Statistical Analysis Plan

Protocol Title:

A Phase I/Ib, Dose Escalation Study to Evaluate Safety and Efficacy of RP6530, a dual PI3K δ/γ inhibitor, in Patients with Relapsed or Refractory T-cell Lymphoma

[redacted]

Protocol: RP6530-1401

(Reference Document: Protocol: Version 7 dated 23 May, 2018)

Phase I/Ib

Statistical Analysis Plan (SAP)

Signature Page

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List of Abbreviations

%	Percentage
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AUEC	Area Under Effect Curve
BID	Twice Daily
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CM	Concomitant Medication
CR	Complete Response
CRF	Case Report Form
CS	Clinically Significant
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	cutaneous T-Cell Lymphoma
CV	Co-efficient of variance
CVA	Cerebrovascular Accident
DLT	Dose limiting Toxicities
DoR	Duration of Response
DRG	Data Review Group
E	Count of Event
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organization For Research and Treatment of Cancer
EOS value	End of Study value
EOT	End of Treatment
ET	Early Termination
GCV	Geometric Co-efficient of variance
GGT	Gamma Glutamyl Transpeptidase
H_1	Alternative Hypothesis
Hb	Hemoglobin
HbA1c	Glycated hemoglobin
HBV	Hepatitis B virus
HCT	Hematocritw3
HCV	Hepatitis C virus
HDL	High-Density Lipoprotein

HIV	Human Immune deficiency Virus
Ho	Null Hypothesis
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ISCL	International Society For Cutaneous Lymphomas
ITT	Intent-to-Treat
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LLT	Lower Level Term
Max	Maximum
MDACC	MD Anderson Cancer Centre
MedDRA	Medical Dictionary
MH	Medical history
Min	Minimum
MRI	Magnetic Resonance Imaging
mSWAT	modified Severity Weighted Assessment Tool
MTD	Maximum Tolerated Dose
n	Number of patients with non-missing data
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Not Clinically Significant
ORR	Overall Response Rate
pAKT	Phospho-AKT
PD	Pharmacodynamics
PET	positron emission tomography
PI3K	Phosphoinositide-3-Kinase
PK	Pharmacokinetics
PLT	Platelet
PP	Per-protocol
PR	Partial Response
PT	Preferred Term
PT/INR	Prothrombin Time/international Normalized Ratio
PTCL	Peripheral T cell Lymphoma
Q_1	First quartile
Q_3	Third quartile
RBC	Red Blood Cells
SAE	Serious Adverse Event
SD	Stable Disease
SOC	System Organ Class
SS	Sezary Syndrome
TEAE	Treatment Emergent Adverse Events
TG	Tri-Glycerides
TIA	Transient Ischemic Attack
T-NHL	T cell Non-Hodgkin Lymphoma

TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
USCLC	United States Cutaneous Lymphoma Consortium
WBC	White Blood Cells
WHO	World Health Organization

SAP

Table of Contents

1. Introduction

1.1 Statistical Analysis Plan

The Statistical Analysis Plan (SAP) is intended to be a comprehensive and detailed description of the methods of data analyses proposed for patients enrolled in Phase I (Dose Escalation) and Phase Ib (Dose Expansion) part of the study.

The first part of protocol (Phase I – dose escalation part) is designed to determine the Maximum Tolerated Dose (MTD) of RP6530 in patients with relapsed/refractory T-cell lymphoma (PTCL/CTCL). The second part of protocol (Phase Ib dose expansion part) is to be conducted once the MTD/optimal dose has been confirmed in dose escalation phase.

Thus, the patient cohorts used for finding MTD will be analyzed under “Dose Escalation” Phase and the patient cohort enrolled in the study after finding MTD for the study will be analyzed under “Dose Expansion” Phase of the study. The patient list of “Dose Expansion” Phase will be provided by Data Management.

The “Statistical Analysis Plan” of the study RP6530-1401 is distinct from the statistical section of the protocol. Any changes or additions to the statistical analysis / methods planned related to the efficacy or safety analysis from the protocol are explained in this SAP. Pharmacokinetic (PK) and Pharmacodynamics (PD) analyses will be performed by other stakeholders and hence the detailed analyses related to PK and PD are not included in this SAP.

This SAP includes following contents that are related to statistical analysis of efficacy, safety data of the study:

- Include statements of the objectives of the trial, as stated in the protocol
- Clearly define all primary, secondary and exploratory end-points of the study
- Details of derived variables and censoring procedures (if applied)
- Define the analysis populations to be used for the statistical analyses
- Provide a full and detailed description of the statistical methods of analyses including details of handling of missing data, drop outs, derived variables, etc.

The SAP may be changed over time due to reasons such as protocol amendments or regulatory feedback. The final SAP should be approved before data base lock. Deviations from the final approved SAP if any will be discussed in the clinical study report.

1.2 Rationale for Study

The δ isoform of PI3K is highly expressed in cells of hematopoietic origin, and strongly implicated in various hematologic malignancies. The γ isoform is associated with T-lymphocytes and neutrophils; there appears to be a significant synergy rather than a redundancy between the two isoforms in various leukemia and lymphomas. As T-cell lymphomas (both CTCL and PTCL) are unmedical need, dual targeting of PI3K δ/γ

therefore is strongly implicated as an intervention strategy in leukemia/lymphomas that are hard to treat by conventional means. RP6530 is a highly specific and orally available, PI3K δ and γ inhibitor with nano-molar inhibitory potency, and several fold selectivity over the alpha and beta isoforms.

Based on the favorable results of pre-clinical and toxicological studies, the first-in-man, Phase I, 3+3 dose escalation study was initiated in Europe in patients with relapsed and/or refractory hematologic malignancies (Study RP6530-1301). Patients received starting dose of 25 mg BID (50 mg/day).

As the safety of 200 mg BID was established in the European study (RP6530-1301), it was reasonable to consider 200 mg BID dose as the starting dose in proposed Phase I study in relapse/refractory T-cell lymphoma in the US study RP6530-1401.

2. Study Design and Objectives

Dose Escalation Phase:

The first part is a Phase 1 dose escalation, 3+3 design, open-label, MTD determination study of RP6530 in patients with relapsed/refractory T-cell lymphoma (PTCL/CTCL). Up to 18 patients will be enrolled in the escalation phase of the study. There will be total 8 cycles in this part. RP6530 is self-administered by the patients orally twice a day in 28-days cycle in absence of disease progression, unacceptable toxicity, or withdrawal from treatment. These patients will be analyzed under “Dose Escalation” Phase of the study.

Dose Expansion Phase:

The second part is Phase 1b dose expansion, open label study to be conducted once the MTD/optimal dose has been confirmed in dose escalation phase. Additional 40 patients, 20 patients of each indication will be enrolled (20 for PTCL and 20 for CTCL) to reach a maximum of 58 patients (including the Phase I patients). There will be total 8 cycles in this part. These patients will be analyzed under “Dose Expansion” Phase of the study.

2.1 Study Objectives

2.1.1 Primary Objectives

The primary objectives are:

- To evaluate the safety and the maximum tolerated dose (MTD) of RP6530 in patients with relapsed/refractory T-cell lymphoma (CTCL/PTCL)
- To evaluate the pharmacokinetic (PK) effects of RP6530

2.1.2 Secondary Objectives

The secondary objectives are:

- To examine the pharmacodynamic (PD) effects of RP6530.

- To assess and the Overall Response Rate (ORR) and Duration of Response (DoR) in patients with relapsed/refractory T-cell lymphoma.

2.1.3 Exploratory Objectives

The Exploratory objectives of this study are:

- Correlation of treatment outcomes with biomarkers which include but are not limited to quantitative and qualitative measurements of cytokines, chemokines and aberrations indicative of PI3K function and RP6530 efficacy.

2.2 Assessment of Objectives

2.2.1 Primary Endpoints

2.2.1.1 Primary Safety Endpoints

AEs, SAEs, Clinically Significant AEs and Dose Limiting Toxicities (DLT).

All AEs including DLTs, regardless of seriousness or relationship to RP6530 (study drug), spanning from the first dose of study drug until 30 calendar days after the last dose of study drug, discontinuation or completion of protocol-specific treatment as defined in the protocol for that patient, are to be recorded in the CRF.

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria.

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of disease will be recorded on the “Trial Discontinuation” CRF. All other on-trial deaths, regardless of attribution, will be recorded on an SAE Report.

Pregnancy, abortion, birth defects, congenital anomalies and overdose of RP6530 are protocol defined events of special interest and recorded as AE. Further Symptomatic and non-symptomatic overdose of RP6530 will be reported in the CRF.

2.2.1.2 Primary Pharmacokinetic Endpoints

PK parameters: $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}tau)}$, C_{max}, t_{max}, λ_z, and $t_{½}$ of RP6530

PK analyses will be performed by a Clinical pharmacology CRO contracted by the Sponsor and PK report with TLFs will be provided by the sponsor to the [redacted] for incorporation in the final CSR. Therefore, PK analysis is not applicable for this SAP. PK analysis will be documented in a separate SAP prepared by a Clinical pharmacology CRO.

2.2.2 Secondary Endpoints

2.2.2.1 Secondary Pharmacodynamic Endpoints

Inhibition of pAKT by RP6530

This secondary pharmacodynamic (PD) endpoint will be assessed using following PD parameters

- Change in pAKT at each cycle, Cycle j i.e at Cycle j – Day 8, Cycle j – Day 22 and Cycle j – Day 29 from Cycle 1 dose 1 that is Pre-Dose 1. Where Cycle j = 1, 2, 3,……8. This will also be checked for association with the Survival or Tumor Response.

This analysis will be done in five Sezary Syndrome (SS) patients at MDACC site only. The statistical analysis of PD will be performed by clinical pharmacology CRO contracted by the Sponsor and the PD report will be provided by sponsor to the [redacted] for incorporation in the final CSR. Therefore, PD analysis is not applicable for this SAP. PD analysis will be documented in a separate SAP prepared by Clinical pharmacology CRO.

2.2.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoint of Overall Response Rate (ORR) and Duration of Response (DoR) will be assessed as below:

- **Overall Response Rate (ORR)**

Overall Response is defined as the best response [e.g. Complete Response (CR) or Partial Response (PR), Stable disease (SD) or disease progression (PD)] documented in the PTCL/CTCL patients treated with RP6530.

ORR is defined as percentage of patients with Complete or Partial Response at any time point during the study, as assessed by investigator.

- **Duration of Response (DoR)**

Duration of Response (DoR), is applicable to patients who achieved CR or PR and it is defined as time from the first documented assessment of CR or PR until the documented tumor disease progression (date of the first occurrence of PD as per investigator's tumor assessment response based on post-treatment radiological assessment (e.g. PET/CT scan) up to predefined cut-off date. The cut-off date is nothing but the last patient last visit date (LPLV) i.e. 10-Dec-2018 when last patient (D8) was moved to compassionate study protocol

In PTCL & CTCL patients, disease will be assessed using imaging assessments at Screening and at subsequent scheduled visits it will be assessed with respect to this baseline assessment using imaging assessments at C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the End of Treatment (EOT). Disease assessment will be performed thereafter if warranted, at the discretion of investigator.

For PTCL patients, CT assessment based tumor response provided by investigator in “Response” field of eCRF module “Restaging for PTCL patient” will be considered for the analysis of ORR and DoR.

For CTCL patients, tumor response provided by investigator in “Global Response” field of eCRF module “Restaging for CTCL patient” (which takes into account of skin response + nodal response + visceral response and blood response) will be considered for the analysis of ORR and DoR.

2.2.2.3 Exploratory Efficacy Endpoints

Correlative biomarkers (e.g. serum cytokines and chemokines)

The listing related to correlative markers will be generated by [redacted], if the data is transferred by sponsor to [redacted] DM team for integrating it with Data Management database. The analysis of correlative biomarkers will be performed and report will be provided by [redacted].

2.3 Change the Primary Objective during the conduct of the study

Not Applicable

2.4 Study Design

Dose Escalation Phase:

The first part of this study is a Phase 1 dose escalation, 3+3 design, open-label, MTD determination study of RP6530 in patients with relapsed/refractory T-cell lymphoma (PTCL/CTCL). 18 patients will be enrolled in the escalation phase of the study. RP6530 is self-administered by the patients orally twice a day in 28-days cycle in absence of disease progression, unacceptable toxicity, or withdrawal from treatment

Sequential dose escalation is with Cohort 1. A minimum of three patients of either CTCL or PTCL will be entered into each opened dose level cohort. The first cohort of patients received RP6530 200 mg twice a day (BID). Dose levels will be increased in successive increments according to the dose escalation scheme as given in below **Table 1**. Dose escalation will be continued until the MTD/optimal dose has been identified or as determined by the DRG based on the available safety, PK and/or efficacy data. Dose determination will be documented appropriately.

Table 1 Dose Escalation Schedule

Dose Level	RP6530 PO BID	Dosing recommendation**	Patients (n)
1*	200 mg BID	Fasting	3-6
2	400 mg BID	Fasting	3-6
3	800 mg BID	Fasting	3-6
3a	800 mg BID	After Food	3-6

*If not tolerated or DLT occurs in over 33% of patients treated, a dose level of Dose Level -1 (i.e. 100 mg BID) will be tested

** In fasting cohorts, patients will fast 2 hours prior to study drug administration and 1 hour after administration. In Fed cohort (After food), patients to take study after food (30 minutes after breakfast and dinner)

Intra-subject dose escalation:

Individual patients may be considered for treatment at a dose level of RP6530 higher than the dose to which they were initially assigned. For a patient to be treated at a higher dose level of RP6530, the patient must not have experienced a DLT at the assigned dose and tolerated the lower dose for at least one cycle of therapy. The patient must have undergone a disease evaluation and been found appropriate to continue on study. The new higher dose must be a dose that has completed evaluation and has not exceeded the MTD. There is no limit to the number of times a patient may have their dose of RP6530 increased. However, the rules remain the same as listed above. At the discretion of the treating investigator(s), the dose escalation may be done in patient who received lower doses (de-escalation) due to safety reason.

During statistical analyses of Dose escalation phase, the patient data will be analyzed according to dose received / assigned initially (initial cohort assigned to the patient).

Alternative Dosing Cohorts

Depending on the nature and the timing of the toxicities encountered and the pharmacokinetic data from continuous daily dosing of RP6530, alternative dosing regimens and schedules may be examined. If in the opinion of the DRG, observed toxicities (DLTs and/or non-dose limiting adverse events of concern) are likely to have resulted from a continuous exposure to the study drug or cumulative effect, alternative dosing regimens or schedules may be explored. The DRG will determine the alternative schedule, based on PK data, nature and timing of toxicities, and the required recovery periods for the observed toxicities encountered. Dose escalation would proceed with an alternative schedule to determine the MTD/optimal dose.

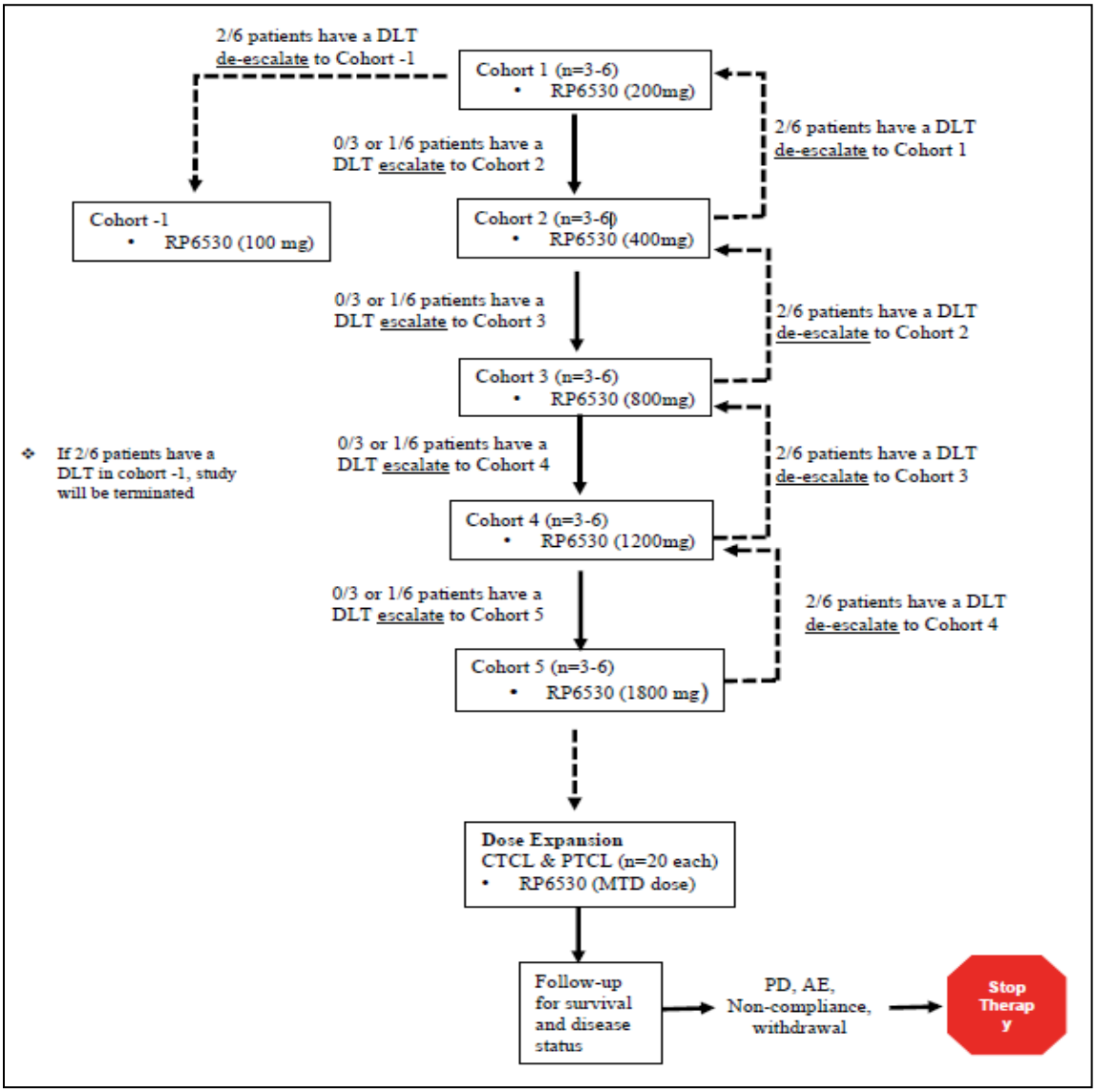
Dose Expansion Phase:

Once the MTD/optimal dose has been confirmed, patients who complete the Dose Escalation Phase will be permitted to enter the expansion cohorts (Phase Ib). Additional 40 patients, 20 CTCL and 20 PTCL patients may be enrolled to reach a maximum of 58 patients (including the Phase I patients) in each of the CTCL and PTCL groups. There will be total 8 cycles in this part of the study.

Table 2 Dose Expansion Schedule

Dose Level	RP6530 PO BID	Patients (n)
CTCL	RP6530 800 mg Fasting	20
PTCL	RP6530 800 mg Fasting	20

2.4.1 Study Flow Chart



2.5 Sample Size and Power Considerations

Dose Escalation Phase:

No formal sample size calculation is performed for this part of study. Sample size up to 18 is considered based on 3+3 dose escalation design of the dose escalation phase of this study

Note: The total number of patients in phase I may exceed depending on MTD.

Dose Expansion Phase:

No formal sample size calculation is performed for this part of study. This trial will enroll up to 58 patients from 5-10 different sites, 40 patients (20 PTCL, 20 CTCL) of dose expansion phase and 18 patients of dose escalation phase will be considered for this part of the study.

2.6 Randomization

Not Applicable as this is a non-randomized, open label study.

2.7 Blinding

Not Applicable as this is a non-randomized, open label study.

3. General Analysis Requirements

3.1 Study Duration

The study duration of each patient included in the study is approximately 8 months. The conduct of the study trial from Screening visit (Day -28 to 0) to End of Treatment visit, is provided in the visit schedule chart.

3.2 Schedule of Study Visits, Visit windows and Procedures

Dose Escalation Phase:

Table 3 Schedule of Assessment – Part 1 Dose Escalation

Cycle		**Cycle 1**				**Cycle 2**				**Cycle 3**		**Cycle C4**		**C5**	**C6**	**C7**	**C8**	**EOT[25]**
Day	D-28 to 0	D1	D8	D15	D22	D1	D8	D15	D22	D1	D15	D1	D15	D1	D1	D1	D1	D1
Window period		±1	±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±30
Study Days	D-28 to 0	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	197	-
Dose escalation visits	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PROCEDURE																		
Informed Consent[1]	X																	
Demographics[2]	X																	
Medical history[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vitals[4]	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X
Physical examination[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X				X				X		X		X	X	X	X	X
LABORATORY TEST/EVALUATIONS																		
Complete blood count[7]	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X
Chemistry panel II[9]	X	X		X		X				X		X		X	X	X	X	X
Serology (HIV, HBV, HCV)	X																	
PT/INR[10]	X	X		X		X				X		X						X

Cycle		**Cycle 1**				**Cycle 2**				**Cycle 3**		**Cycle C4**		**C5**	**C6**	**C7**	**C8**	**EOT[25]**
Day	D-28 to 0	D1	D8	D15	D22	D1	D8	D15	D22	D1	D15	D1	D15	D1	D1	D1	D1	D1
Window period		±1	±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±30
Study Days	D-28 to 0	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	197	-
HbA1c	X																	
Urinalysis (routine)	X	X		X		X				X		X		X	X	X	X	X
Pregnancy test[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECGs[12]	X	X	X	X	X	X												
PK blood samples[13]		X	X	X		X	X	X		X	X	X	X	X	X	X	X	
Biomarker samples[14]	X									X								X
PD samples (pAKT)[15]	-	X	X	-	X	X				X								X
Archived tumor tissue[16]	X																	
DISEASE ASSESSMENT																		
Staging[17]	X	-	-	-	-	-	-	-	-	X	-	-	-	X	-	-	-	X
Radiological Examination[18]	X	-	-	-	-	-	-	-	-	X	-	-	-	X	-	-	X	X
Skin lesion assessment[19]	X	-	-	-	-	-	-	-	-	X	-	-	-	X	-	-	X	X
Skin biopsy[20]	X	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-
Immunophenotyping and TCR gene rearrangement[21]	X	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-
Photograph of skin lesion[22]	X	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	X
Bone marrow, lymph node biopsy /Aspirate[23]	X	-	-	-	-	-	-	-	-	-23a	-	-	-	-23a	-	-	-23a	X

Cycle		**Cycle 1**				**Cycle 2**				**Cycle 3**		**Cycle C4**		**C5**	**C6**	**C7**	**C8**	**EOT[25]**
Day	D-28 to 0	D1	D8	D15	D22	D1	D8	D15	D22	D1	D15	D1	D15	D1	D1	D1	D1	D1
Window period		±1	±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±30
Study Days	D-28 to 0	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	197	-
DRUG ADMINISTRATION & SAFETY EVALUATION																		
Drug administration[24]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug dispensing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE evaluation and reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAE evaluation and reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diary evaluation			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Patient should be re-consented in case informed consent is not obtained ≤28 days prior to the initiation of trial treatment.

2. Demographic profile will include age, sex and race.

3. Detailed history will be taken at screening that includes history of cancer, past history, no of prior therapies and prior medication (in last 4weeks); and other medical history. Abbreviated history will be taken at all subsequent visits.

4. Vitals will include pulse (sitting/supine); blood pressure (sitting/supine); respiratory rate and oral temperature.

5. Weight will be measured at all visits. Height to be measured at screening only.

6. Physical examination will include lymph node and systemic examination. Complete physical examination will be done at screening visit. At subsequent visits, abbreviated examination will be done.

7. This will include Hb, complete blood count, reticulocyte count, total leucocyte and differential count and platelet count. Additional investigations will be performed if clinically indicated. Hematology must be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated.

8. Chemistry Panel I includes Total bilirubin, ALP, AST, ALT, GGT, LDH and Serum electrolytes (Sodium, Potassium, Bicarbonate, Chloride, Magnesium, Phosphorus and Calcium). These tests must be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated. These test will be performed at supplementary visits if clinically indicated.

9. Chemistry Panel II includes blood glucose, urea or blood urea nitrogen, creatinine, albumin, globulin, total protein, Total Cholesterol, TG, LDL and HDL, TSH, T3 and T4. These tests must be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated. These test will be performed at supplementary visits if clinically indicated.

10. This test must be done ≤7 days prior to initiation of treatment. However, if initial examination is obtained within 72 hours of C1D1; this should not be repeated. This test will be performed at supplementary visits if clinically indicated.

11. This is required for women of child bearing potential. A serum pregnancy test will be performed at screening and baseline (within 72 hours) of dosing. Urine pregnancy test will be performed at other visits as indicated.

12. A single ECG will be performed at screening and C1D1 pre-dose. Post-dose ECGs will be performed in conjunction with the 1 hr, 2hr and 4hr post-dose PK collection on C1D1; and on C1D8 (pre-dose), C1D15 (pre-dose), and C1D22 (pre-dose). On C2D1, ECGs will be obtained pre-dose and then one hour post-dose coinciding with the PD collection. Additional ECGs will be obtained if clinically indicated. Triplicate ECGs will be performed to confirm the significant changes of single ECG. All ECGs will be performed on local equipment.

13. PK blood sample collection time points: C1D1 at pre-dose, 0.5, 1, 2, 4, 6, 8 hrs post dose; and C1D8 and C1D15 at predose; C2D1 at pre-dose, 0.5, 1, 2, 4, 6, 8 hrs post dose and C2D8 and C2D15 at pre-dose; C3D1 and C3D15 at pre-dose; C4D1 and C4D15 at pre-dose; Cycle 5 and beyond at predose. Window period for PK sampling will be defined in laboratory manual.

14. Correlative serum biomarkers (e.g. sIL2R CTACK (PTCL); CD30 (MF); IL-31 and IL-32 (CTCL)) will be performed at screening, C3D1 (pre-dose and 1 hr later); at EOT and/ or to confirm a response. Blood will be collected for these biomarkers, serum aliquots will be prepared and will be banked for analysis at later stage.

15. PD samples (pAKT) will be performed on C1D1 (pre-dose and 1 hr later), C1D8 (pre-dose) and C1D22 (pre-dose); C2D1 (pre-dose) and C3D1 (pre-dose) and/ at EOT in 5 sezary syndrome patients.

16. Archival tumor samples will be collected during the trial, if available.

17. Ann-Arbor staging system should be applied in patients with other types of NHL; ISCL/EORTC criteria should be used for CTCL. Patients will be restaged C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the EOT.

18. CT scan (of the chest, abdomen, and pelvis) and other radiological evaluations (X-RAY/MRI/Ultrasound) will be performed at the time of screening within 28 days of screening. PET-CT will be used to assess response in FDG-avid histologies. In CTCL patients with other than presumed stage IA disease, or selected patients with limited T2 disease and the absence of adenopathy or blood involvement, CT scans of chest, abdomen, and pelvis alone ± FDG-PET scan are recommended to further evaluate any potential lymphadenopathy, visceral involvement, or abnormal laboratory tests. In patients unable to safely undergo CT scans, MRI may be substituted. PTCL patients will be evaluated according to the IWG Revised Response Criteria for Malignant Lymphoma. Assessment of CTCL response and progression will be evaluated according to the Response Criteria in Mycosis Fungoides and Se´zary Syndrome by the ISCL/EORTC criteria. In both CTCL and PTCL, disease will be assessed at C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the EOT. Assessment will be performed thereafter if warranted, at the discretion of PI/Co-PI.

19. The assessment of skin lesion will be performed at the time of screening in CTCL patients. The assessments will be performed in PTCL if applicable. For skin scoring, the modified Severity Weighted Assessment Tool (mSWAT) will be used. For local index lesion skin scoring, Composite Assessment of Index Lesion Severity will be used. The disease will be assessed at C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the EOT. Assessment will be performed thereafter if warranted, at the discretion of PI/Co-PI.

20. Skin biopsy will be performed in CTCL patients at screening, on C3D1 (± 7 days) and/or to confirm a complete response. In CTCL patients, skin biopsy should be performed at the most indurated area if only one biopsy.

21. Immunophenotyping to include at least the following markers: CD3, CD4, CD7, CD8 and Ki67. CD30 may also be indicated in cases where lymphomatoid papulosis, anaplastic lymphoma, or large-cell transformation is considered. Clonality of TCR gene rearrangement will be evaluated as part of standard of care and will be an optional. Immunophenotyping will be performed at screening, on C3D1 (± 7 days) and/or to confirm a complete response.

22. CTCL patients will have half body global and up to 5 selected representative index lesions photographed at baseline, at C3D1, End of treatment (EOT), at PR/CR/PD and as required as per the discretion of PI/Co-PI.

23. Bone marrow biopsy: Patients entering the study with low grade lymphoma must have a morphology and flow cytometry performed ≤3 months prior to study entry and/or to confirm a complete response. Patients with high grade lymphoma must have a morphology and flow cytometry performed ≤28 days prior to study entry and/or to confirm a complete response. The lymph node will be required to perform only if the diagnosis is not confirmed at the baseline; and if required at other time points.

23a PTCL patients without measurable disease but assessable disease (e.g. marrow disease without other radiographically measurable disease) will have a bone marrow biopsy at screening /baseline and on C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/or to confirm a complete response. CTCL patients with predominantly blood involvement (confirmed by flow cytometry) will have a bone marrow biopsy at screening /baseline (unless it has been shown to be negative within the last 6 months) and as indicated to confirm a complete response occurring at all other sites. Specific molecular exams for some particular malignancies will be performed according to institutional diagnostic guidelines. If bone marrow aspirate is available, it will be processed and shipped according to the laboratory manual. Bone marrow disease alone may be used for disease assessment. In this case, response would be CR or non-CR only, determined by the morphology of repeat bone marrow biopsy.

24. The study drug RP6530 will be administered orally twice a day in 28-days of cycle. The drug administration will be monitored on C1D1 and C2D1 followed by PK evaluation. On other days, the treatment can be administered at home. The treatment period is at least 8 months. Treatment will be continued in patients experiencing clinical benefit for 2 years unless progression of disease or toxicity warranting discontinuation of therapy. The decision to continue the treatment will be taken by PI-Co-PI after consultation with Sponsor on case to case basis.

25. All patients will undergo the end-of-treatment assessments listed within 30 days after treatment ends. Patients must be followed for adverse events for 30 calendar days after the last dose of study drug.

26. All visits will be ambulatory except C1D1 and C2D1 that involve extended hospital stay for PK assessment.

Dose Expansion:

Table 4 Schedule of Assessment – Part 2 Dose Expansion

Cycle		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	EOT[25]
Day	D-28 to 0	D1	D1	D1	D1	D1	D1	D1	D1	D1
Window period		±1	±1	±3	±3	±3	±3	±3	±3	±30
Study Days	D-28 to 0	1	29	57	85	113	141	169	197	-
PROCEDURE										
Informed Consent[1]	X	-	-	-	-	-	-	-	-	-
Demographics[2]	X	-	-	-	-	-	-	-	-	-
Medical history[3]	X	X	X	X	X	X	X	X	X	X
Vitals[4]	X	X	X	X	X	X	X	X	X	X
Height and weight[5]	X	X	X	X	X	X	X	X	X	X
Physical examination[6]	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X
LABORATORY TEST/ EVALUATION										
Complete blood count[7]	X	X	X	X	X	X	X	X	X	X
Chemistry panel I[8]	X	X	X	X	X	X	X	X	X	X
Chemistry panel II[9]	X	X	X	X	X	X	X	X	X	X
Serology (HIV, HBV, HCV)	X	-	-	-	-	-	-	-	-	-
PT/INR[10]	X	X	X	X	X	-	-	-	-	X
HbA1c	X	-	-	-	-	-	-	-	-	-
Urinalysis (routine)	X	X	X	X	X	X	X	X	X	X
Pregnancy test[11]	X	X	X	X	X	X	X	X	X	X
12-lead ECGs[12]	X	X	X	-	-	-	-	-	-	-
PK blood samples[13]	-	X	X	X	X	X	X	X	X	-
Biomarker samples[14]	X	-	-	X	-	-	-	-	-	X
PD samples (pAKT)[15]	-	-	-	-	-	-	-	-	-	-

Cycle		**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**	**Cycle 8**	**EOT[25]**
Day	D-28 to 0	D1	D1	D1	D1	D1	D1	D1	D1	D1
Window period		±1	±1	±3	±3	±3	±3	±3	±3	±30
Study Days	D-28 to 0	1	29	57	85	113	141	169	197	-
Archived tumor tissue[16]	X	-	-	-	-	-	-	-	-	-
DISEASE ASSESSMENT										
Staging[17]	X	-	-	X	-	X	-	-	-	X
Radiological Examination[18]	X	-	-	X	-	X	-	-	X	X
Skin lesion assessment[19]	X	-	-	X	-	X	-	-	X	X
Skin biopsy[20]	X	-	-	X	-	-	-	-	-	-
Immunophenotyping and TCR gene rearrangement[21]	X	-	-	X	-	-	-	-	-	-
Photograph of skin lesion[22]	X	-	-	X	-	-	-	-	-	X
Bone marrow, lymph node biopsy /Aspirate[23]	X	-	-	-23a	-	-23a	-	-	-23a	X
DRUG ADMINISTRATION AND SAFETY EVALUATION										
Drug administration[24]	-	X	X	X	X	X	X	X	X	-
Drug dispensing	-	X	X	X	X	X	X	X	X	-
Drug compliance	-	-	X	X	X	X	X	X	X	X
AE evaluation and reporting	X	X	X	X	X	X	X	X	X	X
SAE evaluation and reporting	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	-	X	X	X	X	X	X	X	X	X
Diary evaluation	-	-	X	X	X	X	X	X	X	X

1. Patient should be re-consented in case informed consent is not obtained ≤28 days prior to the initiation of trial treatment.

2. Demographic profile will include age, sex and race.

3. Medical History: Detailed history will be taken at screening that includes history of cancer, past history, no of prior therapies and prior medication (in last 4weeks); and other medical history. Abbreviated history will be taken at all subsequent visits.

4. Vitals will include pulse (sitting/supine); blood pressure (sitting/supine); respiratory rate and oral temperature.

5. Weight will be measured at all visits. Height to be measured at screening only.

6. Physical examination will include lymph node and systemic examination. Complete physical examination will be done at screening visit. At subsequent visits, abbreviated examination will be done.

7. Complete blood count will include Hb, complete blood count, reticulocyte count, total leucocyte and differential count and platelet count. Additional investigations will be performed if clinically indicated. Hematology must be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated.

8. Chemistry Panel I includes Total bilirubin, ALP, AST, ALT, GGT, LDH and Serum electrolytes (Sodium, Potassium, Bicarbonate, Chloride, Magnesium, Phosphorus and Calcium). These tests must be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated. These test will be performed at supplementary visits if clinically indicated.

9. Chemistry Panel II includes blood glucose, urea or blood urea nitrogen, creatinine, albumin, globulin, total protein, Total Cholesterol, TG, LDL and HDL, TSH, T3 and T4. These tests must be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of C1D1; they do not have to be repeated. These test will be performed at supplementary visits if clinically indicated.

10. PT/INR test must be done ≤7 days prior to initiation of treatment. However, if initial examination is obtained within 72 hours of C1D1; this should not be repeated. This test will be performed at supplementary visits if clinically indicated.

11. Pregnancy test is required for women of child bearing potential. A serum pregnancy test will be performed at screening and baseline (within 72 hours) of dosing. Urine pregnancy test will be performed at other visits as indicated.

12. ECG: A single ECG will be performed at screening and C1D1 pre-dose. Post-dose ECGs will be performed in conjunction with the 1 hr, 2hr and 4hr post-dose PK collection on C1D1; and on C1D8 (pre-dose), C1D15 (pre-dose), and C1D22 (pre-dose). On C2D1, ECGs will be obtained pre-dose and then one hour post-dose coinciding with the PD collection. Additional ECGs will be obtained if clinically indicated. Triplicate ECGs will be performed to confirm the significant changes of single ECG. All ECGs will be performed on local equipment.

13. PK: C1D1 at pre-dose, C2D1 at pre-dose, C3D1 at pre-dose; C4D1 at pre-dose; Cycle 5 and beyond at pre-dose. Window period for PK sampling will be 1 hr pre-dose.

14. Correlative serum biomarkers (e.g. sIL2R CTACK (PTCL); CD30 (MF); IL-31 and IL-32 (CTCL)) will be performed at screening, C3D1 (pre-dose and 1 hr later); at EOT and/ or to confirm a response. Blood will be collected for these biomarkers, serum aliquots will be prepared and will be banked for analysis at later stage.

15. PD samples (pAKT): pAKT is not applicable to dose expansion.

16. Archival tumor samples will be collected during the trial, if available.

17. Staging: Ann-Arbor staging system should be applied in patients with other types of NHL; ISCL/EORTC criteria should be used for CTCL. Patients will be restaged C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the EOT.

18. Radiological assessment: PTCL: A CT scan (of the chest, abdomen, and pelvis) and other radiological evaluations (X-RAY/MRI/Ultrasound) will be performed at the time of screening within 28 days of screening. PET-CT will be used to assess response in FDG-avid histologies. In CTCL patients with other than presumed stage IA disease, or selected patients with limited T2 disease and the absence of adenopathy or blood involvement, CT scans of chest, abdomen, and pelvis alone ± FDG-PET scan are recommended to further evaluate any potential lymphadenopathy, visceral involvement, or abnormal laboratory tests. In patients unable to safely undergo CT scans, MRI may be substituted. PTCL patients will be evaluated according to the IWG Revised Response Criteria for Malignant Lymphoma. Assessment of CTCL response and progression will be evaluated according to the Response Criteria in

Mycosis Fungoides and Se´zary Syndrome by the ISCL/EORTC criteria. In both CTCL and PTCL, disease will be assessed at C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the EOT. Assessment will be performed thereafter if warranted, at the discretion of PI/Co-PI.

19. Skin lesion Assessment: The assessment of skin lesion will be performed at the time of screening in CTCL patients. The assessments will be performed in PTCL if applicable. For skin scoring, the modified Severity Weighted Assessment Tool (mSWAT) will be used. For local index lesion skin scoring, Composite Assessment of Index Lesion Severity will be used. The disease will be assessed at C3D1 (± 7 days) and C5D1 (± 7 days) and approximately 12 weeks thereafter (± 7 days) and/ or at the EOT. Assessment will be performed thereafter if warranted, at the discretion of PI/Co-PI.

20. Skin biopsy: Biopsy will be performed in CTCL patients at screening, on C3D1 (± 7 days) and/or to confirm a complete response. In CTCL patients, skin biopsy should be performed at the most indurated area if only one biopsy.

21. Immunophenotyping to include at least the following markers: CD3, CD4, CD7, CD8 and Ki67. CD30 may also be indicated in cases where lymphomatoid papulosis, anaplastic lymphoma, or large-cell transformation is considered. Clonality of TCR gene rearrangement will be evaluated as part of standard of care and will be an optional. Immunophenotyping will be performed at screening, on C3D1 (± 7 days) and/or to confirm a complete response.

22. Photograph of skin lesion: CTCL patients will have half body global and up to 5 selected representative index lesions photographed at baseline, at C3D1, End of treatment (EOT), at PR/CR/PD and as required as per the discretion of PI/Co-PI.

23. Bone marrow biopsy: Patients entering the study with low grade lymphoma must have a morphology and flow cytometry performed ≤3 months prior to study entry and/or to confirm a complete response. Patients with high grade lymphoma must have a morphology and flow cytometry performed ≤28 days prior to study entry and/or to confirm a complete response. The lymph node will be required to perform only if the diagnosis is not confirmed at the baseline; and if required at other time points.

23a CTCL patients with predominantly blood involvement (confirmed by flow cytometry) will have a bone marrow biopsy at screening /baseline (unless it has been shown to be negative within the last 6 months) and as indicated to confirm a complete response occurring at all other sites. Specific molecular exams for some particular malignancies will be performed according to institutional diagnostic guidelines. If bone marrow aspirate is available, it will be processed and shipped according to the laboratory manual.

24. The study drug RP6530 800 mg BID in fasting conditions will be administered orally twice a day in 28-days of cycle. The drug should be administered at hospital during hospital visits. On other days, the treatment can be administered at home. The treatment period is at least 8 months. Treatment will be continued in patients experiencing clinical benefit for 2 years unless progression of disease or toxicity warranting discontinuation of therapy. The decision to continue the treatment will be taken by PI-Co-PI after consultation with Sponsor on case to case basis.

25. All patients will undergo the end-of-treatment assessments listed within 30 days after treatment ends. Patients must be followed for adverse events for 30 calendar days after the last dose of study drug.

26. All visits will be ambulatory.

3.3 Study Populations

Patients will be screened to verify that they fulfill all of the eligibility criteria – Inclusion Criteria and Exclusion Criteria listed in the Protocol. Eligible patients will be dosed with the study treatment. Adherence to these criteria as specified in the protocol is essential. At Cycle 1 (Day 1), a patient is dosed if he or she fulfills all screening requirements during the past 28 days as reviewed against the inclusion and exclusion criteria of protocol.

3.3.1 Inclusion Criteria

Dose Escalation Phase and Dose Expansion Phase:

Patients must meet the following criteria in order to be included in this clinical trial:

1. Histologically confirmed T cell Non-Hodgkin Lymphoma (T-NHL) as approved by the Medical Monitor or PI/Co-PI.
2. Disease status defined as:
   - Refractory to or relapsed after ≥ 1 prior treatment lines.
   - Patients who are not eligible for transplantation or any standard and / or approved therapy known to be life prolonging or lifesaving (patients who may be eligible for transplantation or any standard and /or approved therapy but have declined therapy, or in the investigators opinion based on the patient's condition, an investigational therapy may benefit more than existing approved therapies are eligible for the study).

3. Patients with a measurable or evaluable disease.
   - In case of radiologically measurable lesions, the longest diameter should be ≥ 2cm in PTCL patients.
   - PTCL patients with non-measurable lesions but assessable disease (e.g. marrow disease without other radiographically measurable disease) can be enrolled in dose-escalation phase as approved by PI/Co-PI.

4. Adequate organ system function, defined as follows:
   - Patients with haemoglobin levels and/or neutrophil and platelet counts under these values will be eligible in the case abnormalities are due to tumor dissemination or infiltration and according to physician's discretion and under his direct responsibility.

     a. Hemoglobin ≥8 g/dL

     b. Absolute neutrophil count (ANC) ≥0.75 x 10^9/L

     c. Platelets ≥50 x 10^9/L
   - Total bilirubin ≤1.5 times the upper limit of normal (ULN)

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or 5 x the ULN if known liver involvement.
- Creatinine ≤2.0 mg/dL OR calculated creatinine clearance ≥ 50 mL/min as calculated by the Cockcroft-Gault method

5. ECOG performance status ≤2.

6. Life expectancy of at least 12 weeks.

7. Patients must be ≥18 years of age.

8. Ability to swallow and retain oral medication.

9. Female patients who are not of child-bearing potential or female patients of child-bearing potential who have a negative serum pregnancy test within 72 hours prior to initial trial treatment. Female patients of child-bearing potential, and all male partners must consent to use a medically acceptable method of contraception throughout the study period and for 4 weeks plus 5T1/2 (48 hrs) after the last dose of RP6530. A barrier method of contraception must be included.

10. Male patients willing to use adequate contraceptive measures throughout the study period and for 12 weeks plus 5T1/2 (48 hrs) after the last dose of RP6530.

11. Willingness and ability to comply with trial and follow-up procedures.

12. Ability to understand the nature of this trial and give written informed consent.

3.3.2 Exclusion Criteria

Dose Escalation Phase and Dose Expansion Phase:

Patients who meet any of the following criteria will be excluded from trial entry:

1. Any cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) in the last 3 weeks or the last 5T1/2 of the agent, whichever is shorter. Limited palliative radiation <2 weeks.

2. Autologous hematologic stem cell transplant within 3 months of study entry. Allogeneic hematologic stem cell transplant within 12 months. Active graft-versus-host disease.

3. Active HBV, HCV or HIV infection.

4. Use of an investigational drug in the last 4 weeks prior to the first dose of RP6530

5. Treatment with GS-1101 (CAL-101, idelalisib), IPI-145, TGR-1202 or any drug that specifically inhibits PI3K/ mTOR (including temsirolimus, everolimus), AKT or BTK Inhibitor (including Ibrutinib) in last 6 months.

6. Patient has received wide field radiotherapy (including therapeutic radioisotopes such as Yttrium-90) ≤ 28 days or limited field radiation for palliation ≤ 14 days prior to starting RP6530 or has not recovered from side effects of such therapy.

7. Ongoing immunosuppressive therapy including systemic corticosteroids (prednisone or equivalent ≤10 mg daily allowed as clinically warranted). Patients are allowed to use topical or inhaled corticosteroids.

8. Known history of drug-induced liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver or portal hypertension.

9. Patients with uncontrolled Diabetes Type I or Type II (HbA1c >8% assessed locally).

10. Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:

- Symptomatic, or history of documented congestive heart failure (New York Heart Association functional classification III-IV [see Appendix B])
- QTcF > 470 msec
- Angina not well-controlled by medication
- Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting in the past 6 months
- Active or uncontrolled severe infections requiring IV antibiotics
- Patients with hemophilia or even Von Willebrand's disease should be excluded.

11. Herbal preparations/medications must be discontinued 7 days prior to first dose of study drug.

12. Presence of other active cancers, or history of treatment for invasive cancer ≤ 3 years. Patients with stage I cancer who have received definitive local treatment at least 3 years previously, and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e. non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.

13. Women who are pregnant or lactating.

14. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

15. Concurrent condition that in the investigator's opinion would jeopardize compliance with the protocol.

16. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol.

3.3.3 Withdrawal / Discontinuation Criteria

Dose Escalation Phase and Dose Expansion Phase:

Patients will be discontinued from trial treatment for any of the following reasons:

- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values related to drug toxicity
- Consent withdrawal
- Patient requests to discontinue treatment

- Pregnancy
- Inability of the patient to comply with trial requirements
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (at the investigator's discretion)
- Non-compliance/lost to follow-up
- Discontinuation of the study by the Sponsor

After withdrawal from protocol treatment, patients will be followed for AEs for 30 calendar days after their last dose of trial drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patients' medical records and as a comment on the Case Report Form (CRF).

All patients who have CTCAE grade 3 or 4 laboratory abnormalities at the time of withdrawal will be followed until the laboratory values have returned to grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve because of the underlying disease. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the CRF.

3.4 Treatment Assignment and Treatment Groups

This is a study of a single study drug with no placebo or comparator drug.

All patients will receive RP6530 as per drug and dose escalation schedule.

Dose Escalation Phase:

RP6530: Dosing will begin on Cycle 1/Day 1 (C1D1) with continuous oral twice daily dosing (BID) in 28 days cycle. RP6530 will be self-administered by the patients. Tablet (s) of relevant strength should be taken at approximately the same time each day. In case of fasting state, patients will fast 2 hours prior to study drug administration and 1 hour after administration. In case of Fed state (After food), patients need to take study drug after food (30 minutes after breakfast and dinner).

Dose Expansion Phase:

Once MTD is decided in Dose Escalation Phase, the same dose will be used in Dose Expansion Phase.

4. Statistical Methods

Statistical analysis will be performed for Dose escalation and Dose Expansion phases of the study for CTCL, PTCL and for all patients (combined data). Three separate sets of Tables and Graphs will be generated as below depending on data availability.

Set 1: All Patients (Combined CTCL and PTCL)

Set 2: CTCL Patients

Set 3: PTCL Patients

For Listings, only one Set for All Patients (Combined CTCL and PTCL) will be generated

4.1 Analysis Datasets

The patient cohort used for finding MTD will be analyzed under “Dose Escalation” Phase and even if intra escalation of Dose happens the subject will be analyzed in the same cohort as per the first dose for safety and efficacy analysis.

The patient cohort enrolled in the study after finding MTD for the study will be analyzed under “Dose Expansion” Phase of the study. The patient list of “Dose Expansion” Phase will be provided by Data Management as an external data along with data extracts.

4.1.1 Safety Population

Dose Escalation Phase and Dose Expansion Phase:

The safety population will include all patients who have received at least one dose of study medication.

This population will be used for safety analysis.

4.1.2 Intent to Treat Population

Dose Escalation Phase and Dose Expansion Phase:

The ITT population will include all safety population who provide efficacy assessment as follows.

- For PTCL patients – efficacy assessment with respect to “Imaging / Scan/Bone Marrow Biopsy (i.e. “Bone Marrow Involvement” field in PTCL without measurable but assessable disease)” should be available on “RESTAGING” domain of eCRF
- For CTCL patients – efficacy assessment with respect to mSWAT score/global response should be available on “RESTAGING” domain of eCRF

This population will be used for efficacy analysis.

4.1.3 Per Protocol Population

Dose Escalation Phase and Dose Expansion Phase:

PP population will include all ITT population without major protocol violations.

Major protocol deviations related to efficacy assessment and impacting outcomes / endpoints will therefore lead to exclusion patient from PP population. Criteria for exclusion from PP population will be determined and documented prior to data base lock.

This population will be used for efficacy analysis.

4.1.4 Protocol Deviations

Dose Escalation Phase and Dose Expansion Phase:

The major protocol deviations are those which may significantly affect the validity/interpretation of efficacy endpoints and may require exclusion of data / patient from the respective efficacy analysis. The review of all protocol deviations will be performed and the protocol deviations impacting statistical analysis of respective endpoint will be evaluated. The decision taken related to Data / Patient exclusion from respective analysis will be documented in “Protocol Deviation Listing”.

Thus, final Protocol Deviation Listing will be used at analysis level to find the analysis populations of different endpoints and final Protocol Deviation Listing will be used to summarize major and minor protocol deviations.

The summary of major protocol deviations (PD) will be provided by dose cohort using the safety population. Overall summary of Minor PD (all) by dose cohort will be provided using safety population.

4.2 Timing of Analysis

4.2.1 Interim Analysis

Dose Escalation Phase:

There is no formal interim analysis planned for this part of the study. However, safety review will be performed at the end of each cohort to determine MTD/optimal dose.

Dose Expansion Phase:

There is no formal interim analysis planned for this part of the study.

However, safety review will be performed at every 3 months to understand any safety concerns.

4.2.2 Final Analysis

The final analysis is applicable to all dosed patients in the study (combining Dose Escalation and Expansion Phase). Data collected up to end of treatment for all endpoints will be analysed at the time of Final Analysis. The final analysis shall be done after the third assessment of last patient has been completed or before in case of early discontinuation and as per the predefined cut-off date of “Last patient Last Visit” (i.e. 10-Dec-2018 when last patient (D8) was moved to compassionate study protocol) used for final database lock. The analysis will be started after final database lock is performed.

4.3 Methods for Handling Missing Data

Dose Escalation Phase and Dose Expansion Phase:

Values obtained at Unscheduled visits prior to administration of first dose of RP6530 (Pre-dose on C1D1) will be considered to derive Baseline values.

For “Tumor Assessment” response provided by investigator, the values obtained at the unscheduled visits Post Dose 1 (Post dose on C1D1) will be considered for analysis and also it will be provided in listings. If “PD” response is obtained at unscheduled visit for “Tumor Assessment” data then the result will be considered in the analysis.

4.3.1 Handling Missing Data Not Due to Dropouts

Dose Escalation Phase and Dose Expansion Phase:

No imputation will be made for missing values, thus missing data will be treated as missing.

4.3.2 Handling missing data Due to Dropouts

The scheduled parameter values, in general, visit-specific evaluations will be taken as nominal visit value without any consideration of window days around the cycle days.

4.3.3 Handling of Screen Failures / Ineligible Patients

Study patients who are screened but do not meet the eligibility criteria (i.e., screening failures) or any other reason(s) for Screen Failure will be entered into a CRF. Screening numbers assigned to Patients who are screen failures will not be reused. Listing for Screen Failure patients will be provided with a reason of screen failure.

4.4 Statistical Analysis

All statistical analysis relating to the study will be performed using statistical software, SAS version 9.2 or higher. The quantitative variables will be summarized using “Summary Statistics” - Number of patients, Missing data [n (Missing)], Mean, Standard Deviation, Median, Minimum (Min), Maximum (Max) and 95 % Confidence Interval (CI) wherever applicable. The qualitative variables will be summarized as number and percentage and if specified 95% CI will be presented. All analyses will be conducted on safety population unless stated otherwise. All data used in summaries will be listed.

All below sections are applicable to Dose Escaltion and Dose Expansion phases unless specified explicitely.

4.4.1 Derived Data

4.4.1.1 Treatment Start Date

Treatment start date is the First dosing Date defined as the date when the patient has been confirmed as taken the study drug at the clinic/home (even if the patient has not taken the study drug at the clinic, and there is evidence of the patient taking at least one dose of the drug).

For patients who did not take at least one dose of study drug yet randomized i.e. if “Treatment Start Date” (Treatment Start date is nothing but Date of Dispensing IMP as per eCRF as first dose is taken at site) field

is completely blank i.e. complete date is missing then the treatment start date will not be defined and will be kept blank.

4.5 Baseline Values

Baseline value of any parameter other than plasma concentration is defined as the latest non-missing value of the parameter prior to administration of first dose of RP6530.

Unscheduled values prior to administration of first dose of RP6530 (Pre-dose on C1D1) will be considered to derive Baseline values.

If Plasma concentration value is missing for time t=0 (Pre-first dose value) then it will be set to 0.

4.5.1.1 Date of Birth

For Date of Birth, if day and month are missing then the day/month will be imputed as 01/JAN and if only day is missing then 01 of that month will be imputed for “Day”.

Age = [Date of Screening Visit – Date of Birth] / 365.25. The format used for presenting age will be ##.##

If DOB is completely missing and “Age in years” is available then that Data will be used for analysis.

4.5.1.2 End of Study Value

End of Study value (EOS value) of any parameter is defined as the latest non-missing assessment of the parameter post first dose administration of RP6530. Thus, in addition to scheduled visit assessments, early termination assessments and unscheduled visit assessments will also be used to derive End of Study value.

If ‘End of treatment (EOT)’ is performed for any patient, then End of study value is not presented in listing however it is used for the analysis in table

4.5.1.3 Clinical Laboratory Data

If a laboratory value for any laboratory parameter is being provided as <x.y (or >x.y), then for analysis purpose the numerical value will be imputed as x.y – 0.1 (or x.y + 0.1).

4.5.2 Patient Disposition

The Number and percentage of patients who were screen failures; along with the reason for screen failure will be provided. The number and percentage of patients included in the study will be provided.

A Patient is called a completer if he/she has completed the cycle 8, Day 1 visit, i.e. did not discontinue the study treatment prior to cycle 8. The withdrawal/discontinuation of subjects will be summarized along with reasons for discontinuation using safety populations.

The summary of all protocol deviations (major/minor) will be provided using the safety population.

The number and percentage of patients in each of analysis populations will also be provided using safety population. Listing will be provided for analysis population

4.5.3 Baseline Characteristics

The baseline parameters will be the parameters assessed just prior to Cycle 1/ Day 1 dosing (prior to first dose intake) of the patient.

At baseline Demography (age, gender, Race), Vital Signs, Physical Examination, Laboratory Evaluations, ECOG performance status, Outcome to last therapy (Relapse or refractory), median prior therapies smoking/alcohol status and Medical History will be summarized for safety population.

4.5.3.1 Demographics

For this analysis, Safety population will be used.

Demographic data will include Age (years), gender, race. The type of variable, and the corresponding analysis, is presented in the table below:

Table 5 Details of Demographic Variables

Variable	Type of Variable	Type of Analysis	Unit of Measurements	Formulae for Derived Variable
Age (Derived variable)	Quantitative	Summary Statistics	Years	Age = [Date of Screening Visit (Day -28 to Day 0) – Date of Birth] / 365.25 Format: Numeric field ##.##
Gender	Qualitative	Frequency and Percentage	Not applicable	--
Race	Qualitative (Asian, White/Caucasian, Afro-American, Hawaiian/Pacific Islander, Indo-American)	Frequency and Percentage	Not applicable	--

Quantitative Variable (Age) will be summarized as n, Mean, Standard Deviation, Median, Max, and Min and Qualitative variable (Gender and Race) will summarized as n (%) i.e. frequency and percentage.

4.5.3.2 Medical History and Concomitant Illness (Pre-existing Conditions)

Medical History will be those medical events which would have occurred during past and stopped prior to dosing of RP6530 i.e. stop date of the condition should be < First dosing Date in the CRF. Pre-existing conditions (Concomitant Illness) are those medical events which are ongoing at the time of first dosing date with RP6530 i.e. stop date of condition should be ≥ first dosing date in CRF. If the stop date is missing or partial such that the stop date of the event could not be determined unambiguously with respect to first dosing date, the event will be considered as Pre-existing conditions.

Medical history and pre-existing conditions will be coded using the MedDRA dictionary, Version 18.1 or higher. The exact version of the dictionary will be mentioned in the footnote of the respective Listing and/or Table. Medical history and pre-existing conditions of all the patients will be summarized as n (%), E where n = Number of Patients with at least one Medical history/Pre-existing conditions (patients counted once if the patient reported one or more Medical history/Pre-existing conditions), % = (n / N) *100 where N=Number of patients in the safety Population and E = Count of Medical history/Pre-existing conditions (One patient may be counted more than once) by system organ class/preferred term. For this analysis, safety population will be used. If Any 'System Organ Class' is missing in MedDRA coding then 'Code Not Available#' will be used and If Preferred Term is missing in MedDRA coding then the same will be replaced by Medical Condition/ Surgical Procedure reported by investigator with followed by special character '#'.

4.5.3.3 Prior Medications/Therapies

Medications will be coded as per the WHO DDE. Prior Medications will be summarized in one table and will be presented using WHO Drug Name (Preferred Term) as the 5th Level Term Chemical Substance, ATC Class as 3rd Level ATC and the ATC Class as the 1st Level ATC in the order ATC Level 1 within that ATC level 3 and then ATC Level 5. The version of the WHO DDE used will be 'Version 2016' or later. The exact version will be mentioned in the footnote of the respective Listing and/or Table. If WHO Drug Name (Preferred Term) is not coded then the same will be replaced by "Generic Term" and indicated by "#". If 'ATC Level 1' and 'ATC Level 3' is missing in WHO-DDE coding then 'Code Not Available#' will be used

Prior medications will be classified as follows:

- Prior medications stopped prior to First Dose of RP6530 i.e. [stop date of medication] should be < first dose date

Medications that were stopped before the dose of RP6530 are referred to as Prior medications stopped before first dose.

- Prior medications ongoing at the time of first dose i.e. Medication Start Date < first dose date </= Stop Date

Medications that were started before the start of study drug and were continuing at the time of first dose of study drug i.e. post exposure RP6530 are referred to as Prior medications ongoing at the time of First Dose of RP6530. If the stop date is missing or partial such that the stop date of the medication could not be determined unambiguously with respect to date of first dose of study dose or if the start date is missing or partial and stop date of medication is after the date of first dose of study dose, then the medication will be considered as Prior medications ongoing at the time of first Dose of RP6530.

Cancer Therapies that were given before the start of study drug i.e. cancer therapies prior to first dose of study drug are referred to as Prior therapies. Prior therapies will not be coded as per the WHO DDE so will be presented by term reported by investigator.

Prior medications for each of the above classifications and prior therapies will be summarized as n (%), E where n = Number of Patients with at least one Prior Medication/ Prior therapies (patients counted once if the patient reported one or more Prior Medication/ Prior therapies), % = (n / N) *100 where N=Number of patients in the safety Population and E = Count of Prior Medication / Therapy (One patient may be counted more than once) by ATC class and WHO Drug Name (Preferred Term) for prior medication and by therapy reported by investigator for prior therapies. For this analysis, safety population will be used.

4.5.3.4 ECG

The abnormalities of ECG, if any, will be collected at Screening visit (Day -28 to Day 0) and cycle1/day1 visit (before dose). The ECG results will be summarized as Normal/ Abnormal - Not clinically significant / Abnormal - clinically significant with frequency (n) and percentage (%) of patients using safety population. The last available value before dosing will be considered for analysis.

Triplicate ECG will be performed for any visit, if 12-lead ECG result is found to be “Abnormal – CS” for respective visit. Thus, at analysis level, for each visit, derived “Final ECG Results” will be used for summarizing ECG data. For each patient the “Final ECG Result for any visit” is nothing but the latest ECG result available either from 12-lead ECG or from Triplicate ECG for respective visit. The ECG results will be summarized as Normal/ Abnormal - Not clinically significant / Abnormal - clinically significant with frequency (n) and percentage (%) of patients using safety population.

4.5.3.5 Serology

The Serology assessment (HBV, HCV, and HIV tests) will be performed at screening only. Serology response at baseline will be categorised as “Positive” and “Negative”.

Different Serology tests will be summarized as frequency (n) and percentage (%) using safety population.

4.5.3.6 Pregnancy test

Any pregnant patient who got dosed by mistake will be summarized with protocol violations for violating inclusion/exclusion criterion.

If the patient becomes pregnant during the study then patient will be discontinued from the study.

4.5.3.7 Eastern Co-operative Oncology Group Performance Status

The Eastern Cooperative Oncology Group performance status (ECOG PS) will be assessed at screening (Day -28 to 0) and cycle 1/day 1 (before dose) visit. The ECOG PS will be summarized with frequency (n) and percentage (%) of different performance scale as mention in below

Table 6 using the safety population.

Table 6 Eastern Cooperative Oncology Group performance status

ECOG Performance scale	ECOG Performance Status
0	asymptomatic
1	symptomatic, fully ambulatory
2	symptomatic in bed less than 50% of day
3	symptomatic, in bed more than 50% of day but not bedridden
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Note: If ECOG PS ≥ 2 during screening, then the patient will not be eligible for the study.

4.5.4 Efficacy Analysis

4.5.4.1 Secondary Efficacy Analysis

The evaluation of secondary efficacy endpoint is imaging-based tumor/skin based assessments by investigator in PTCL/CTCL patients treated with RP6530. All baseline imaging-based tumor assessments are to be performed on screening (Day -28 to 0) of the study. The disease will be assessed at subsequent scheduled visits using CT scan/skin assessment to re-evaluate with respect to this baseline assessment at visits Cycle 3/Day 1 (± 3 days), Cycle 5/Day 1 (± 3 days) and End of study treatment. Tumor Assessment will be performed thereafter if warranted, at the discretion of investigator.

The secondary efficacy endpoints are Overall Response Rate (ORR) & Duration of Response (DoR).

Intent to Treat (ITT) and Per-protocol population (PP) will be used for the secondary efficacy analysis.

- **Overall Response Rate (ORR)**

ORR is defined as percentage of patients with Complete or Partial Response at any time point during the study, as assessed by investigator.

ORR will be summarized as frequency, percentages along with two-sided 95%, using Clopper-Perason Exact method in SAS.

- **Duration of Response (DoR) for Responders (CR/PR):**

DoR will be derived based on responders (i.e., patients who achieved CR or PR during the study) only in the following manner:

- For responders who had PD (or died for any reason), DoR (in days) = (PD Date – First Response Date + 1, where Date of Disease Progression Based on overall response visit date if not available then Date of Disease Progression mentioned on end of study CRF or Date of death and the First Response Date is the date when CR or PR was first observed)+1
- For the rest responders, the DoR = (Date of visit when last scheduled tumor assessment response was provided by investigator which is showing documented CR/PR response irrespective of status of patient on “Participants Trial Completion Assessment Page”– Date of visit when tumor assessment response was provided by investigator which is showing documented CR/PR response first time) +1

Duration of Response (DoR) is applicable to patients showing CR or PR and it is defined as time from the first documented assessment of CR or PR until the documented tumor disease progression (date of the first occurrence of PD as per investigator’s tumor assessment response based on post-treatment CT scan performed or Date of Disease Progression mentioned on end of study CRF up to predefined cut-off date. The cut-off date is nothing but the last patient last visit date till End of the study i.e. 10-Dec-2018 when last patient (D8) was moved to compassionate study protocol. If patient do not show the response CR or PR during the study, then the duration of response is considered as 0. For patients who complete the study and CR / PR response if still continues or if patient is discontinued due to any reason then DoR will be calculated using the date of visit when last scheduled tumor assessment response was provided by investigator which is showing documented CR/PR response (objective evidence of response). Duration of response will be calculated in days as follows:

DoR for Responders (Days) = Min [Date of Disease Progression Based on overall response visit date if not available then Date of Disease Progression mentioned on end of study CRF] or (If Disease Progression is not observed then Date of visit when last scheduled tumor assessment response was provided by investigator which is showing documented CR/PR response irrespective of status of patient on “Participants Trial Completion Assessment Page”) – Date of visit when tumor assessment response was provided by investigator which is showing documented CR/PR response first time +1

DoR (days) will be summarized descriptively as Minimum, Maximum and Median along with 95% CI for median. For calculating confidence interval for median normality is not assumed and distribution-free 95% confidence intervals for median will be calculated using following code in SAS:

```
Title 'Analysis of Duration of Response (DoR)';
ods select Quantiles;
proc univariate data=<<Dataset Name>> ciquantdf (alpha=0.05);
  var <<Variable Name e.g. DoR>>;
run;
```

In PTCL & CTCL patients, disease will be assessed using imaging assessments at Screening and at subsequent scheduled visits it will be assessed with respect to this baseline assessment using imaging assessments at C3D1 (± 3 days) and C5D1 (± 3 days) and at the End of Treatment (EOT). Assessment will be performed thereafter if warranted, at the discretion of investigator.

For PTCL patients, imaging assessments based tumor response provided by investigator in “Response” field of eCRF module “Restaging for PTCL patient” will be considered for the analysis of ORR and DoR.

For CTCL patients, tumor response provided by investigator in “Global Response” field of eCRF module “Restaging for CTCL patient” (which takes into account of skin response + nodal response + visceral response and blood response) will be considered for the analysis of ORR and DoR.

Exploratory analysis of DoR for Responders (CR/PR) will also be performed considering Time of Duration till Discontinuation:-

The calculation of DoR will remain same as above except for discontinued patients if documented tumor disease progression is not recorded after achieving the response (CR or PR) then for those patients the duration of response will be from the first assessment of CR or PR until the date of **discontinuation**.

The formula used to calculate for DoR is modified as follows:
DoR for Responders (CR/PR) [Days] = DoR for Responders (CR/PR) (Days) till Discontinuation = Min [Date of Disease Progression Based on overall response visit date if not available then Date of Disease Progression mentioned on end of study CRF] or (If patient discontinued without observing Disease Progression then Date of Discontinuation) or (If Date of Discontinuation is not available then Date of visit when last scheduled tumor assessment response was provided by investigator which is showing documented CR/PR response)– Date of visit when tumor assessment response was provided by investigator which is showing documented CR/PR response first time +1

- **Other Secondary Endpoints**

In addition to ORR, the following analysis will also be performed. The percentage of subjects along with 95% CI will be calculated using each scheduled tumor assessment time point responses provided by investigator along with Best Overall Response (BOR). BOR (Derived Variable – Derived once from Screening to EOT) is derived from all time point responses available up to EOT. The following hierarchy will be followed to derive BOR from all available time point tumor responses

- Complete response (CR),
- Partial Response (PR)
- Stable Disease (SD)
- Progression of Disease (PD),
- Not Evaluable
- Not Assessed

All Listings related to Radiological Evaluations, Disease Evaluations, Morphology & Cytogenetic Evaluations, Disease Assessment for CTCL and PTCL Patients and Staging of PTCL and CTCL patients will be provided with respect to PTCL and CTCL patients wherever Applicable.

In Disease Assessment of CTCL patient for skin mSWAT, Total Score will be calculated of Patch, Plaque and Tumor at analysis level for all body region by doing summation of “Subtotal lesion BSA × Weighting

Factor" of Patch, Plaque and Tumor at each visit. Also Total of "Degree/Size of Index lesion 1-5" will be calculated at analysis Level.

In Disease Assessment of CTCL patient for Radiological assessment of Lymph node, Total sum of Products of Measurements will be calculated at analysis level for all Tissue site by doing summation of "Products of measurements" of all Tissue site at each visit.

In Disease Assessment of PTCL patient for dominant nodes and non-dominant nodes, Total sum of Products of Measurements will be calculated at analysis level for all Tissue site by doing summation of "Products of measurements" of all Tissue site at each visit.

All Efficacy Listings will be presented for Safety Population and Tables will be presented for both FA and PP Population.

Swimmer Plot and Water Fall Plot will be plotted for each efficacy evaluable patients using ITT population.

For swimmer plot, treatment duration will be considered on x-axis and patient with Dose cohort on X-axis. Bar color will be presented with best tumor response. Following three parameters will be displayed in the swimmer plot.

1. First Tumor response
2. First CR/PR Response
3. Continuation of treatment

Water fall plot will be plotted for each evaluable patients using ITT population considering patient number on X-axis and % change from baseline on Y-axis. Bar colour will represent the Best response in the study. For % change from Nadir result, if value is captured with any special character then that special character will be removed and converted the result into numeric format and that numeric result will be used for the plotting of graph. Following points will be taken into consideration while plotting the Water Fall plot.

1. For any patient, if BOR is present at only one visit then respective change from Nadir value is considered as change from baseline on Y-axis. If BOR is present for more than one visit then maximum value of % change from nadir will be used by ignoring the sign i.e. Minimum if the value is negative or maximum if the value is positive to select the respective change from Nadir value as change from baseline on Y-axis.
2. For PTCL patient with "non-measurable lesion but assessable disease", if "% change from Nadir" is blank and patient has "CR" response throughout the study then check the "Disease assessment" module of eCRF. In "Disease assessment" module, if "Bone Marrow Involvement" is marked as "No" then that patient will be presented in the graph followed by "#" and footnote will be added as "#Patient has "CR" response as positive bone marrow became negative"
3. For any patient, if numeric variable of "% change from Nadir" is blank and in the character variable if the text is present as "This PD due to new lesion" and patient has "PD" response in the study then it will be considered as "Progression Disease" due to new lesion. This patient will be presented as "% change

from nadir" value 25% with patient number followed by "*"in the graph and footnote will be added as "*Patient has new lesion so % change from Nadir value is imputed with 25%."

4. For any patient, if character and numeric variable of "% change from Nadir" is blank and patient has "PD" response in the study then it will considered as "Progression Disease" as per the clinical judgement of investigator (Clinical progression). This patient will be presented as "% change from nadir" value 25% with patient number followed by "**"in the graph and footnote will be added as "**Patient has "clinical progression" so % change from Nadir value is imputed with 25%."

4.5.4.2 Safety Analysis

4.5.4.3 Primary Safety Analysis

Maximum Tolerated Dose (MTD):

Patients who experienced DLT at 200 mg BID, at 400 md BID, at 800 mg BID will be presented with frequency and percentage against respective dose level.

The Primary endpoints are based on Safety and Dose limiting Toxicities (DLT) of RP6530.

Primary safety endpoint will be assessed as

1. Number and percentage of patients reporting at least one Adverse Event (AE) during the study.
2. Number and percentage of patients reporting at least one Serious Adverse Event (SAE) during the study.
3. Number and percentage of patients reporting at least one grade 3 and grade 4 AE during the study.
4. Number and percentage of patients reporting at least one drug related AE during the study.
5. Number and percentage of patients reporting at least one clinically significant (CS) AE due to abnormal CS result as per investigator discretion for laboratory, Electrocardiogram (ECG) or vital signs during the study.

The above safety endpoints will be summarized by dose cohort. Adverse Events (AEs) will be assessed at each scheduled day of each cycle i.e. AEs will be assessed from screening to till end of the treatment assessment.

6. Number and percentage of patients who experienced at least one Dose Limiting toxicity (DLT) during the usage of RP6530 study treatment. The analysis will be summarized by dose cohort.

   For filtering of DLT data, the field on AE page "Reported as DLT" will be used. If this field is ticked then that patient is considered as "DLT" for that event.

4.5.4.4 Secondary Safety Analysis

Not Applicable

4.5.4.5 Adverse Events (AEs)

Assessment of AE (Includes Serious Adverse Events, DLTs):

An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or medical condition occurring after signing of the consent form i.e. Day -28 to 0, even if the event is not considered to be causally related to investigational products. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with drug administration, whether or not related to the product.

Adverse Events (AEs) will be coded using MedDRA, Version 18.1 or higher.

All AEs including DLTs, regardless of seriousness or relationship to RP6530 (study drug), spanning from the first dose of study drug until 30 calendar days after the last dose of study drug, discontinuation or completion of protocol-specific treatment as defined in the protocol for that patient, are to be recorded in the CRF

After 30 days of completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or Deaths assessed by the investigator as treatment related are to be reported.

DLTs will not be presented separately for Dose expansion Phase of the study and will be treated as AEs.

DLT Assessment:

DLT assessment is applicable only for Dose Escalation Phase. For Dose Expansion phase it will not be analyzed separately and will be part of AEs.

DLT will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE).

All toxicities should be considered to be related to RP6530 unless there is a clear alternative explanation. A toxicity is considered dose-limiting if it occurs during the first cycle (4 weeks) of treatment with RP6530 and is considered related to RP6530. DLT is be defined as the following:

A. Hematological DLTs:

- Grade 4 Anaemia
- Grade 4 neutropenia (absolute neutrophil count [ANC] <500/μL) for >7 days, or Grade ≥3 febrile neutropenia (ANC <1000/μL with fever >38.5ºC [101ºF]
- Grade 4 thrombocytopenia for >7 days, or grade ≥3 thrombocytopenia associated with Grade >2 bleeding

B. Non-Hematological DLTs:

- Grade ≥3 non-hematologic toxicity with exception of:
    - Grade ≥3 diarrhea or nausea that does not resolve to ≤ Grade 2 within 48 hours despite treatment; and

- If ≥1.5 ULN of bilirubin or >3 ALT/AST elevation that does not resolve to ≤ Grade 1 within 7 days

- Treatment delay of ≥14 days due to unresolved toxicity
- Non-hematologic toxicity of Grade 2 (at any time during treatment) that in the judgment of the DRG, is dose-limiting.
- For certain toxicities such as laboratory assessments without a clear clinical correlate (e.g. lipase increase without signs of a clinical pancreatitis) a discussion between the Investigator and Medical Monitor may take place if this adverse event (AE) should be assessed as DLT necessitating dose reduction.

Table for "DLT Assessment and Discontinued due to DLT" will be summarized using frequency and percentage. Following filtration rule will be followed for DLT assessment:

1. DLT assessment will be applicable for Dose escalation cohorts.

2. Cohort of Dose for the study group will be decided based on first dose received by patients at Cycle 1 Day 1 visit (i.e. Dose details captured under "Trial Medication Dispensing" Domain of CRF)

3. DLT evaluable population will be calculated based on following algorithm During Cycle 1 of treatment.

- Patient receives at least 80% of planned doses of RP6530 doses OR received RP6530 for the first 21-days continuously; Following formula will be used to derive the number of days patient received the study drug

  Number of days patient received study drug = (Date of EOT visit performed if not available then Date of Withdrawal on EOT page in "PARTICIPANTS TRIAL COMPLETION ASSESSMENT" domain - Date of first Dose Dispense at cycle 1/Day 1) +1.

  For any patient if overall treatment duration is less than or equal to 22 days and overall compliance is less than 100% then that patient will not be considered for DLT assessment.

AND

- Patient completes all required safety evaluations (at least for three visits after the first dose);
- Patients who experience a DLT will be considered evaluable regardless of the number of doses received.

Patient with DLT and "Discontinued due to DLT" will be calculated based on following algorithm. 2. The patient will be assessed for "Adverse Event" occurrence in all visit using field "DLT assessment" will be filtered from AE page of CRF as follows:.

For any patient, if "Reported as DLT" is marked as "Yes", then that patient will be considered to have as "DLT".

For any patient, if “Reported as DLT” is marked as “Yes” and “Dropped due to this AE?” is marked as “Yes”, then that patient will be considered as “Discontinued due to DLT”.

Summary of AEs

Adverse Events (AEs) will be coded using MedDRA, Version18.1 or higher. The version of the dictionary will be mentioned in the footnote of the respective Listing and/or Table. All AEs will be classified on the basis of Preferred Term and System Organ Class (SOC). AE summaries will include SAEs.

All safety analysis will be summarized over time. Listings for all the AEs and SAEs will be provided for each patient. Any AE will be summarized as n (%), E.

Where,

n is the number of patients who experienced that particular AE

% Percentages w.r.t. number of patients who experienced event within particular category

E Number of times that particular AE experienced by patients.

An overall summary of number of Patients within each of the categories described in the sub-section mentioned below will be provided. If Any ‘System Organ Class’ is missing in MedDRA coding then ‘Code Not Available#’ will be used and If Preferred Term is missing in MedDRA coding then the same will be replaced by AE term reported by investigator with followed by special character ‘#’.

Analysis:

Listings of TEAEs and Non-TEAEs will be provided

The TEAEs will be summarized by each of the dose cohort (200 mg BID- Fasting, 400 mg BID- Fasting, 800 mg BID- Fasting, 800 mg BID- After Food) as follows:

- Number and percentage of patients along with total number of events experiencing at least one TEAE will be tabulated by dose cohort.
- Number and percentage of patients along with total number of events experiencing treatment-emergent AEs by SOC and preferred term will be tabulated by dose cohort.
- Number and percentage of patients experiencing treatment-emergent AEs by preferred term (ignoring SOC) along with total number of events will be tabulated by dose cohort.
- Number and percentage of patients along with total number of events experiencing treatment-emergent AEs within specific SOC/Preferred term by intensity (maximum intensity will be captured in the CRF) and separately by outcome, will be tabulated by dose cohort
    - Intensity Grade
        - 1 = Mild
        - 2 = Moderate
        - 3 = Severe
        - 4 = Life threatening
        - 5 = Death
    - Outcome

- 1 = Resolved
- 2 = Resolving
- 3 = Not Resolved
- 4 = Resolved with Sequelae
- 5 = Fatal
- 6= Unknown

- Number and percentage of patients along with total number of events experiencing discontinuations due to treatment-emergent AEs will be tabulated by dose cohort. For filtering data related to discontinuations due to AE, the field on AE page “Dropped due to this AE?” will be used. If this field is ticked for “Yes” then the patient will be considered as discontinued due to AE.

Number and percentage of patients along with total number of events experiencing drug-related treatment-emergent AEs (assessed as Attribution =”Related”) will be tabulated by dose cohort. For filtering drug related AE data, the field on AE page “Attribution” will be used. If this field is ticked as “Related” and AE is Treatment Emergent AE then the respective AE will be considered as “Drug Related AE”.

4.5.4.6 Deaths, Serious Adverse Events and Significant Adverse Events

Dose Escalation Phase and Dose Expansion Phase:

Serious adverse events (SAEs) are those events recorded as “Serious” on the Adverse Events page of the (e)CRF. A summary of serious TEAEs by SOC and PT will be prepared.

SAEs will be classified as Serious Treatment Emergent Adverse Events (TEAEs) and Serious Non-Treatment Emergent Adverse Events (Non-TEAEs).

For Serious Non-TEAEs only Overview Table will be presented. Separate Listings will also be provided for Serious Non-TEAEs.

A summary of serious TEAEs will be analyzed by dose cohort, same as mentioned in section 4.5.5.3 “Adverse Events (AEs)”.

TEAEs leading to Death are those events whose outcome are recorded as “Fatal” on the Adverse Events page of the (e)CRF. A summary of TEAEs leading to death by SOC and PT will be prepared.

4.5.4.7 Significant Events of Special Interest

The Events like pregnancy, Abortion, birth defects, and congenital anomalies are the events of special interest and will be analyzed separately as Significant Events of special interest.

For filtering data related to Pregnancy, the study conclusion page will be used. If the reason for discontinuation in the study conclusion page is marked as “Pregnancy” then such patients will considered as having events of special Interest.

For filtering data related to birth defects, and congenital abnormalities, if the SAE Criteria is marked as

The analysis of these events will also be presented separately. These events will be summarized with frequency (total number of events) and percentage (Subjects who experienced only one event).

4.5.4.8 Vital Signs

Assessment:

The Vital Signs parameters will be assessed at all scheduled visit from screening (Day -28 to Day 0) to End of study treatment in both part of study. Vital signs measurement will consist of the following assessments:

- Systolic Blood Pressure (mm of Hg)
- Diastolic Blood Pressure (mm of Hg)
- Pulse Rate (beats/ minute)
- Respiratory rate (breaths/ minute)
- Weight (kg)
- Height (m) only at screening
- Oral temperature (˚C)

For other subsequent visits (except screening) all parameters will be recorded except Height.

Findings Related to Vital Sign:

All CS findings at screening or at cycle 1 day 1 (before dose) will be recorded as medical history or concomitant illness. Out of Normal range values of vital sign parameter will be flagged as Abnormal – CS, Abnormal – NCS. If this concomitant illness worsens during the study period after start of the treatment then it will be captured as AE. All CS findings in vital signs identified post screening will be captured as AE.

Analysis:

The quantitative Analysis of Vital Sign will be not be presented. Only shift analysis of qualitative results of vital sign will be presented.

Out of range values of Vital Signs will be flagged as Abnormal - CS, and Abnormal - NCS in data listings.

The number and percentage of patients who shift from abnormal or normal value at baseline to normal or abnormal at each post baseline visit will be summarized for each vital sign parameters. The abnormal values will be further classified as Abnormal – CS and Abnormal - NCS in shift table.

The Reference Ranges considered for vital signs are as follows:

- Oral Temperature: 33.2-38.2 degree Celsius (both inclusive)
- Pulse rate: : 60 to 100 beats per minute (both inclusive)
- Respiratory rate: 12 to 18 breaths per minute (both inclusive)
- Blood Pressure (Systolic): 90 mm Hg ≤ Systolic BP ≤ 119 mm Hg
- Blood Pressure (Diastolic): 60 mm Hg ≤ Diastolic BP ≤ 79 mm Hg
- Weight: 35 kg to 92 kg (both inclusive)

Listing of abnormal values (CS/NCS) for vital sign parameters will be provided for patients for whom abnormal vital sign values are observed for that visit, for any vital sign parameter.

Shift table for Vital Sign will be provided for each post baseline visit and EOS value w.r.t baseline visit.

The shift analysis results will be presented as Normal, Abnormal- Clinically Significant (Abnormal – CS), Abnormal – Not Clinically Significant (Abnormal – NCS) and Not Done. Percentages will be calculated w.r.t. number of patients included in Safety population for each dose cohort.

4.5.4.9 Physical Examinations

Assessment:

Physical Examination will be performed at Screening Visit (Day -28 to Day 0) and all scheduled day of each cycle (Cycle 1 to Cycle 8).

Physical examination will include lymph node and systemic examination.

Physical Examination include General Appearance, Skin, Eyes, Ears, Nose & Throat , Head, Neck & Thyroid, Heart, Lungs, Chest, Abdomen, Extremities, Genitalia, Anorectal, Lymph Nodes, Muscular-Skeletal, Neurological and Others.

Findings Related to Physical Examination:

Abnormal findings at screening or at cycle 1 day 1 (before dose) in physical examinations will be flagged as Clinically Significant (CS)/Not Clinically Significant (NCS) in data listings. All CS findings in physical examination at screening or at cycle 1 day 1 (before dose) are included as medical history or concomitant illness. If this concomitant illness worsens during the study period after start of the treatment then it will be captured as AE. All CS findings in physical examination identified post screening will be captured as AE.

Analysis:

Physical examination results will not be summarized visit wise. Patient wise listing of physical examination data (all visits) will be provided.

Assessment of Physical Examination will include:

1. General Appearance
2. Skin
3. Eyes, Ears, Nose & Throat
4. Head, Neck & Thyroid
5. Heart
6. Lungs
7. Chest (including Breast)
8. Abdomen
9. Extremities
10. Genitalia
11. Anorectal

12. Lymph Nodes
13. Muscular-Skeletal
14. Neurological
15. Others

Shift table for Physical Examination will be provided for each post baseline visits and EOS value w.r.t baseline visit. For Other Physical Examination Shift Table will not be provided

The shift analysis results will be presented as Normal, Abnormal- Clinically Significant (Abnormal – CS), Abnormal – Not Clinically Significant (Abnormal – NCS) and Not Done. Percentages will be calculated w.r.t. number of patients included in Safety population for each dose cohort.

Listing of abnormal values (CS/NCS) for Physical examination parameters will be provided for patients for whom abnormal physical examination results are observed for that visit, for any physical examination.

4.5.4.10 Clinical Laboratory Evaluation

Assessments:

Clinical laboratory tests constitute the assessments related to local laboratories.

- Haematology:
  - WBC
  - RBC
  - Hb
  - PT/INR
  - HCT
  - MCV
  - PLT
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
  - Reticulocytes
- Biochemistry Panel I:
  - Total Bilirubin
  - ALK PHOS (ALP)
  - ALT
  - AST
  - Gamma-Glutamyl Transpeptidase (GGT)
  - LDH
- Biochemistry Panel II:
  - Glucose
  - HbA1C
  - BUN
  - Creatinine

  - Albumin
  - Total Globulin
  - Total Protein
  - Total Cholesterol
  - Triglycerides
  - LDL
  - HDL
  - TSH
  - T3
  - T4
- Urinalysis: Physical parameter-
  - Appearance
- Urinalysis: Laboratory parameter-
  - Nitrate
  - Sodium
  - Potassium
  - Calcium
  - Phosphate
  - Protein
  - RBC
  - WBC
  - Casts
  - Glucose
  - Ketone bodies
  - Bilirubin
  - Urobilinogen
  - Creatinine
  - Specific Gravity
  - pH
- Serum Electrolytes: Laboratory parameter-
  - Bicarbonate
  - Sodium
  - Potassium
  - Calcium
  - Chloride
  - Magnesium
  - Phosphorous

The laboratory tests included in the hematology and Chemistry panel I will be performed at screening visit and all scheduled day of each cycle. Any other laboratory assessment which is not defined in the protocol, will be done as required based on investigator's discretion but these other laboratory assessments will not be analyzed and will be provided in listing.

Hematology panel includes Hemoglobin, complete blood count, reticulocyte count, total leucocyte, differential count and platelet count.

Chemistry Panel I includes Total bilirubin, ALP, AST, ALT, GGT, LDH and Serum electrolytes (Sodium, Potassium, Bicarbonate, Chloride, Magnesium, Phosphorus and Calcium)

Chemistry Panel II includes blood glucose, urea or blood urea nitrogen, creatinine, albumin, globulin, total protein, Total Cholesterol, TG, LDL and HDL, TSH, T3 and T4 and HbA1c. Total protein and albumin tests will be performed; and globulin will be calculated by deducting value of albumin from total protein.

Haemetology, Chemistry Panel I, Chemistry Panel II t will be performed at screening visit and Day 1 of each cycle. For Dose Escalation Phase these tests additionally will be performed at Day 15 of cycle 1,

Urinalysis will be performed on screening, Day 1 of each cycle.

PT/INR will be performed on screening as well as on Day 1 of Cycle 1 to Cycle 4 and at the end of the treatment. For Dose Escalation Phase this test additionally will be performed at Day 15 of cycle 1,

All Serology test (HIV, HBV, HCV) will be performed on screening visit only.

Pregnancy test will be performed for women of child bearing potential. Serum Pregnancy test will be performed on screening / baseline and urine pregnancy test will be performed for all scheduled day of each cycle as indicated.

Findings Related to Laboratory Abnormalities:

Abnormal results for any of the laboratory evaluations at screening visit or at Cycle 1/Day 1 before dose and if clinically significant in the judgment of the investigator are to be reported as medical history or concomitant illness. Worsening of Pre-existing conditions from screening visit/ Visit 1(Day 0), if felt to be clinically significant in the judgment of the investigator, are to be recorded as AEs or SAEs.
If Laboratory results are normal at screening visit/ Visit 1(Day 0) but abnormal and clinically significant at subsequent visits then it will be reported as an AE.

Analysis:

Laboratory parameters will be assessed at different applicable scheduled days of respective cycles as mentioned in visit scheduled chart in **Table 3** for escalation phase and visit scheduled chart in **Table 4** for expansion phase

Laboratory parameter Total Globulin value will be calculated using the following formula and this calculated value of Total Globulin will be used for the statistical analysis.

Total Globulin = Total Protein – Albumin

The quantitative results of Laboratory variables (Hematology, Biochemistry Panel I, and Biochemistry Panel II) will not be analyzed.

The Laboratory tests are performed in local laboratories so all laboratory results will be converted in SI unit and then SI converted value will be presented in listing. The clinical laboratory assessments will be analysed

using Observed Case approach for missing values i.e. missing data will be treated as missing. If a laboratory value has been provided as <x.y (or >x.y), the numerical value will be imputed as per section 4.5.1.3. For this analysis, Safety population will be used.

Laboratory results, will be flagged as Normal, Abnormal- Clinically Significant (Abnormal – CS), Abnormal – Not Clinically Significant (Abnormal – NCS) as per the significance reported by investigator in eCRF, for abnormal laboratory values and presented in laboratory listing

Moreover Abnormal laboratory values for Laboratory tests for whom CTCAE Grading are provided in CTCAE, Version 4.03, at each time point will also be classified in CTCAE Grade as “Grade 1”, “Grade 2”, “Grade 3”, “Grade 4” and “Grade 5”. If abnormal values cannot be graded as per CTCAE, Version 4.03 grading then will be presented as “Cannot be graded”.

The Flag “High” or “Low” will not be derived using normal reference ranges for urinalysis. The investigator’s reported qualitative results will be used directly for the analysis.

Shift table for Laboratory test will be provided for each post baseline visits and EOS value w.r.t baseline visit.

The shift analysis results will be presented as Normal, Abnormal- Clinically Significant (Abnormal – CS), Abnormal – Not Clinically Significant (Abnormal – NCS) and Not Done. Percentages will be calculated w.r.t. number of patients included in Safety population for each dose cohort.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at Screening and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the Investigator as more severe than expected for the patient’s condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs. The severity of this AE provided by investigator may not match with calculated CTCAE grading calculated at analysis level as investigator will assess value taking into consideration baseline laboratory values and his overall clinical judgement.

The additional laboratory test will be presented in listings only it will not be analyzed in the table.

Listing of abnormal values (CS/NCS) for laboratory parameters will be provided for patients for whom abnormal laboratory results are observed for that visit for any laboratory parameters.

4.5.4.11 Concomitant Medications

Assessment:

Medications/Therapies that were started on or after the treatment start date (Cycle 1, Day 1 Date) will be referred to as Concomitant Medications. If above conditions cannot be determined unambiguously, the medication/therapy will be considered Concomitant Medication.

Concomitant medications will be coded as per WHO DDE. The version of the WHO DDE used will be 'Version 2016' or higher. The exact version will be mentioned in the footnote of the respective Listing and/or Table.

Analysis:

Concomitant Medication will be summarized using WHO Drug Name (Preferred Term) as the 5th Level Term Chemical Substance (ATC Level 5), ATC class as 3rd level ATC and Anatomical Therapeutic Chemical (ATC) Class as 1st Level ATC in the order ATC Level 1 within that ATC level 3 and then ATC Level 5. If ATC Level 5 is missing in coded list then generic term as reported by investigator will be used and indicated by "#".If Any 'ATC Level 1' and 'ATC Level 3' is missing in WHO-DDE coding then 'Code Not Available#' will be used

Concomitant medications will be summarized as Number and percentage of patients classified as per Anatomical Therapeutic Chemical (ATC) Class 1st, ATC Class 3rd and WHO Drug Name (Preferred Term – 5th level chemical substance term). Details of each medication such as, dose, frequency, route, etc. will be included in the data listing and will not be summarized.

4.5.4.12 Electrocardiograms (ECG)

Assessment:-

A standard Electrocardiogram (12 or 3 leads ECG) will be performed at screening and all scheduled day of cycle 1 i.e. Day 1, Day 8, Day 15, Day 22 and Day 1 of Cycle 2.

For Dose Escalation Phase, a single ECG will be performed at screening and C1D1 pre-dose. Post-dose ECGs will be performed in conjunction with the 1 hr, 2hr and 4hr post-dose PK collection on C1D1; and on C1D8 (pre-dose), C1D15 (pre-dose), and C1D22 (pre-dose). On C2D1, ECGs will be obtained pre-dose and then one hour post-dose coinciding with the PD collection.

For Dose Expansion Phase, a single ECG will be performed at screening, C1D1 pre-dose and C2D1 pre-dose and one hour post-dose.

Additional ECGs will be obtained if clinically indicated. Triplicate ECGs will be performed to confirm the significant changes of single ECG. All ECGs will be performed on local equipment.

An overall evaluation will be done by the investigator. All ECGs must be evaluated by a qualified physician for the presence of abnormalities. Only clinically significant abnormalities will be reported as AEs after inclusion visit.

Analysis:

Final ECG results which will be derived from 12-lead ECG and Triplicate ECG results. 12-lead ECG and Triplicate ECG results will be captured as "Normal", "Abnormal – CS" and "Abnormal – NCS". These results will be used to derive Final ECG results as follows:

For any visit while deriving Final ECG results at analysis level, the 12-lead ECG result will be considered first.

1. If 12-lead ECG result is “Normal” or “Abnormal – NCS” then final ECG results will remain same as 12-lead ECG result.
2. If 12-lead ECG result is “Abnormal – CS” then Triplicate ECG result will be checked as follows:
    a. If Triplicate ECG result is present for respective visit (Triplicate ECG performed) then final ECG results will be considered as results of Triplicate ECG for that visit.
    b. If Triplicate ECG result is not present for respective visit (Triplicate ECG not performed) then final ECG results will remain same as 12-lead ECG result for that visit.

Final ECG results will be derived for each visit. However, Final ECG results will not be summarized visit wise. Patient wise listing of ECG data (all visits) will be provided. Shift table for ECG will be provided for each post baseline visits and EOS value w.r.t baseline visit.

The shift analysis results will be presented as Normal, Abnormal- Clinically Significant (Abnormal – CS), Abnormal – Not Clinically Significant (Abnormal – NCS) and Not Done. Percentages will be calculated w.r.t. number of patients included in Safety population for each dose cohort.

4.5.5 Pharmacokinetics and Pharmacodynamic Analysis

4.5.5.1 Pharmacokinetics Parameters

The statistical analysis of PK will be performed by clinical pharmacology CRO contracted by the Sponsor and PK report will be provided by sponsor. Therefore, PK analysis is not applicable for this SAP.

4.5.5.2 Pharmacodynamics Parameters

The statistical analysis of PD will be performed by clinical pharmacology CRO contracted by the Sponsor and PD report will be provided by sponsor. Therefore, PD analysis is not applicable for this SAP.

5. Evaluation of Treatment Compliance and Exposure

5.1 Compliance to Study Drug

Compliance to study treatment will be ascertained by total planned dose of RP6530 dispensed at each cycle i/Day j and total dose consumed at that particular cycle i/Day j.

Listing of Treatment compliance will be provided along with planned dose and actual dose administered to each patient as <80%, 80%-100%, 100%-120% and >120%. Compliance to Treatment for the Study will be summarized based on following compliance categories: <80%, 80%-100%, 100%-120% and >120%. Compliance category at each cycle will be derived based on compliance calculation at each cycle.

Calculation of Exposure of treatment / Compliance at any cycle will be calculated based on different following scenario,

Details of Tablet Return in next visit	No. of tablets returned	No. of tablets neither returned nor consumed	Patient Compliance with study in next visit when Drug is dispensed	Drug Exposure Calculation	Compliance will be derived based on formula	Compliance Category
Data captured completely	Data Present	Data Present	Yes	Calculated using the formula	Calculated using the formula	Compliance Category will be derived based on calculated compliance
Data captured completely	Data Present	Data Present	No	Calculated using the formula	Calculated using the formula	Compliance Category will be derived based on calculated compliance
Data captured completely	Data Present	Data Present	Data missing	Calculated using the formula	Calculated using the formula	Compliance Category will be derived based on calculated compliance
Data Missing Partially	Data Present	Data Not Present (Will be imputed as 0)	Yes	Calculated using the formula	Calculated using the formula	Compliance Category will be derived based on calculated compliance
Data Missing Partially	Data Present	Data Not Present (Will be imputed as 0)	No	Calculated using the formula	Calculated using the formula	Compliance Category will be derived based on calculated compliance
Data Missing Partially	Data Present	Data Not Present (Will be imputed as 0)	Data missing	Calculated using the formula	Calculated using the formula	Compliance Category will be derived based on calculated compliance
Data Missing Partially	Data Not Present (Will be imputed as 0)	Data Present	Yes	Calculated using the formula	Calculated using the formula	Compliance Category will be derived based on calculated compliance
Data Missing Partially	Data Not Present (Will be imputed as 0)	Data Present	No	Calculated using the formula	Calculated using the formula	Compliance Category will be derived based on calculated compliance
Data Missing Partially	Data Not Present (Will be imputed as 0)	Data Present	Data missing	Calculated using the formula	Calculated using the formula	Compliance Category will be derived based on calculated compliance
Data Missing Completely	Data Not Present (Will not be imputed)	Data Not Present (Will not be imputed)	Yes	Calculated using the formula	Not calculated	Compliance Category will be considered as **“>=80% -<=100%”**
Data Missing Completely	Data Not Present (Will not be imputed)	Data Not Present (Will not be imputed)	No	Calculated using the formula	Not calculated	Compliance Category will be considered as **“<80%”**
Data Missing Completely	Data Not Present (Will not be imputed)	Data Not Present (Will not be imputed)	Data missing	Calculated using the formula	Not calculated	Compliance Category will not be derived and kept blank (missing)

- Details of Tablet Return means “No. of tablets returned” Field and “No. of tablets neither returned nor consumed” field present on “TRIAL MEDICATION” page of CRF
- If “No. of tablets returned” Field is non-missing and “No. of tablets neither returned nor consumed” field is missing then “No. of tablets neither returned nor consumed” field will be imputed with zero or vice versa

Compliance Formula -

Compliance of study Drug for **respective visits**:-

- Compliance to treatment at cycle i/Day j = {[Actual number of tablets taken at cycle i/Day j] / [Number of tablets planned to be administered at cycle i/Day j]}*100

Where,

Actual number of tablets taken at cycle i/Day j = [Total number of RP6530 tablet dispensed at cycle i/Day j – Total number of RP6530 tablet returned at cycle i/Day j+1 – Total number of RP6530 tablet neither returned nor consumed at cycle i/Day j+1]

Number of tablets planned to be administered at cycle i/Day j = Number of tablets to be taken per day for Cycle i/Day j* Number of planned days between the current cycle and the next cycle when drug accountability is performed

Where, Number of planned days between the current cycle and the next cycle when drug accountability is performed will be calculated as follows,

For **except Last visit** = (Date of Dose Dispense in next cycle i/Day j which is nothing but the date of tablets return of previous visit - Date of Dose Dispense in current cycle i/Day j)

For **Last visit** = (Date of EOT visit performed if not available then Date of Withdrawal on EOT page in "PARTICIPANTS TRIAL COMPLETION ASSESSMENT" domain - Date of last Dose Dispense at cycle i/Day j) +1.

Overall Compliance of study Drug:-

- Total Compliance to Treatment for the Study for patient y = [Compliance to treatment at cycle i/Day j for patient i + Compliance to treatment at cycle i/Day j+1 for patient i + …… + Compliance to treatment at last cycle/Day for patient y when dose is administered] / Total Number of cycles when dose of RP6530 administered to patient y

Temporarily hold of study drug or dose reduction or discontinuation of study drug, if that happen during the middle of the cycle, will not be accounted in the calculation of the compliance during that cycle as the precise data is not available in eCRF; and thus, in overall compliance calculation.

5.2 Exposure to Study Drug

Listing will be provided for administration details of RP6530 including start time of dosing, total calculated dose along with total dose administered at each cycle during patient participation in study (total duration of exposure for each patient and duration from previous dose).

Duration of exposure/ Duration of treatment will be analyzed and tabulated for overall and cycle wise using following formula. Table will be summarized as n, Mean, Standard Deviation, Median, and Range (Max - Min) by using safety population.

Drug Exposure / Duration of Treatment Formula -

Duration of Drug Exposure / Duration of Treatment for respective visits:-

- Duration of Drug Exposure / Duration of Treatment at cycle i/Day j except Last visit = (Date of Dose Dispense in next cycle i/Day j which is nothing but the date of tablets return of previous visit - Date of Dose Dispense in current cycle i/Day j)
- Duration of Drug Exposure / Duration of Treatment for Last visit = (Date of EOT visit performed if not available then Date of Withdrawal on EOT page in "PARTICIPANTS TRIAL COMPLETION ASSESSMENT" domain - Date of last Dose Dispense at cycle i/Day j) +1

Duration of Drug Exposure / Duration of Treatment for overall visit:-

- Duration of Drug Exposure / Duration of Treatment = (Date of EOT visit performed if not available then Date of Withdrawal on EOT page in "PARTICIPANTS TRIAL COMPLETION ASSESSMENT" domain - Date of first Dose Dispense at cycle 1/Day 1) +1

5.3 Statistical Analytical Issues

5.3.1 Changes in the Planned Analysis From Protocol

There is no change in any planned analysis from protocol

6. Statistical Tables to be Generated

Following are the minimum tables presented in Statistical analysis

14.1 Demographic and Baseline Summary

Table 14.1.1 Summary of Patient Disposition and Populations

Table 14.1.2 Summary of Reasons for Screen Failures and Dropouts Prior to Dosing

Table 14.1.3 Summary of Reason for Discontinuations

Table 14.1.4 Summary of Major Protocol Deviations

Table 14.1.5 Summary of Minor Protocol Deviations

Table 14.1.6 Summary of Demographics and Other Baseline Characteristics

Table 14.1.7 Summary of Surgical and Medical History by Dose Cohort

Table 14.1.8 Summary of Concomitant/Current Illness at the Time of Start of the Treatment by Dose Cohort

Table 14.1.9 Summary of Prior Medications Stopped before Treatment Start, by Dose Cohort by ATC Class

Table 14.1.10 Summary of Prior Medications Ongoing at Treatment Start, by Dose Cohort by ATC Class

Table 14.1.11 Summary of Prior Therapies, by Dose Cohort by ATC Class

Table 14.1.12 Summary of Baseline Characteristics – Serology at Baseline by Dose Cohort

Table 14.1.13 Summary of DLT Assessment by Dose Cohorts of Dose Escalation Phase

14.2 Efficacy Analysis

14.2.1 Primary Efficacy Analysis …..Not Applicable

14.2.2 Secondary Efficacy Analysis

Table 14.2.2.1 Summary of Best Overall Response (BOR) – ITT Population

Table 14.2.2.2 Summary of Best Overall Response (BOR) – PP Population

Table 14.2.2.3 Summary of Overall Response Rate (ORR) by Dose Cohort

Table 14.2.2.4 Summary of Duration of Response (DoR) by Dose Cohort

Table 14.2.2.5 Summary of Duration of Response (DoR) in without Radiologically Documented Dieases Progression by Dose Cohort

14.3 Safety Analysis

14.3.1 Display of Adverse Events

Table 14.3.1.1 Overview of Non-Treatment Emergent Adverse Events

Table 14.3.1.2 Overview of Treatment Emergent Adverse Events by Dose

Table 14.3.1.3 Summary of All Treatment Emergent Adverse Events by SOC and PT by Dose

Table 14.3.1.4 Summary of Dose Limiting Toxicities by SOC and PT by Dose

Table 14.3.1.5 Summary of Protocol Defined Events of Special Interest by SOC and PT by Dose

Table 14.3.1.6 Summary of All Treatment Emergent Adverse Events by Intensity, Outcome for Each Dose

Table 14.3.1.7 Summary of All Related Treatment Emergent Adverse Events by Intensity, Outcome for Each Dose

Table 14.3.1.8 Summary of All Treatment Emergent Adverse Events Leading to Discontinuations by SOC and PT by Dose

Table 14.3.1.9 Summary of Related Treatment Emergent Adverse Events Leading to Discontinuations by SOC and PT by Dose

Table 14.3.1.10 Summary of All Treatment Emergent Adverse Events by Relatedness by Dose

Table 14.3.1.11 Summary of Non Serious Treatment Emergent Adverse Events by Relatedness by Dose

14.3.2 SAE Data and Listings of Deaths, Other Serious and Significant Events

Table 14.3.2.1 Overview of Serious Treatment Emergent Adverse Events by Dose

Table 14.3.2.2 Summary of Serious Treatment Emergent Adverse Events by SOC and PT by Dose

Table 14.3.2.3 Summary of All Serious Treatment Emergent Adverse Events by Intensity, Outcome for Each Dose

Table 14.3.2.4 Summary of All Related Serious Treatment Emergent Adverse Events by Intensity, Outcome for Each Dose

Table 14.3.2.5 Summary of All Serious Treatment Emergent Adverse Events Leading to Discontinuations by SOC and PT by Dose

Table 14.3.2.6 Summary of Related Serious Treatment Emergent Adverse Events Leading to Discontinuations by SOC and PT by Dose

Table 14.3.2.7 Summary of All Fatal Serious Treatment Emergent by SOC and PT by Dose

Table 14.3.2.8 Summary of Serious Treatment Emergent Adverse Events by Relatedness by Dose

Table 14.3.2.9 Summary of Grade 3 and Grade 4 Treatment Emergent Adverse Events (Signficant AE) by SOC and PT by Dose

Table 14.3.2.10 Summary of Grade 3 and Grade 4 Treatment Emergent Adverse Events (Signficant AE) by Relatedness by Dose

14.3.4 Laboratory Data and Abnormal Laboratory Value Listings

Table 14.3.4.1 Summary of Abnormal Laboratory Results by Dose Cohort and CTCAE Grade

Table 14.3.4.2 Summary of Shifts from Baseline to Each Post Baseline visits for Hematology Laboratory result by Dose Cohort

Table 14.3.4.3 Summary of Shifts from Baseline to Each Post Baseline Visits for Biochemistry Laboratory result by Dose Cohort

Table 14.3.4.4 Summary of Shifts from Baseline to Each Post Baseline Visits for Urinalysis Laboratory result by Dose Cohort

Table 14.3.4.5 Summary of Shifts from Baseline to Each Post Baseline Visits for Serum Electrolyte Laboratory result by Dose Cohort

14.3.5 Other Safety

14.3.5.1 Vitals, Physical Examinations, ECG, ECOG, Pregnancy and Radiological Evaluation Data

Table 14.3.5.1.1 Summary of Shifts from Baseline to Each Post Baseline Visits for Vital Sign result by Dose Cohort

Table 14.3.5.1.2 Summary of Shifts from Baseline to Each Post Baseline Visits for Physical Examination result by Dose Cohort

Table 14.3.5.1.3 Summary of Shifts from Baseline to Each Post Baseline Visits for ECG result by Dose Cohort

14.3.5.2 Concomitant Medications

Table 14.3.5.2.1 Summary of Concomitant Medications/Therapies, by Dose Cohort by ATC Class

14.3.5.3 Drug Compliance Analysis

Table 14.3.5.3.1 Drug Compliance – Safety Population

Table 14.3.5.3.2 Duration of Exposure / Treatment – Safety Population

7. Statistical Listings to be Generated

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Listing 14.3.2.1 Fatal SAEs

Listing 14.3.2.2 Non-Fatal SAEs

14.3.4 Abnormal Findings

Listing 14.3.4.1 Abnormal Laboratory Values

Listing 14.3.4.2 Abnormal Physical Examination Results

Listing 14.3.4.3 Abnormal Vital Signs Values

16.2 Patient Data Listings

16.2.1 Discontinued Patients

Listing 16.2.1.1 Screen Failures and Drop out During Screening

Listing 16.2.1.2 Eligibility Review

Listing 16.2.1.3 Reasons for Withdrawal of Patient from the Study

16.2.2 Protocol Deviations

Listing 16.2.2.1 Protocol Deviations during the Study – Major

Listing 16.2.2.2 Protocol Deviations during the Study – Minor

16.2.3 Patients Excluded from the Efficacy Analysis

Listing 16.2.3.1 Analysis Populations

16.2.4 Demographic Data

Listing 16.2.4.1 Demographic Data

Listing 16.2.4.2 Baseline Disease Characteristics

Listing 16.2.4.3 Medical History, Surgical History and Concomitant/Current Illnesses

Listing 16.2.4.4 Prior Medication

Listing 16.2.4.5 Prior Therapy

Listing 16.2.4.6 Smoking and Alcohol Status

Listing 16.2.4.7 Baseline Serology Assessment

16.2.5 Compliance and Study Drug Exposure Data

Listing 16.2.5.1 Study Drug Dose Exposure – Drug Dispensed Details

Listing 16.2.5.2 Study Drug Dose Exposure – Drug Accountability

Listing 16.2.5.3 Study Drug Compliance Visit Wise

16.2.6 Efficacy Listings

Listing 16.2.6.1 Radiological Examination

Listing 16.2.6.2 Photographs for Disease Evaluation

Listing 16.2.6.3 Bone Marrow Aspirate Specimen

Listing 16.2.6.4 Morphology & Cytogenetic Evaluations

Listing 16.2.6.5A Disease Characteristics – Staging, CTCL Patients

Listing 16.2.6.5B Disease Characteristics – Staging, PTCL Patients

Listing 16.2.6.6 Disease Assessment for CTCL Patients - Skin [Modified Severity Weighted Assessment Tool (mSWAT)]

Listing 16.2.6.7 Disease Assessment for CTCL Patients - Skin (Composite Assessment of Index Lesion Severity)

Listing 16.2.6.8 Disease Assessment for CTCL Patients - (Skin Biopsy and Immuno-phenotyping)

Listing 16.2.6.9 Disease Assessment for CTCL Patients - Radiological Assessment of Lymph Node

Listing 16.2.6.10 Disease Assessment for CTCL Patients - Lymph Node, Visceral involvement and Blood involvement

Listing 16.2.6.11 Disease Assessment for PTCL Patients - Lymphoma, Lesion

Listing 16.2.6.12 Disease Assessment for PTCL Patients - Dominant Nodes

Listing 16.2.6.13 Disease Assessment for PTCL Patients – Non-Dominant Nodes

Listing 16.2.6.14 Disease Assessment for PTCL Patients – Extra-nodal Lesions

Listing 16.2.6.15 Disease Assessment – Response

Listing 16.2.6.16 Visit Wise Response

16.2.7 Adverse Events Listings

Listing 16.2.7.1 Non Treatment Emergent Adverse Events

Listing 16.2.7.2 Treatment Emergent Adverse Events

Listing 16.2.7.3 Treatment Emergent Adverse Events – Dose Limiting Toxicities

Listing 16.2.7.4 Treatment Emergent Adverse Events – Significant AEs

Listing 16.2.7.5 Treatment Emergent Serious Adverse Events

16.2.8 Listings of Individual Laboratory Measurements by Patient

Listing 16.2.8.1 Listing of Clinical Laboratory Normal Reference Ranges

Listing 16.2.8.2 Clinical Laboratory Evaluations by Patients - Hematology

Listing 16.2.8.3 Clinical Laboratory Evaluations by Patients - Biochemistry

Listing 16.2.8.4 Clinical Laboratory Evaluations by Patients - Urinalysis

Listing 16.2.8.5 Clinical Laboratory Evaluations by Patients - Additional Laboratory Tests

Listing 16.2.8.6 Clinical Laboratory Evaluations by Patients - Serum Electrolyte

16.2.9 Other Safety Listings

Listing 16.2.9.1 12-Lead ECG Results

Listing 16.2.9.2 ECOG Performance Status

Listing 16.2.9.3 Physical Examination

Listing 16.2.9.4 Vital Signs

Listing 16.2.9.5 Pregnancy Test

Listing 16.2.9.6 Concomitant Medication

8. Statistical Graphs to be Generated

14.3 Efficacy Figures

Figure 14.3.1 Duration of Treatment in Efficacy Evaluable Patients – ITT Population

Figure 14.3.2 Percent Change in Target Lesion – ITT Population