC). The highest doses of the combination (Tenalisib at 800 mg BID plus Romidepsin IV 14 mg/m^2) will be considered as optimal in case there is no DLT at this dose level.

Dose escalation scheme:

Cohort	***N***	***Tenalisib[1]***	***Romidepsin[2]***
Cohort 1	*3-6*	*Tab. 400 mg PO twice a day*	*IV 12 mg/m^2 on Day 1, 8 and 15*
Cohort 2	*3-6*	*Tab. 600 mg PO twice a day*	*IV 12 mg/m^2 on Day 1, 8 and 15*
Cohort 3	*3-6*	*Tab. 800 mg PO twice a day*	*IV 14 mg/m^2 on Day 1, 8 and 15*

Note: Alternate dose levels/dosing schedules may be considered by the SRC if deemed essential based on emerging safety and PK data.

[1]In case the dose (e.g. 800 mg BID) is leading to DLT of the combination, the dose of Tenalisib will be reduced to lower dose (e.g. 600 mg BID) and will be evaluated for safety in a separate cohort.

[2]In case the dose (e.g. 14 mg/m^2) is leading to DLT of the combination, the dose of Romidepsin will be reduced to lower dose (e.g.12 mg/m^2) and if required further to 10 mg/m2 and will be evaluated for safety in a separate cohort.

DLT assessment: *The data of at least 3 patients will be required for DLT assessment. DLT assessment period will be* ***28-days*** *(inclusive) (will begin on C1D1 and end on C2D1), unless extended by the medical monitor. In the first cycle, patients must have been treated with at least 2 doses of Romidepsin and minimum 14 days with Tenalisib to be considered eligible for safety analysis unless identified to have a DLT. Patients who experience a DLT will be considered evaluable regardless of the number of doses received.*

Individual patients will be considered for ***Intra-subject dose*** *escalation at the discretion of investigator after discussion with medical monitor.*

5.2 Phase II: Dose Expansion

After establishing the MTD/optimal dose, the Phase II (expansion part) will be opened as approved by the SRC to enroll two groups of patients.

Group	***N***	***Patient Population***	***Tenalisib***	***Romidepsin***

Group 1	*12*	*Patients with R/R PTCL*	*MTD/ Optimal dose*	*MTD/ Optimal dose on Day 1, 8 and 15*
Group 2	*12*	*Patients with R/R CTCL*	*MTD/ Optimal dose*	*MTD/ Optimal dose on Day 1, 8 and 15*

5.2.1 Number of subjects

- *Phase I: Total 2-18 patients will be enrolled in 3 escalating cohorts unless additional dose levels are required to reach MTD/ optimal dose.*

- *Phase II: Total 24 patients with relapsed/refractory TCL will be enrolled.*

5.3 Study Stopping Rules

- ***Stopping Rule for Dose Escalation:*** *The SRC will be in charge of reviewing safety data following the final treatment dose (Day 28 of Cycle 1) of the last patient in each cohort and will decide whether or not it is possible to proceed to the next cohort.*

- ***Suspension of Patient Enrollment:*** *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 SRC. The SRC will have discretion to terminate the trial if an additional death occurs that can be attributed to the study drug.*

- ***Stopping Rule for Dose Expansion:*** *After establishing the MTD/optimal dose, the Phase II expansion part will be opened as approved by the SRC. The SRC will continue to monitor safety of the combination (or toxicity trends that may be of concern) at interval of 3 months from initiation of expansion cohort till the completion of the study. Safety/toxicity will be monitored across cohorts combined together. The SRC will have discretion to terminate the trial if there are major safety concerns.*

- ***Study Stopping:*** *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.*

6. Sample Size Considerations

Part 1: *In Dose Escalation, three patients per cohort are considered appropriate for the assessment of overall safety and tolerability and for providing adequate confidence for dose escalation. No formal sample size and power analysis is done. Accordingly, total 2-18 patients will be enrolled in 3 escalating cohorts unless additional dose levels are required to reach MTD/ optimal dose. Optimal dose will be determined by the SRC.*

Part 2: *Total 24 patients with relapsed/refractory TCL will be enrolled in two groups (12 patients in each group). Twelve patients per group is considered appropriate for assessment of preliminary anti-tumor activity of the combination. However, the SRC may modify the sample size due to unforeseen clinical situations.*

7. Analysis Populations

7.1 All Enrolled Patients

The enrolled patients are those who have consented and screened with eligibility verified as per the Inclusion-Exclusion criteria mentioned in study protocol.

7.2 Safety Population Set

The Safety Population set *will include all subjects who receive at least 1 dose of the study medication.* This set will be used for reporting safety data, patient demographic data and any available patient baseline characteristics as reported in the Case Report Form (CRF).

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

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

Note: In order to offer sufficient time for assessing the effectiveness of the study medications, patients who provide the post-baseline efficacy assessment; at least on Cycle 3 Day 1 or are discontinued from study at Cycle 3 Day 1 shall be evaluated for mITT analysis set. Programmatically, if the patient received at least 1 dose of study medication and have provided at least Cycle 2 Day 22 efficacy assessment, then he/she will be qualified for mITT analysis set.

7.4 Per-Protocol (PP) Population Analysis Set

The PP Population is a subset of the modified Intent-to-Treat Population 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 compromise 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 from the enrolled subject (e.g., there is no documentation of informed consent);
    - Informed consent is obtained after initiation of study procedure;
    - Enrollment of subject who has failed to meet the eligibility criteria.

The list of protocol deviations with categorization with respect to major and minor deviations will be generated prior to the study database lock. Sponsor's Medical monitor will review all deviations prior to database lock and 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.

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

There are no formal statistical hypotheses tested in this study.

9.2 Interim Analysis

No formal interim analysis is planned for this study.

9.3 Handling of Missing Data

9.3.1 Missing Dates for Adverse Events and Concomitant Medications

Missing dates (either completely or partially) of adverse events and concomitant medications will be imputed as explained below for the purposes of calculation of durations.

For end of concomitant medications or adverse events:

- **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 (Objective Response Rate and Duration of Response), if the last objective response 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

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

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

All the patient data including, demographics, medical history, prior/concomitant medications, safety data (where appropriate) and efficacy data will be summarized by following two modes of representation:

1. Dose Escalation (Cohort 1, Cohort 2, Cohort 3, All Cohorts), Dose Expansion (Group 1, Group 2, Both Groups) and Overall.

2. PTCL, CTCL and Overall

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

10.1 Patient Disposition

A tabular presentation of the patient disposition will be provided. It will include the number of patients screened, enrolled, dosed, completed the treatment, as well as the number of dropouts, with reasons for dropouts, number in each population sets, number of patients with dose reduction, drug interruptions (transient discontinuation) and dose discontinuation (permanent discontinuation) etc. All patients' data will be used for this analysis. This data will also be listed.

10.2 Demographic and Baseline Characteristics

Analysis set: Safety

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

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

Disease characteristics will include time from initial diagnosis to treatment, subtype of PTCL, subtype of CTCL, staging at screening, number of prior therapies, number of subject relapsed or refractory to the last therapy, time from date of last therapy to study treatment, ECOG performance status at screening, etc.

10.3 Medical and Surgical History

Analysis set: Safety

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 24.0].

10.4 Prior and Concomitant Medications

Analysis set: Safety

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 first dose of study drug.

The medication data will be coded using WHO-Drug dictionary (WHODRUG GLOBAL B3 March, 2021) and the non-drug treatments data will be coded using MedDRA dictionary [Version 24.0].

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

All the efficacy analyses will be based on the data collected in the Dose escalation and Dose Expansion Phase of the study.

Note: The analyses outlined below are subject to availability of adequate data.

10.5.1 Objective Response Rate (ORR)

It is *defined as sum of CR and PR rates, assessed according to the Lugano Classification for initial evaluation, staging, and response assessment of Hodgkin/non-Hodgkin lymphoma in PTCL patients; and according to the modified Severity Weighted Assessment Tool (mSWAT) in CTCL patients.*

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). The corresponding listing will also be provided.

Also, the Conversion rate, defined as the conversion from partial response (PR) to CR or from SD to PR/CR that occurs during the first 7 months of treatment (till Cycle 8 Day 1) will be summarized for the Overall group of patients using frequency, percentage and the 95% CI (Using exact method based on binomial distribution, subject to availability of adequate data). This data will not be listed.

$$Conversion\ Rate\ = \frac{Total\ number\ of\ conversions * 100}{SD\ or\ PR\ at\ the\ first\ efficacy\ assessment}$$

Note: First efficacy assessment = Cycle 3 Day 1.

10.5.2 Duration of Response (DoR)

It is *defined as time from the initial response to documented disease progression.*

The DoR will be presented for patients with confirmed complete response or partial response.

This data will be summarized using the Kaplan-Meier method. Also, data will be displayed graphically for: PTCL subjects in dose escalation and dose expansion together, CTCL subjects in dose escalation and dose expansion together, and overall.

The patients who did not progress or die without disease progression will be censored at the date of their last disease assessment. The following reports will be generated:

- The Q1, median and Q3 DoR time will be provided along with 95% CI for the Q1, median, and Q3 DoR time will be presented using Brookmeyer-Crowley method (subject to availability of adequate data).
- The number and % of patients with progressive disease will be provided.
- The number and % of patients censored (further divided by reasons for censoring) will be provided.
- Kaplan-Meier curves will be produced.
- DoR data will be listed.

10.5.3 Best Overall Response (BOR)

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 CR, PR, SD, and PD, as reported in the CRFs for overall subjects. This data will also be listed.

10.6 Safety Analysis

10.6.1 Treatment Exposure and Compliance

Analysis set: Safety

The treatment exposure and Treatment compliance 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 patient 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 swimmer plot for duration on treatment will be provided individually for the patients with PTCL, CTCL and Overall. The BOR (CR/ PR/ SD/ PD) obtained for each patient at Cycle 3 Day 1 efficacy assessment will be used for representing the responses for each patient in graphical representation.

- The treatment compliance as reported for each patient in the eCRF, will be summarized descriptively for each cycle. This data will be listed for individual patient.

  Note: If the patient fails to return the study treatment on the scheduled return cycle, then that patient data will be not be considered for calculating the compliance at the respective return cycle. This approach will be applied for both the summary table and the listing presentation of treatment compliance.

10.6.2 Adverse Events

Analysis set: Safety

Note:

- If needed, adverse event data may be presented for all patients.
- The dose reduction information will be compiled using the treatment exposure page and AE page of eCRF through common AE number.

The frequency of adverse events (AEs) will be computed by counting each patient only once per MedDRA [Version 24.0] 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 TEAE
- Treatment Related TEAEs
- Serious TEAEs
- Treatment Related Serious TEAEs
- Grade 3 or 4 TEAEs
- Treatment Related Grade 3 or 4 TEAEs
- DLTs (Note: Applicable for dose escalation phase only)
- TEAEs leading to drug interruptions
- Related TEAEs leading to drug interruptions
- Serious TEAEs leading to drug interruptions
- Treatment Related Serious TEAEs leading to drug interruptions
- TEAEs leading to dose reduction
- Related TEAEs leading to dose reduction
- Serious TEAEs leading to dose reduction
- Treatment Related Serious TEAEs leading to dose reductions

- TEAEs leading to drug withdrawn permanently
- Treatment Related TEAEs leading to drug withdrawn permanently
- Serious TEAEs leading to drug withdrawn permanently
- Treatment Related Serious TEAEs leading to drug withdrawn permanently
- 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:

- DLTs (Note: Applicable for dose escalation phase only)
- TEAEs
- Related TEAEs
- Non-TEAEs
- Grade 3, 4 and 5 TEAEs
- Related Grade 3, 4 and 5 TEAEs
- Treatment-Emergent SAEs
- Related Treatment –Emergent SAEs
- TEAE with maximum CTCAE grade
- Treatment-Related TEAEs with maximum CTCAE grade per suspected drug(s) [Tenalisib, Romidepsin or Combination]
- Deaths
- TEAEs leading to drug interruptions
- TEAEs leading to dose reduction
- TEAE leading to drug withdrawn permanently

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

- Any non-TEAE
- TEAEs
- Related TEAEs
- SAEs
- Treatment Emergent Grade 3, 4 and 5 AEs
- Treatment Related Grade 3, 4 and 5 AEs
- Treatment Related SAEs
- TEAEs leading to drug interruptions
- TEAEs leading to dose reduction
- TEAE leading to drug withdrawn permanently

10.6.3 Clinical Laboratory Tests

Analysis Set: Safety

Laboratory data will be presented per cycle for each phase.

Baseline will be defined in each phase of the study. The baseline measurement will be the last pre-treatment measurement taken on or before Cycle1 Day1 in respective phase. For Dose Escalation phase, the baseline will be the last pre-treatment measurement taken on or before the Cycle 1 Day 1 dose for Romidepsin, and for Dose Expansion phase, the baseline will be the last pre-treatment measurement taken on or before Cycle 1 Day 1 dose of Romidepsin or Tenalisib whichever is earlier.

Absolute values of laboratory parameters will be presented at each visit using descriptive statistics (n, mean, median, standard deviation, minimum and maximum values).

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 (ALP)*	*Urea or blood urea nitrogen*	*Glucose*	*INR*
CBC with differentials	*Alanine aminotransferase (ALT)*	*Albumin*	*Protein*	
Platelet count	*Aspartate aminotransferase (AST)*	*Total protein*	*Specific gravity*	
WBC (Total and differentials)	*Lactate dehydrogenase (LDH)*	*Total Cholesterol*	*Microscopic exam*	
Red blood cell count	*Gamma-glutamyl transferase*	*Triglyceride (TG)*		
Absolute neutrophil count	*Sodium*	*LDL*		
Absolute lymphocyte count	*Potassium*	*HDL*		
	Calcium	*TSH*		
	Phosphorous	*T3 (Total or Free)*		
	Bicarbonate or Carbon Dioxide (CO2)	*T4 (free)*		
	Chloride	*Creatinine*		
	Magnesium			

10.6.4 Physical Examinations

Analysis Set: Safety

Physical examination data will be listed for Screening visit in each phase of the study.

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). Weight will also be included here.

Baseline will be defined in each phase of the study. The baseline measurement will be the last pre-treatment measurement taken on or before Cycle1 Day1 in respective phase. For Dose Escalation phase, the baseline will be the last pre-treatment measurement taken on or before the Cycle 1 Day 1 dose for Romidepsin, and for Dose Expansion phase, the baseline will be the last pre-treatment measurement taken on or before Cycle 1 Day 1 dose of Romidepsin or Tenalisib whichever is earlier.

Absolute values of Vital Signs data will be summarized descriptively (n, mean, median, standard deviation, minimum and maximum) per cycle for every scheduled timepoint. 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

- Baseline will be defined in each phase of the study. The baseline measurement will be the last pre-treatment measurement taken on or before Cycle1 Day1 in respective phase. For Dose Escalation phase, the baseline will be the last pre-treatment measurement taken on or before the Cycle 1 Day 1 dose for Romidepsin, and for Dose Expansion phase, the baseline will be the last pre-treatment measurement taken on or before Cycle 1 Day 1 dose of Romidepsin or Tenalisib whichever is earlier.
- 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 for every scheduled timepoint.
- A summary of abnormal ECG results will also be provided per cycle in each phase 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

Baseline will be defined in each phase of the study. The baseline measurement will be the last pre-treatment measurement taken on or before Cycle1 Day1 in respective phase. For Dose Escalation phase, the baseline will be the last pre-treatment measurement taken on or before the Cycle 1 Day 1 dose for Romidepsin, and for Dose Expansion phase, the baseline will be the last pre-treatment measurement taken on or before Cycle 1 Day 1 dose of Romidepsin or Tenalisib whichever is earlier.

ECOG performance status (0=Normal activity, 1=Symptoms, but ambulatory, 2=In bed < 50% of the time, 3 and above=In bed > 50% of the time or 100% bedridden or are Dead), as reported in the eCRF, will be summarized per cycle in each phase with number and percentage for each status category. This data will also be listed.

11. Pharmacokinetic (PK) Analysis

PK analysis is not applicable for this SAP. The same will be prepared by a Clinical pharmacology Clinical Research Organization appointed by Rhizen and the analysis results will be shared for inclusion in the study report.

12. Exploratory analysis

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

This is not applicable for this SAP. The same will be prepared by Rhizen and the analysis results will be shared for inclusion in the study report.

13. Protocol Deviations

Analysis set: Safety

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

14. Listings

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

- Screened patients
- Patients Eligibility
- Patient visits
- Study completion/Reasons for discontinuation/withdrawal of patient from the study
- Analysis populations
- Cancer Diagnosis
- Prior therapy
- mSWAT assessment
- Serology Assessment
- Study drug exposure
- Study drug accountability
- Target lesion assessment
- Non-target lesion assessment

- Disease Response assessment
- Overall tumor assessment
- Pregnancy test
- Investigator's Comments

15. References

1. Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. Biometrics. 38: 29-41, 1982.