STATISTICAL ANALYSIS PLAN

An integrated Phase I/IIa, randomized, double-blind, placebo controlled study to evaluate the safety, tolerability and pharmacokinetics of single and multiple ascending dose(s) of oral RP3128 (CRAC channel modulators) in healthy volunteers and to evaluate the effect on Late Phase Asthmatic Response(LAR) to allergen challenge in patients with mild asthma

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STATISTICAL ANALYSIS PLAN Final Version Approvals

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Reviewed By: Signature: _____ Prajak Barde Medical Director Rhizen Pharmaceuticals SA	Date: 23 June 2017.

Revision History

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1 GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT (SGOT)	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
AST (SGPT)	Aspartate Aminotransferase
AUC	Area Under the Curve
AUC_{0-t}	Area Under the Plasma-Concentration Time Curve from Zero Up to the Last Measurable time point
AUC_{0-inf}	Area Under the Curve from Zero extrapolated to infinite time
BUN	Blood Urea Nitrogen
bpm	Beats per minute
CFB	Change from Baseline
CK	Creatinine kinase
CM	Concomitant Medication
C_{av}	Average concentration during the dosing interval
C_{max}	Peak Drug Concentration
C_{min}	Lowest observed plasma concentration in the dosing interval
C_{trough}	Plasma concentration at the end of the dosing interval
CRAC	Calcium Release Activated Calcium Channel
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FSH	Follicular Stimulating Hormone
GGT	Gamma Glutamyl Transpeptidase
HCV	Hepatitis C Virus
HIV	Human Immune Deficiency Virus
Hr	Hour
HV	Healthy Volunteers

Abbreviation	Description
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
LAR	Late Phase Asthmatic Response
LPS	Lipopolysaccharide
K_{el}	Apparent terminal elimination rate constant
MAD	Multiple ascending dose
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of mercury
MMSE	Mini Mental State Examination
MTD	Maximum Tolerated Dose
PCP	Phencyclidine
PFT	Pulmonary Function Test
PI	Principal Investigator
PK	Pharmacokinetic
PR	P wave, R wave interval
PT	Preferred Term
QRS	Q wave, R wave, and S wave complex
QTcB	QT wave complex corrected for heart rate using Bazette's formula
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SDTM	Study Data Tabulations Model
SOC	System Organ Class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
$t_{1/2}$	Half life
TEAE	Treatment Emergent AE
T_{max}	Time of C_{max}
K_{el}	Terminal Rate Constant

2 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide a thorough description of statistical methods and presentation of the study data to be used for the analysis of data generated from the Single Ascending Dose (SAD) part and the Multiple Ascending Dose (MAD) part of the clinical trial described in protocol: "An integrated Phase I/IIa, randomized, double-blind, placebo controlled study to evaluate the safety, tolerability and pharmacokinetics of single and multiple ascending dose(s) of oral RP3128 (CRAC channel modulators) in healthy volunteers and to evaluate the effect on Late Phase Asthmatic Response(LAR) to allergen challenge in patients with mild asthma."

This SAP is based on protocol RP3128-1601 Final Version 2 dated 22March2017. This document provides the detail statistical analysis plan for the SAD part and the MAD part of the protocol.

The SAP includes details of data handling procedures and statistical methodology. The SAP also provides the shells for the Tables, Listings, and Graphs (TLGs) to be delivered to Rhizen Pharmaceuticals SA, Inc.

The final statistical analysis will proceed in accordance with this SAP as approved by both Rhizen Pharmaceuticals SA and Inflamax Research Limited. Any deviation from this SAP will be documented in the final Clinical Study Report (CSR).

For this study, the Study Data Tabulation Model (SDTM) as well as the Analysis Data Model (ADaM) specifications will be prepared by Inflamax Research and provided to the Sponsor. SDTM Model 1.4 and SDTM Implementation Guide (SDTM IG) version 3.2 will be used ADaM Model 2.1 and ADaM Implementation Guide (ADaM IG) version 1.0 will be used. SDTM/ADaM datasets will be provided separately for SAD and MAD parts.

The following documents were also reviewed in preparation of this SAP:

- Electronic Case Report Form (eCRF) SAD Final Version 1.0 dated 31OCT2016
- Electronic Case Report Form (eCRF) MAD Final Version 1.0 dated 31OCT2016
- eCRF Completion Guidelines SAD&MAD Final v1.0 dated 31OCT2016
- Data Management Plan Final v1.0 dated
- Codelist Details dated 28OCT2016
- Safety Monitoring Committee charter, version 2.0, dated 21DEC2016

3 TUDY OBJECTIVES

The study objectives related to the SAD and MAD portion of the trial are described below.

3.1 PRIMARY OBJECTIVE

- Part 1 (SAD) - to investigate the safety and tolerability of single ascending oral doses of RP3128 in Healthy Volunteers (HV).
- Part 2 (MAD) - to investigate the safety and tolerability of once a day multiple ascending oral doses of RP3128 at three dose levels (highest safe doses identified in SAD) in HV.

3.2 SECONDARY OBJECTIVE

- Part 1 (SAD) - To characterize the pharmacokinetic (PK) profile of single ascending oral doses of RP3128 in HV.
- Part 2 (MAD) - To characterize the multiple dose PK profile of oral RP3128 at steady state when administered once day, at three dose levels in HV.
- Part 2 (MAD) - To evaluate ex-vivo effect of RP3128 on various biomarkers (Th1, Th2 and Th17 cytokines) following Lipopolysaccharide (LPS) or CD3/CD28 stimulation.

3.3 BRIEF DESCRIPTION

This is a phase I, single-center, double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability, and PK of single or multiple ascending dose (SAD or MAD) of RP3128 in healthy volunteers.

There were 5 cohorts in SAD and 3 cohorts in MAD. In the first part of the study (Part 1, SAD), single dose of RP3128/placebo was administered on Day 1. In the second part (Part 2, MAD), multiple doses of RP3128/placebo were administered once a day from Day 1 to Day 7. In both SAD and MAD, the cohorts were dosed sequentially so that a minimum of 8 days was allowed between dose of previous cohort and the initiation of next cohort. Progression to the next higher dose occurred only after confirming safety, tolerability and PK of existing dose. In case of safety concern, additional subjects may be added to cohort for safety assessment as per the decision of Safety Review Committee (SRC).

In addition, sentinel design was applied. Within each cohort, 2 sentinel subjects was dosed first for safety assessment. Safety and tolerability data up to 24 hours was reviewed along with any observation up to 36 hours by the investigator prior to dosing the remaining subjects at that dose level. The remainder of the cohort was dosed sequentially at least 48 hours after confirming safety and tolerability of sentinel cohort.

3.4 SUBJECT SELECTION

Healthy male subjects and female subjects of non-childbearing between the ages of 18 and 45 years were randomized at the study site.

All subjects must give written informed consent to be enrolled into the study Subjects were considered eligible to participate in this study if all inclusion criteria was satisfied and no exclusion criteria was met at screening. Please refer to the Protocol for detailed inclusion/exclusion criteria.

3.5 DETERMINATION OF SAMPLE SIZE

The sample size has been selected without performing a power calculation to provide descriptive information on the safety, tolerability, and PK following administration of RP3128. This trial enrolled up to 56 HV (32 in SAD and 24 in MAD). Number of subjects enrolled in this study is in line with standard phase I studies and is considered sufficient to provide descriptive information on the pharmacokinetics, safety and tolerability of RP3128 while minimizing exposure to humans. The actual number of dose cohorts will depend upon the emerging safety data.

3.6 TREATMENT ASSIGNMENT

Subjects who entered the treatment phase was assigned a unique 4-digit randomization number in the format of XYZZ to identify study part (X), cohort number (Y) and subject identifier (ZZ). The first 2 randomization numbers XY01 and XY02 in each cohort represents the sentinel subjects in Part number X and cohort number Y. For SAD and MAD parts, X is 1 and 2 respectively. For the SAD part, number Y is denoted by 1 to 5 for 5 cohorts, whereas for MAD part the number Y is denoted by 1 to 3 for 3 cohorts. Once any subject or randomization number is assigned, it cannot be reassigned to any other subject.

Allocation to treatment was based on a predetermined random order. Randomization to RP3128 or placebo took place for each cohort separately. The randomization lists were generated by an unblinded staff at Inflamax Research using the computer program Statistical Analysis System (SAS®) and managed according to the site's standard operating procedures (SOPs). Separate randomization ratios were used for study SAD Part and MAD Part as indicated in the tables below.

Dose escalation cohorts for Part 1 (SAD)

Cohort	Dose level	n	Sentinel cohort RP3128: Placebo	Remaining cohort RP3128: Placebo	Total cohort RP3128: Placebo
S1	25 mg	4	1:1	2:0*	3:1
S2	50 mg	6	1:1	3:1	4:2
S3	100 mg	6	1:1	3:1	4:2
S4	200 mg	8	1:1	5:1	6:2
S5	400 mg	8	1:1	5:1	6:2

*Single blind (subject)

Dose escalation cohorts for Part 2 (MAD)

Cohort	Dose level	N	Sentinel cohort RP3128: Placebo	Remaining cohort RP3128: Placebo	Total cohort RP3128: Placebo
M1	25 mg	8	1:1	5:1	6:2
M2	100 mg	8	1:1	5:1	6:2
M3	400 mg	8	1:1	5:1	6:2

3.7 ADMINISTRATION OF STUDY MEDICATION

Depending on the cohort, specific dose/doses of RP3128/placebo was dispensed by pharmacy staff during the study. RP3128/placebo capsules was administered orally in the morning with approximately 240 mL (8 fluid ounces) of water at room temperature by the subject. For SAD part, the doses in 5 planned cohorts were 25 mg, 50 mg, 100 mg, 200 mg and 400 mg. For MAD part, the doses in 3 planned cohorts were determined to be 25mg, 100mg, and 400mg considering the safety and PK profile of RP3128 in SAD.

4 ENDPOINTS

4.1 PRIMARY ENDPOINTS

The primary endpoints for both SAD and MAD parts are as follows:

- Incidence of AEs
- Changes in vital signs (blood pressure, pulse rate, respiratory rate, oral temperature) and weight
- Changes in 12-lead ECG parameters
- Changes in clinical laboratory assessments (hematology, chemistry, urinalysis)

4.2 SECONDARY ENDPOINTS

The secondary endpoints include PK parameters and biomarker assessments

SAD-PK Endpoints:

- Maximum observed plasma concentration (C_{max})
- Time to maximum observed plasma concentration (T_{max})
- Area under the plasma concentration-time curve from time zero until the last time point with measurable concentration (AUC_{0-t})
- Area under the plasma concentration-time curve from time zero to infinity (AUC_{0-inf})
- Apparent termination elimination rate constant (K_{el})
- Apparent terminal elimination half-life ($t_{1/2}$)

MAD-PK Endpoints:

- Maximum observed plasma concentration in the dosing interval (C_{max}) (Day 1, Day 7)
- Lowest observed plasma concentration in the dosing interval (C_{min}) (Day 7)
- Plasma concentration at the end of the dosing interval (C_{trough}) (Day 3, Day 5, Day 7)
- Average concentration during the dosing interval (C_{av}) (Day 7)
- Time to maximum plasma concentration (T_{max}) (Day 1, Day 7)
- Area under the plasma concentration-time curve from time zero until the last time point with measurable concentration (AUC_{0-24}) (Day 1, Day 7)
- Degree of fluctuation [(C_{max}-C_{min})/C_{av}] (Day 7)
- Swing [(C_{max}-C_{min})/C_{min}] (Day 7)
- Terminal half-life ($t_{1/2}$) (Day 1, 7)

MAD-Biomarker Endpoints:

- Levels of various biomarkers (Th1, Th2 and Th17 cytokines) following LPS or CD3/CD28 stimulation

5 ANALYSIS POPULATION

5.1 RANDOMIZED POPULATION

The randomized population consists of all eligible subjects who are randomized to receive a treatment regardless whether they are actually treated. These subjects are grouped by their randomized treatment group. The randomized population will be used to summarize subject disposition from randomization through termination.

5.2 SAFETY POPULATION

The Safety population will include randomized subjects who receive at least one dose of study drug (RP3128 or placebo) during treatment phase. Subjects will be analyzed as treated, if any subjects received the study drug different from the drug they were randomized to receive. There will be separate safety populations each for SAD and MAD parts. The Safety population will be used for all analyses of safety endpoints, biomarker endpoints, as well as demographics and baseline characteristics.

5.3 PHARMACOKINETIC (PK) POPULATION

The PK population will include all safety subjects with sufficient concentration-time data to determine PK parameters and no major protocol deviations. The PK population will be used for all analyses of PK endpoints.

5.4 PROTOCOL DEVIATIONS

All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment will be listed. The list of protocol deviations will be reviewed by the Sponsor, the PI, the study statistician and the study scientist before unblinding the study.

6 GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1 SUMMARY STATISTICS

The standard summary statistics that will be calculated for quantitative and qualitative variables are:

- Quantitative:
  - Standard Statistics for both Safety/PK: Number of subjects, mean, median, standard deviation (SD), minimum and maximum of the raw data
  - Additional Statistics for PK: coefficient of variance (PK concentration and PK parameters), geometric mean, and geometric CV (%) (PK parameters AUC and Cmax in SAD part and AUC_{0-24}, C_{max}, C_{min}, C_{trough} in MAD part)
- Qualitative: number of subjects (n), number of missing observations (nmiss), absolute and relative frequencies (%) per category.

Demographics and disposition will be summarized by treatment group and overall.

Data collected pre- and post-dose during the treatment period (e.g., vital signs, ECG, and clinical laboratory) will be summarized by treatment group (dose level), visit and/or time point. For quantitative variables (ECG measurements, vital signs, hematology, etc.), change from baseline will be calculated and summarized by treatment, visit and/or time point together with baseline and post-dose value. For qualitative variables (e.g., ECG interpretation, urinalysis), standard summary of frequencies will be calculated by treatment, visit and/or time points. For safety lab data only, shift table will be produced to present the change of reference range indicator from baseline to post-dose. PK parameters will be summarized by treatment group, and visit (if applicable). All subjects assigned and treated with Placebo in different cohorts will be pooled together and summarized as a single group.

6.1.1 Summary Statistics Reporting Precision

Summary statistics will be presented to the following degree of precision:

Table 1. Reporting Precision

Statistics	**Degree of Precision**
Mean (of all kinds), Median	One more decimal place than the raw data
Standard deviation, Standard error	Two more decimal places than the raw data

Minimum, Maximum	The same number of decimal places as the raw data
Percent, Coefficient of Variance	Two decimal places for PK parameters, and one decimal place for all other parameters
PK Concentration, AUC, Cmax	The same number of decimal places as LLOQ

All fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12, - 0.30, not .12, - .30).

6.2 KEY DEFINITIONS

The day of administration of the first dose of study drug during the treatment period is defined as Study Day 1. Study Day -1 is the day before dosing, all assessments prior to Study Day 1, including the Screening and Check-in Visits, will have negative study days.

The baseline observation will be the last non-missing value prior to the first dose of study drug.

Nominal Time is the scheduled measurement time relative to time 0. Time 0 is precisely defined for each analysis below.

For AEs, onset time from dosing will be calculated as the difference between the event and dosing start date/time. Onset time from dosing will be expressed in days, hours and minutes. If time is missing, onset time from dosing will be calculated as the difference between the start date and dosing date plus 1 and expressed in days when the event date is on or after the dosing date; otherwise, onset time from dosing will be calculated only as difference between the start date and dosing date and expressed in negative numbers.

Duration will be calculated for AEs that resolve as the difference between the AE resolution date/time and onset date/time and will be expressed in days, hours and minutes. If time is missing, duration will be calculated as the difference between the resolution date and onset date plus 1 and expressed in days. AE onset time from dosing and duration of AE will only be derived when both start and end dates are complete.

6.3 ATTRIBUTION OF TREATMENT-EMERGENT AE FOR IMCOMPLETED AE DATE/TIME

AEs with incomplete start dates and times will be attributed to treatment according to the following algorithm:

1. Only the year is reported: If the year is after the year of the dose, the event will be considered as treatment-emergent. If the year is the same as the day of the dose, the event will not be considered as treatment-emergent.

2. Only the month and year are reported: If the month is after the month of the first dose, event will be considered as treatment-emergent. If the month is the same as the month of the first dose, the event will not be considered as treatment-emergent.
3. Only the time is missing: If the event occurred on or after the day of the first dose in the treatment period, then the event will be considered as treatment-emergent. Otherwise, the event will not be considered as treatment-emergent.

7 DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1 SUBJECT DISPOSITION AND WITHDRAWALS

For subject disposition, the following frequencies (number and percent) will be displayed by treatment group and overall for the randomized population:

- Subjects in the Randomized Population (number only)
- Subjects in the Safety Population (number only)
- Subjects in PK population
- Subjects who completed the study
- Subjects who discontinued early, as well as reasons for subject discontinuation

The denominators for the percent calculations will be the number of safety subjects per treatment group or overall.

A listing of randomization scheme will include the subject's identification, cohort, date of randomization, and treatment assignment.

Subjects' completion/discontinuation status will be listed by cohort/treatment and will include date of completion/early discontinuation, date of dosing and, for those who discontinued early, the specific reason(s) for discontinuation.

All deviations captured in eCRF will be listed. The list of protocol deviations will be reviewed by the Sponsor, the PI, the lead statistician and the study scientist and finalized before unblinding the treatment.

A listing of subjects excluded from the analysis populations will also be produced.

7.2 BASELINE CHARACTERISTICS

Demographics (age, sex, race, ethnicity), informed consent date, weight, height and BMI at screening will be listed and summarized using descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum for quantitative variables and the proportion of subjects for qualitative variables) by treatment group and overall for the safety population. No formal statistical comparison between groups will be performed.

Concomitant medication/medical history data, including clinical events, will be listed for all safety subjects.

7.3 TREATMENT COMPLIANCE

Subject must take study drug at the study site. Failure of treatment compliance will lead to termination of study. The necessary measures will be employed to ensure treatment compliance. The study drug will be dispensed or administered according to applicable standard operating procedures (SOPs). Study drug administration will be listed and ordered by cohort, treatment, subject and visit/day.

8 ANALYSIS OF PHARMACOKINETICS

The PK population will be used for all PK analysis and listings.

8.1 MEASUREMENTS

A 4 ml of blood sample were collected at each planned time point for measurement of drug concentration in plasma. The time and date of collection of each sample was recorded in CRF.

8.2 COLLECTION SCHEDULE

For SAD part, blood samples will be collected for plasma levels of RP3128 on Day 1 (Pre-dose, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0, 24.0 and 48 hr), Day 5, Day 8 and Day 15. For MAD part, blood samples will be collected for plasma levels of RP3128 on Day 1 (Pre-dose, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0 and 24.0 hr), Day 3, Day 5, Day 7 (Pre-dose, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0 and 24.0 hr), Day 9 (48 hr), Day 10 (72 hr), Day 11 (96 hr), Day 12 (120 hr), Day 13 (144 hr) and Day 15 (192 hr).

8.3 DERIVED DATA AND HANDLING OF MISSING OR BELOW LLOQ DATA

8.3.1 Derivation of PK Parameters

PK parameters for RP3128 will be derived with validated SAS programs for all RP3128 dose levels by non-compartmental analysis of the plasma concentration data using actual sampling times.

The following pharmacokinetic variables will be derived:

SAD:

- Maximum observed plasma concentration (C_{max})
- Time to maximum plasma concentration (T_{max})
- Terminal half-life ($t_{1/2}$)
- Area under the plasma concentration-time curve from time zero until the last measurable time point (AUC_{0-t})
- Area under the plasma concentration-time curve from time zero to infinity time (AUC_{0-inf})
- Elimination rate constant (K_{el})

MAD:

- Maximum observed plasma concentration in the dosing interval (C_{max}) (Day 1, Day 7)

- Lowest observed plasma concentration in the dosing interval (C_{min}) (Day 7)
- Plasma concentration at the end of the dosing interval (C_{trough}) (Day 3, Day 5, Day 7)
- Average concentration during the dosing interval (C_{av}) (Day 7)
- Time to maximum plasma concentration (T_{max}) (Day 1, Day 7)
- Area under the plasma concentration-time curve from time zero until the last time point with measurable concentration (AUC_{0-24}) (Day 1, Day 7)
- Degree of fluctuation [(C_{max}-C_{min})/C_{av}] (Day 7)
- Swing [(C_{max}-C_{min})/C_{min}] (Day 7)

The PK parameters will be estimated as follows:

- The C_{max} and the corresponding T_{max}, C_{min} and C_{trough} will be read directly from the concentration-time plot (observed data, not predicted data by the program).
- AUCs will be calculated using the linear trapezoidal rule.
- The terminal elimination rate constant (K_{el}) will be determined by log linear regression obtained on at least the 3 last quantifiable concentrations and will not include C_{max}. The adjusted square of the correlation coefficient (R-square adjusted) for the goodness of fit of the regression line through the data points must be at least 0.80 for the K_{el} value to be considered reliable. If fewer than 3 quantifiable concentrations are available after Cmax or if R-square is less than 0.80, the K_{el} will be left uncalculated.
- $t_{1/2}$ is calculated by the program as ln2/ K_{el}. If K_{el} is not calculable, then $t_{1/2}$ will also remain missing.
- The AUC from 0 to infinity is calculated by the program as: $AUC_{0-inf} = AUC_{0-t} + AUC_{t-inf}$ where t is the sampling time point of the last measurable concentration. AUC_{t-inf} is calculated by the program as: C_t/ K_{el}, where C_t is the observed concentration at time t and K_{el} is the elimination rate constant during the apparent terminal elimination phase. If K_{el} is not calculable, AUC_{0-inf} will be set to missing.
- The AUC extrapolation to infinity (AUC_{t-inf}) must be ≤20% of the total area for AUC_{0-inf} to be considered reliable.

8.3.2 Handling of Missing Plasma Concentration Data or below LOQ

Plasma concentrations can only be missing if the sample was not collected. These missing concentrations will be considered as non-informative missing and will not be imputed.

However, if a plasma sample was collected, but the resulting assay failed to detect a quantifiable concentration, these will be imputed in the following way:

- Concentration values below the assay's lower limit of quantification (<lower limit of quantification (LLOQ) or below the limit of quantification (BLQ)) in pre-dose samples and

in samples taken before the time of the first quantifiable concentration will be treated as zero.

- All sample collected prior to dosing will be treated as zero.
- Post-dose BLQ values after the first quantifiable time point that are flanked and followed by quantifiable concentrations will be set to LLOQ.
- Post-dose BLQ values after the first quantifiable time point that are not followed by quantifiable concentrations will be set to LLOQ.
- For PK profiles with no values reported above the LLOQ, these BLQ values will be set to LLOQ.

8.4 DATA SUMMARIZATION

PK parameters and plasma concentration data will be summarized by treatment using the following descriptive statistics (Table 2):

Table 2. PK Summary Statistics

Variable	Summarized with:
Plasma concentration at each time point	n, arithmetic mean, SD, CV%, minimum, median and maximum
AUCs, C_{max}, C_{min}, C_{trough}, C_{av}	n, arithmetic mean, SD, CV% (calculated as 100%*SD/mean), minimum, median, maximum, geometric mean and geometric CV% (calculated as $CV = 100\% \times \sqrt{e^{z^2} - 1}$, where z^2 is the variance of ln(PK parameter)
$t_{1/2}$, K_{el}, T_{max} ,degree of fluctuation, swing	n, arithmetic mean, SD, CV%, minimum, median, maximum

Samples taken outside the sampling windows may be excluded from by-time point summary statistics; this will be determined prior to unblinding.

8.5 DATA PRESENTATION

The actual sampling time of PK blood sample collection will be listed for each cohort and will include the deviation in time from the protocol scheduled time, if applicable.

Individual subject plasma concentration data will be listed by subject, time point and treatment and will be summarized at each time point by treatment group for the Safety population. Individual subject PK parameters will be listed in a table by subject and will be summarized by treatment group for the PK population.

PK parameters of secondary interest, namely R-square adjusted, the number of data points used for estimating K_{el}, the upper and lower time point used for estimation of K_{el}, and the % AUC extrapolation from t_{last} (last time point of blood draw) to infinity will be listed by subject and dose level/cohort to enable verification of the exclusions, if any, of data from the summary statistics of the PK parameters of primary interest.

9 SAFETY

The analysis population used for safety analyses will be the Safety population. Safety will be assessed on the basis of AE, clinical laboratory data, vital signs, ECG parameters, MMSE and physical examinations.

9.1 ADVERSE EVENTS

All subjects in the Safety population will be included in the adverse event analysis.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary (Version 19.1 or higher)

An AE is defined as any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign symptom (for example, an abnormal laboratory finding), or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

In this study, all AEs that occur after any subject has been screened through the post-treatment follow-up period, whether or not they are related to the study, must be recorded on the eCRF, and must include the following: date and time of onset, date and time of resolution, severity, seriousness, causality (relationship to study medication), actions required, and outcome. Clinically significant and severe AEs must be examined to determine whether they meet criteria of a dose-limiting toxicity.

A treatment-emergent AE (TEAE) is any that is new in onset or was aggravated in severity or frequency following the first dose of study drug, up to and including the last visit of the study. Treatment emergence will be determined by comparing the AE start date/time with the actual date/time of first dose. In the case that the AE start date/time are incomplete, treatment emergence will be imputed according to the algorithm in SAP Section 6.5.

Adverse events will be listed chronologically by cohort/treatment, subject and AE start date/time. This listing will include all data collected in the eCRF, along with the derived variables: onset time since first dose, duration of AE and the coded variables system organ class (SOC) and preferred term (PT). Time since dose and duration will be calculated as described in SAP Section 6.3. In addition, serious AEs (SAEs) will be listed separately, if any occurs.

The summary of AEs will be limited to TEAEs only. In cases where severity is missing for a TEAE, the TEAE will be considered to be the highest degree of severity: Severe. In cases where relationship information is missing for a TEAE, the TEAE will be considered to be reasonably related. Displays of TEAEs will include:

- Overall Summary of TEAEs

  This table will include the number of events, number and percent of subjects who experienced TEAEs, serious TEAEs, severe TEAEs, related TEAEs and TEAEs leading to study discontinuation, summarized by treatment group.

- Summary of TEAEs by SOC, PT and Treatment Group

  A summary of the number of events, number and percent of subjects who experienced at least one TEAE, as well as the number of events, number and percent of subjects who experienced each specific SOC, and PT will be presented by treatment group (including pooled placebo and pooled RP3128). If a subject has more than one occurrence of the same PT then the PT will be counted only once for that subject under the SOC at which it was experienced.

- Summary of TEAEs by SOC, PT, Treatment Group and Maximum Severity

  A summary of the number and percent of subjects who experienced at least one TEAE by maximum severity as well as the number and percent of subjects who experienced each specific SOC and PT by maximum severity will be presented by treatment group. For this analysis, if a subject has more than one occurrence of the same PT, then the PT will be counted only once for that subject under the maximum severity at which it was experienced.

- Summary of TEAEs by SOC, PT, Treatment Group and Maximum Relationship

  A summary of the number and percent of subjects who experienced at least one TEAE by maximum relationship as well as the number and percent of subjects who experienced each specific SOC and PT by maximum relationship will be presented by treatment group. For this analysis, if a subject has more than one occurrence of the same PT, then the PT will be counted only once for that subject under the maximum relationship at which it was experienced.

9.2 LABORATORY EVALUATIONS

All subjects in the Safety population will be included in the safety laboratory analysis.

9.2.1 Collection Schedule

At screening, Serology, Tuberculin test / QuantiFeron- TB®-Gold test, Alcohol and urine drug screening will be done to assess eligibility for the study. Drug screening includes opiates, methadone, cocaine, amphetamine, cannabinoids, barbiturates, and benzodiazepines. Alcohol will be screened using alcohol breath test. If the subject has a positive result, the subject will be considered a screen failure and must be excluded from the study. The result will be listed by cohort/treatment, subject and visit.

Female subjects will undergo a serum pregnancy test (quantitative β-HCG) test at screening.

UPT (Urine pregnancy tests) will be performed at later time points in case of suspected pregnancy. The result will be listed by cohort/treatment, subject and visit.

Follicular Stimulating Hormone (FSH) will be evaluated at screening to confirm post-menopausal status for the females who reported having no menses less than 12 months.

For SAD part, the clinical laboratory evaluations, including Clinical chemistry, hematology, serum electrolyte, coagulation and urinalysis, will be performed at screening, Day -1, Day 2, Day 3, Day 8 and Day 15. For MAD part, the clinical laboratory evaluations, including Clinical chemistry, hematology, serum electrolyte, coagulation and urinalysis, will be performed at screening, Day -1, Day 2, Day 5, Day 7, Day 8 and Day 15. If blood, nitrites or leukocytes are abnormal, automatically microscopic urinalysis will be performed. Additional investigations will be performed if clinically indicated.

Laboratory assessment times are shown below in Table 3.

Table 3. Laboratory Parameters Assessment Times

Visit/Day	Clinical Laboratory	Serology	FSH	Drug and alcohol screen	Pregnancy testing
Screening	✓	✓	✓	✓	✓
Day -1 (Check-in)	✓			✓	✓
Day 2	✓				
Day 3	✓(SAD)				
Day 5	✓(MAD)				
Day 7	✓(MAD)				
Day 8	✓				
Day 15	✓				

9.2.2 Derived and Imputed Data

Some numeric lab values may be reported as '>n.n' or <n.n; these will be analyzed in the summary statistics as n.n. For example, potassium recorded as >9.0 mmol/L would be summarized as 9.0 mmol/L.

Baseline is defined as the last non-missing observation prior to first dosing on Day 1.

9.2.3 Data Summarization and Presentation

Laboratory sample data and values from laboratory assessments will be listed chronologically by cohort/treatment, subject, and visit. Abnormal findings in laboratory data will be listed with a flag for clinical significance based on investigator judgment. Abnormal laboratory findings will also be provided in a separate listing.

For quantitative data, change-from-baseline (CFB) will be calculated as the difference between the post-dose visit and baseline. For the SAD part, CFB will be calculated for Day 2, Day 3 (at discharge), Day 8, and Day 15. For the MAD part, CFB will be calculated for Day 2, Day 5, Day 7, Day 8 (at discharge), and Day 15.

The laboratory will assign a reference range indicator to all test results by comparing the actual test value to the reference range. The quantitative results will have indicator values of Low, High, and Normal, while the qualitative results will have indicator values of Normal and Abnormal. . The investigator or designee will review non-normal results to judge their clinical significance.

Quantitative results will be summarized for baseline, post-dose visits and CFB values by treatment group using standard summary statistics (n, mean, SD, minimum, median and maximum). Qualitative results (e.g., some tests in urinalysis) will be summarized by treatment group using frequency and percentage. The reference range indicator data will also be tabulated using frequency and percentage for both quantitative and qualitative results. No inferential tests will be conducted on lab data.

In addition, 3 by 3 shift tables will be produced to compare the change in reference range indicator from baseline to Day 3 for the SAD / Day 8 for the MAD part for each laboratory test. For parameters where only two possible values are available (i.e., Normal and Abnormal), the Abnormal values will be counted as High (H) in the 3 by 3 table.

9.3 VITAL SIGNS

All subjects in the Safety population will be included in the vital signs analysis.

9.3.1 Measurements

Vital signs will consist of blood pressure (systolic and diastolic blood pressure, mmHg), heart rate (beats per minute (bpm)), respiratory rate (breaths/min), temperature (°C) and weight. At

screening, vital signs will be assessed in the supine position after the subject has rested for at least 3 minutes. Blood pressure and pulse will be assessed again after three minutes in the standing position. At other time points, vitals will be measured after 3 minutes supine rest. Vitals should be completed within +/- 30 minute of schedule timing to avoid overlapping.

Height and weight (without shoes) will be collected at Screening and BMI will be calculated. Height, weight and BMI will be collected and calculated at other time points (check-in, follow-up and ET visit).

9.3.2 Collection Schedule

For SAD, vital signs on screening, Day -1 (at the time of admission), Day 1 (pre-dose, 30 min, 1, 2, 4, 6, 8, 12 and 24 hrs post dose), Day2, Day 3, Day 5, Day 8 and Day 15. For MAD, vital signs on screening, Day -1 (at the time of admission), Day 1 & Day 2 (pre-dose, 30 min, 1, 2, 4, 6, 8, 12 and 24 hrs post dose), Day 3, Day 4, Day 5, Day 6, Day 7 (pre-dose, 30 min, 1, 2, 4, 6, 12 hrs post dose), Day 8, Day 9, Day 11 and Day 15. Assessment times for vital sign parameters are presented below in Table 4 & 5.

Table 4. Vital Sign Assessment Times (SAD)

Visit/Day	Vital Sign Assessment Times
Screening	✓
Check-in Day -1	✓
Day 1 (Treatment)	pre-dose, 30 min, 1, 2, 4, 6, 8, 12 and 24 hrs post dose
Day 3 (Discharge)	✓
Day 5	✓
Day 8	✓
Day 15	✓

Table 5. Vital Sign Assessment Times (MAD)

Visit/Day	Vital Sign Assessment Times
Screening	✓
Check-in Day -1	✓

Day 1 (Treatment)	Pre-dose, 30 min, 1, 2, 4, 6, 8, 12 and 24 hrs post dose
Day 3 (Treatment)	✓
Day 4 (Treatment)	✓
Day 5 (Treatment)	✓
Day 6 (Treatment)	✓
Day 7 (Treatment)	Pre-dose, 30 min, 1, 2, 4, 6, 8, 12 and 24 hrs post dose
Day 8 (Discharge)	✓
Day 9	✓
Day 11	✓
Day 15	✓

9.3.3 Derived and Imputed Data

Baseline will be defined as the last non-missing observation prior to the dosing on Day 1.

9.3.4 Data Summarization and Presentation

Vital signs data will be listed chronologically by cohort/treatment, subject, visit/day, and time point when applicable.

Baseline values, absolute values and change from baseline for each post-dose time point will be summarized by treatment group using standard descriptive statistics. Off-treatment vital signs (e.g., Screening, Day -1, Unscheduled visit) will be listed but not otherwise analyzed. No inferential tests will be conducted.

Weight (without shoes) is measured at screening, check-in, follow-up and ET visit, the screening observation is used to summarize demographics, and the last non-missing observation prior to dosing on Day 1 (mostly likely the check-in observation) is defined as baseline to calculate weight change at post-doing visits.

9.4 ECG

All subjects in the Safety population will be included in the ECG analysis.

For SAD, a standard 12-lead ECG will be performed with the subject in a supine position at

Screening, Day -1 (at the time of admission), Day 1 (pre-dose, 15, 30, 45 min, 1, 2, 4, 6, 8, 12 and 24 hrs post dose), Day 3, Day 5, Day 8 and Day 15 or Early Termination. For MAD, a standard 12-lead ECG will be performed with the subject in a supine position at Screening, Day -1 (at the time of admission), Day 1 (pre-dose, 15, 30, 45 min, 1, 2, 4, 6, 8, 12 and 24 hrs post dose), Day 5, Day 7 (pre-dose, 15, 30, 45 min, 1, 2, 4, 6, 8, 12 and 24 hrs post dose), Day 8 and Day 15 or Early Termination. Triplicate ECG will be taken 1 minute apart on screening, Day 1 (pre-dose) and for confirmation of abnormality detected in the single ECG measurement based on Investigator judgement.

For each assessment, the ECG will be reviewed by the qualified physician and the interpretation will be recorded in the eCRF as normal, abnormal but not clinically significant, abnormal and clinically significant. In addition, the standard ECG parameters including ventricular rate (VR), and intervals for PR, QRS, QT, and QTcB (Bazette's corrections for heart rate) will be recorded.

Baseline will be defined as the last non-missing observation prior to dosing on Day 1.

All ECG data will be listed chronologically by cohort/treatment, subject, visit/day, and time point. Abnormal ECG results will be provided in a separate listing.

Overall interpretation of ECG measurements will be summarized by treatment at each time point using frequencies. Baseline values, absolute values, and CFB will be summarized by treatment group using standard descriptive statistics for VR, PR interval, QRS duration, and QT interval. Off-treatment ECG data (e.g., Screening, Day -1, and Unscheduled visits) will be listed but not otherwise analyzed. No inferential tests will be conducted on ECG data.

9.5 PHYSICAL EXAMINATION

For SAD, a complete physical examination will be performed at screening, Day -1, Day 3, Day 8 and Day 15, or if necessary at the Early Termination visit. For MAD, a complete physical examination will be performed at screening, Day -1, Day 4, Day 8 and Day 15, or if necessary at the Early Termination visit. This exam will include general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed. Information for all physical examinations must be included in the source documentation at the study site and will not be recorded the CRF. Significant findings that are present prior to informed consent are included in the Relevant Medical History CRF. Significant findings observed after informed consent signature which meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event CRF. No listings and summary tables will be produced separately.

9.6 COGNITIVE TEST

A cognitive test (e.g. Mini-Mental State Examination (MMSE)) will be performed at Screening and Day 3 (SAD)/ Day 8 (MAD) to assess the effect of drug on cognitive function.

MMSE data will be listed chronologically by cohort/treatment, subject, and visit/day. The classification of MMSE results as normal/abnormal follows the rules in Table 6. Such information will also be included in the listing.

Baseline will be defined as the observation collected at screening. Baseline values, absolute values, and CFB will be summarized by treatment group using standard descriptive statistics. No inferential tests will be conducted on MMSE data.

Table 6. Classification of Normal/Abnormal MMSE Results

Classification	Description	Rules
Normal	No cognitive impairment	Score 24-30 (inclusive)
Abnormal	Cognitive impairment	Score <24

10 EXPLORATORY ANALYSES

Exploratory assessments will be conducted on blood biomarkers (Th1, Th2 and Th 17 cytokines) in MAD part only. Blood samples will be collected at baseline (Day1, pre-dose), and Day 7 (pre-dose and 4 hrs post dose). See laboratory manual for biomarker processing instructions.

In the descriptive analysis, two types of baselines are considered to calculated CFB values. First, set Day 1 pre-dose value as baseline and calculate CFB for all collection time points after the first dosing on Day 1. Second, set Day 7 pre-dose value as baseline and calculate CFB for the 4-hour post-dose time point on Day 7. Descriptive statistics (number of observations, mean, standard deviation, median, minimum and maximum) will be provided for baseline (Day 1, pre-dose), Day 7 (Pre-dose), change from Baseline to Day 7 (Pre-dose), Day 7 (4 hrs Post-dose), change from Baseline to Day 7 (4 hrs Post-dose), and change from Day 7 (Pre-dose) to Day (4 hrs Post-dose) by treatment.

Paired t-test will be applied on CFB values 1) between Day 1 pre-dose and Day 7 (pre-dose) and 2) between Day 7 pre-dose and Day 7 4 hrs post-dose to determine whether the change within placebo and RP3128 is significant or not.

The CFB values in cytokine expression levels will be compared between placebo and RP3128 using an ANCOVA with the CFB values as the dependent variable, treatment as a fixed effect and corresponding baseline as a covariate. Three different types of CFB will be used: 1) CFB from Day 1 (Pre-dose) to Day 7 (Pre-dose), 2) CFB from Day 1 (Pre-dose) to Day 7 (4 hrs Post-dose), and 3) CFB from Day 7 (Pre-dose) to Day 7 (4 hrs Post-dose). The LSMeans, Standard Errors for each treatment and treatment difference will be presented together with the corresponding 95%-confidence interval and p-value.

11 INTERIM ANALYSES

There is no interim analysis planned in this study. Please note that the results of SAD and MAD will be produced separately. As stated in the protocol, the escalation to next dose level was decided based on the review of blinded safety data from each cohort. Also the dose levels for MAD part was determined based on full blinded safety review of all SAD cohorts. Therefore, the results of the SAD portion of the trial shall have no effect on the MAD), unless there are safety considerations recommended by the Safety Monitoring Committee.

12 CHANGES TO PLANNED ANALYSES

Due to the nature of the study design of multiple-ascending dose, a few additional endpoints of PK parameters were added to the MAD part.

13 APPENDIX:

APPENDIX A LIST OF CLINICAL LABORATORY TESTS (PART 1-3)

Hematology

- Hemoglobin, Hematocrit, Red blood Cell count, White blood cell count (WBC) with differentials, mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), platelet count

Coagulation parameters

- Prothrombin time, Activated partial prothrombin time (APTT)

Clinical Chemistry

- Liver function test: Total bilirubin, Bilirubin (Conjugated and unconjugated), Alkaline Phosphatase, Gamma-GT (GGT), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT),
- Lactate dehydrogenase, Creatinine kinase (CK)
- Kidney function test: Creatinine, Blood Urea nitrogen (BUN), Uric acid
- Lipid profile: Cholesterol, Triglyceride, HDL-Cholesterol, LDL- Cholesterol.
- Total protein, albumin, Glucose
- Electrolytes: Sodium, potassium, calcium, bicarbonates and phosphates

Serology (Screening only)

- HBsAg, Anti-HCV, Anti-HIV 1, 2

Hormones (Post-menopausal female only) (Screening only)

- FSH

Tuberculin test / QuantiFeron- TB®-Gold test (Screening only)

Pregnancy test (female only)

- Serum B-HCG
- Urine pregnancy test (UPT) will be performed at later time points in case of suspected pregnancy.

Alcohol and urine drug screen

- Opiates, methadone, cocaine, amphetamine, cannabinoids, barbiturates and benzodiazepines.
- Alcohol (breath test)

Urinalysis

- pH, hemoglobin, urobilinogen, ketones, glucose, protein, blood, leukocytes and nitrites

APPENDIX B : **PART 1** (SAD) – SCHEDULE OF EVENTS

		Assessment period						
Visits	**Screening**	**CPU confinement**				**Ambulatory/ follow up visit**		
Study Day	**-28 to -1**	**-1 Admission**	**1**	**2**	**3 (Discharge)**	**5**	**8 (±1)**	**15 (±1) EOS**[14]
Confinement[1]		X	X	X	-	-	-	-
Ambulatory visits[2]		-	-	-	-	X	X	X
Informed consent[3]	X		-	-	-	-	-	-
Medical history[4]	X	X	-	-	-	X	X	X
Demographics[5]	X	-	-	-	-	-	-	-
Physical examination[6]	X	X	-	-	X	-	X	X
Vital signs[7]	X	X	X	X	X	X	X	X
Eligibility assessment	X	X	-	-	-	-	-	-
12-lead ECG[8]	X	X	X	X	X	X	X	X
Clinical laboratory[9]	X	X	-	X	X	-	X	X
Drug and alcohol screen[10]	X	X	-	-	-	-	-	-
HBsAg, HCV, HIV	X	-	-	-	-	-	-	-
Tuberculin test / QuantiFeron-TB ®-Gold test	X							
Randomization	-	-	X	-	-	-	-	-
Pregnancy test (female) [11]	X	X	-	-	-	-	-	-
Cognitive test (e.g. MMSE)	X	-	-	-	X	-	-	-
Study drug administration	-	-	X	-	-	-	-	-
PK sampling blood[12]	-	-	X	X	X	X	X	X
Adverse events[13]	X	X	X	X	X	X	X	X

Concomitant medication	X	X	X	X	X	X	X	X

Foot notes:

1. CPU confinement: subjects will enter the CPU on Day -1 (afternoon) and will be discharged on Day 3 (morning) after safety assessment.
2. Ambulatory visit: Day 5, Day 8 and Day 15.
3. Informed Consent must be obtained ≤28 days prior to the initiation of trial treatment.
4. Detailed history will be taken at screening this include present history, past history, allergy, family history, concomitant medication and prior medication (in last 6 weeks); and other medical history. Abbreviated history will be taken at all subsequent visits.
5. Demographic will age, sex and race.
6. Physical examination includes local and systemic examination and measuring height and weight. Detailed examination will be performed at screening, Day -1, Day 3, Day 8 and Day 15. At other time point, examination will be done as clinically indicated.
7. Vitals (temperature, systolic and diastolic blood pressure, respiratory rate and pulse rate) on screening, Day -1 (at the time of admission), Day 1 & Day 2 (pre-dose, 30 min, 1, 2, 4, 6, 8, 12 and 24 hrs post dose), Day 3, Day 5, Day 8 and Day 15. At screening, vital signs will be assessed in the supine position after the subject has rested for at least 3 minutes. Blood pressure and pulse will be assessed again after three minutes in the standing position. At other time points, vitals will be measured after 3 minutes supine rest. Vitals should be completed within +/- 30 minute of schedule timing to avoid overlapping; however, in case of adverse events, safety evaluations including vitals and ECGs to be prioritized.
8. ECG (single measurement unless stated otherwise): on screening, Day -1 (at the time of admission), Day 1 & Day 2 (pre-dose, 15, 30, 45 min, 1, 2, 4, 6, 8, 12 and 24 hrs post dose), Day 3, Day 5, Day 8 and Day 15. Triplicate ECG will be taken 1 minute apart on screening, Day 1 (pre-dose) and for confirmation of abnormality detected in the single ECG measurement based on Investigator judgement.
9. Laboratory assessment: Clinical chemistry, hematology, serum electrolyte, coagulation and urinalysis will be performed. Additionally, FSH will be evaluated at screening to confirm post-menopausal status. Lab investigations will be performed on screening, Day -1, Day 2, Day 3, Day 8 and Day 15. If blood, nitrites or leukocytes are abnormal, automatically microscopic urinalysis will be perform. Additional investigations will be performed if clinically indicated.
10. Drug and alcohol screen: This will include screening for opiates, methadone, cocaine, amphetamine, cannabinoids, barbiturates, and benzodiazepines. Alcohol will be screened using alcohol breath test.
11. Pregnancy test: β-HCG will be conducted in serum at screening. UPT will be performed at later time points in case of suspected pregnancy.
12. PK time points: Day 1 (Pre-dose, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0, 24.0 and 48 hrs) and at Day 5, Day 8 and Day 15. Window period for sample collection will be outlined in pharmacokinetic manual
13. In case of drug related SAE/AE or treatment discontinuation due to adverse event, the subjects will be followed till the resolution/stabilization of the AE or 30 days after the last study dose whichever is the earlier.
14. In all subjects, telephone assessments for adverse events and concomitant medications are performed 3 days prior to the EOS visit and as required by physician.

APPENDIX C: **PART 2** (MAD) — SCHEDULE OF EVENTS

Study Day	**Screening**	**Assessment period**														
		Admission		**CPU Confinement**						**Discharge**	**Ambulatory visits**					
Study Day	**-60 to -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	15 (±1) **EOS**[18]
Confinement[1]	-	X	X	X	X	X	X	X	X	-	-		-			-
Ambulatory visits[2]	-	-	-	-	-	-	-	-	-	-	X	X	X	X	X	X
Informed consent[3]	X		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical history[4]	X	X	-	-	-	-	-	-	-	-	X	-	X	-	-	X
Demographics[5]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical examination[6]	X	X	-	-	-	X	-	-	-	X	-	-	-	-	-	X
Vital signs[7]	X	X	X	X	X	X	X	X	X	X	X	-	X	-	-	X
Eligibility assessment	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12-lead ECG[8]	X	X	X	X	-	-	X	-	X	X	-	-	-	-	-	X
Clinical laboratory[9]	X	X	-	X		-	X	-	X	X	-	-	-	-	-	X
Drug and alcohol screen[10]	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HbsAg, HCV, HIV	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tuberculin test / QuantiFeron- TB ®-Gold test	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
EEG[11]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Randomization	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Pregnancy test (female) [12]	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Cognitive test (e.g. MMSE)	X	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-
Study drug dispensing[13]	-	-	X	X	X	X	X	X	X	-	-	-	-	-	-	-
Study drug administration[14]	-	-	**X**	**X**	**X**	**X**	**X**	**X**	**X**	-	-	-	-	-	-	-
PK sampling blood[15]	-	-	X	X	X	-	X	-	X	X	X	X	X	X	X	X
Biomarkers[16]	-	-	X	-	-	-	-	-	X	-	-	-	-	-	-	-
Adverse events[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Foot notes:

1. CPU confinement: Subjects will enter the CPU on Day -1 (afternoon) and will be discharged on day 8 after safety assessment.
2. Ambulatory visit: Day 9, Day 10, Day 11, Day 12, Day 13 and Day 15.
3. The screening assessments will be performed ≤ 60 days prior to initiation of treatment and informed consent will be obtained prior to initiating any study procedures.
4. Detailed history will be taken at screening this include present history, past history, allergy, family history, concomitant medication and prior medication (in last 8 weeks); and other medical history. Abbreviated history will be taken at all subsequent visits.
5. Demographic will age, sex and race.
6. Physical examination includes local and systemic examination and measuring height and weight. Detailed examination will be performed at screening, Day -1, Day 4, Day 8 and Day 15. At other time point, examination will be done as clinically indicated. Height will only be measured at screening.
7. Vitals (temperature, systolic and diastolic blood pressure, respiratory rate and pulse rate) on screening, Day -1 (at the time of admission), Day 1 (pre-dose, 30 min, 1, 2, 4, 6, 12 and 24 hrs post dose), Day 3, Day 4, Day 5, Day 6, Day 7 (pre-dose, 30 min, 1, 2, 4, 6, 12 hrs post dose), Day 8, Day 9, Day 11 and Day 15. At screening, vital signs will be assessed in the supine position after the subject has rested for at least 3 minutes. Blood pressure and pulse will be assessed again after three minutes in the standing position. At other time points, vitals will be measured after 3 minutes supine rest. Vitals should be completed within +/- 30 minute of schedule timing to avoid overlapping; however, in case of adverse events, safety evaluations including vitals and ECGs to be prioritized.
8. ECG (single measurement unless stated otherwise): on screening, Day -1 (at the time of admission), Day 1 (pre-dose, 30 min, 1, 2, 4, 6, and 8 hrs post dose), Day 2, Day 5, Day 7 (pre-dose, 30 min, 1, 2, 4, 6, and 8 hrs post dose), Day 8 and Day 15. Triplicate ECG will be taken approximately 1 minute apart on screening and Day 1 (pre-dose). Duplicate repeats will be performed for confirmation of abnormality detected in the single ECG measurement based on Investigator judgement.

9. Laboratory assessment: Screening, Day -1 (at the time of admission), Day 2 (pre-dose), Day 5 (pre-dose), Day 7 (pre-dose), Day 8 (at discharge) and Day 15. Clinical chemistry, hematology, serum electrolyte, coagulation and urinalysis will be performed. Additionally, FSH will be evaluated at screening to confirm post-menopausal status. If blood, nitrites or leukocytes are abnormal, automatically microscopic urinalysis will be perform. Additional investigations will be performed if clinically indicated.
10. Drug and alcohol screen: This will include screening for opiates, methadone, cocaine, amphetamine, cannabinoids, barbiturates, and benzodiazepines. Alcohol will be screened using alcohol breath test.
11. EEG will be performed if clinically indicated in case of any symptom.
12. Pregnancy test: β-HCG will be conducted in serum at screening. UPT will be performed at later time points in case of suspected pregnancy.
13. Study drug (RP3128/placebo) will be dispensed on Day 1 to Day 7.
14. Study drug (RP3128/placebo) will be administered once a day from Day 1 to Day 7 at CPU.
15. PK time points: Day 1 (Pre-dose, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0 and 24.0 hr), Day 3, Day 5, Day 7 (Pre-dose, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0 and 24.0 hrs), Day 9 (48 hrs), Day 10 (72 hrs), Day 11 (96 hrs), Day 12 (120 hrs), Day 13 (144 hrs) and Day 15 (192 hrs). Blood will be collected for PK. Window period for sample collection will be outlined in pharmacokinetic manual.
16. Biomarkers: The blood sample will be collected at baseline (Day 1), Day 7 (pre-dose and 4 h post dosing). Measurement of biomarkers (Th1, Th2, and Th17 cytokines) following LPS or CD3/CD28 challenge.
17. In case of drug related SAE/AE or treatment discontinuation due to adverse event, the subjects will be followed till the resolution/stabilization of the AE or 30 days after the last study dose whichever is the earlier.
18. Window for study assessments: ECG: +/- 15 minutes of the scheduled time; Pre-dose procedures: within 2 hours of dosing.

14 TABLE AND LISTING

The following TL shells are provided as a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study but are intended to show the general layout of the Tables and Listings that will be included in the final report. Tables and Listings are numbered following the International Conference on Harmonization (ICH) structure. Table headers, variables names and footnotes will be modified as needed following a review of the blinded data and also following data analyses. Please note that all summary tables and listings will be generated using SAS® Version 9.2 or higher.

Table 14.1.1.S/M Disposition of Subjects (SAD/MAD)
Randomized Population

	Pooled Placebo	RP3128 25 mg	RP3128 50 mg	RP3128 100 mg	RP3128 200 mg	RP3128 400 mg	Total n (%)
Number of Subjects Randomized (N)	xx	xx	xx	xx	xx	xx	xx
Number of Subjects in Safety Population (N)	xx	xx	xx	xx	xx	xx	xx
Number of Subjects in PK Population [n (%)]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of Subjects who Completed the Study [n (%)]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of Subjects who Discontinued Early [n (%)]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Allergic Reaction / Anaphylaxis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Concomitant Medication Interfering W/ PK	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Emesis Within 10 hrs Post Dose	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lost to Follow-up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Physician Decision	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Protocol Deviation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Serious Adverse Event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Study Terminated by Sponsor	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Withdrawal by Subject	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are calculated based on the number of subjects in the Safety population per treatment group and overall.

Table 14.1.2.S/M Summary of Demographics (SAD/MAD)
Safety Population

	Pooled Placebo (N=xx)	RP3128 25 mg (N=xx)	RP3128 50 mg (N=xx)	RP3128 100 mg (N=xx)	RP3128 200 mg (N=xx)	RP3128 400 mg (N=xx)	All Subjects (N=xx)
Age (years)*							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Minimum	xx	xx	xx	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	xx	xx	xx
Sex, n (%)							
n	xx	xx	xx	xx	xx	xx	xx
Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…							

*Age at Informed Consent
Note: Percentages are calculated based on the number of subjects in the Safety population per treatment group and overall.
Programming Note: Table will also include race, ethnicity, height (cm), weight (kg), and BMI (kg/m2).

Table 14.1.3.M Summary of Drug Administration (MAD)
Safety Population

	Pooled Placebo (N=xx)	RP3128 25 mg (N=xx)	RP3128 100 mg (N=xx)	RP3128 400 mg (N=xx)
Number (%) of subjects who received all doses	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Number of Days on Treatment				
n	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx
Minimum	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx

Table 14.2.1.1.X.S RP3128 Plasma Concentrations (ng/mL) by Time Point (SAD)
Safety Population
<Dose Level>

		Time Point													
	Cohort /Subject	0h	0.25h	0.5h	1h	2h	4h	6h	8h	12h	24h	48h	96h	168h	336h
	xxxx	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	…..	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Statistics															
N		xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean[1]		xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
SD		xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
CV (%)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum		xxx	xxx	xxx	Xxx	Xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Median		xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Maximum		xxx	xxx	xxx	Xxx	Xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

N= Number of subject for which plasma sample was collected at each time point.
[1]Mean calculated based on number of subjects (N).

Programming Note: X will be assigned as 1, 2, 3…. as per each RP3128 dose level. Time point may vary depending on the actual number of sample collection.

<Dose Level> = RP3128 25 mg, 50 mg, 100 mg, 200 mg, 400 mg in SAD

Table 14.2.1.1.1.X.M RP3128 Plasma Concentrations (ng/mL) by Time Point (MAD) – Day 1
Safety Population
<Dose Level>

		Time Point									
	Cohort /Subject	0h	0.25h	0.5h	1h	2h	4h	6h	8h	12h	24h
	xxxx	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	…..	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Statistics											
N		xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean[1]		xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
SD		xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
CV (%)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum		xxx	xxx	xxx	Xxx	Xxx	xxx	xxx	xxx	xxx	xxx
Median		xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Maximum		xxx	xxx	xxx	Xxx	Xxx	xxx	xxx	xxx	xxx	xxx

N= Number of subject for which plasma sample was collected at each time point.
[1]Mean calculated based on number of subjects (N).

Programming Note: X will be assigned as 1, 2, 3…. as per each RP3128 dose level. Time point may vary depending the actual data.

<Dose Level> = RP3128 25mg, 100mg, 400mg in MAD

Table 14.2.1.1.2.X.M RP3128 Plasma Concentrations (ng/mL) by Time Point (MAD) – Day 7
Safety Population
<Dose Level>

		Time Point															
	Cohort /Subject	0h	0.25h	0.5h	1h	2h	4h	6h	8h	12h	24h	48h	72h	96h	120h	144h	192h
	xxxx	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	…..	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Statistics																	
N		xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean[1]		xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
SD		xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
CV (%)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum		xxx	xxx	xxx	Xxx	Xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Median		xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Maximum		xxx	xxx	xxx	Xxx	Xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

N= Number of subject for which plasma sample was collected at each time point.
[1]Mean calculated based on number of subjects (N).

Programming Note: X will be assigned as 1, 2, 3…. as per each RP3128 dose level. Time point may vary depending the actual data.

<Dose Level> = RP3128 25mg, 100mg, 400mg in MAD

Table 14.2.1.2.X.S RP3128 – Summary of PK Parameters (SAD)
PK Population
<Dose Level>

Cohort/Subject	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	K_{el} (1/h)	$T_{1/2}$ (h)
xxxx	xxx	Xxx	xxx	xxx	xxx	xxx
xxxx	xxx	Xxx	xxx	xxx	xxx	xxx
…..	xxx	Xxx	xxx	xxx	xxx	xxx
Statistics						
N	xx	xx	xx	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
CV (%)	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xxx	xxx	xxx	xxx	xxx	xxx
Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Maximum	xxx	xxx	xxx	xxx	xxx	xxx
Geo Mean[1]	xxx.x	xxx.x	xxx.x	NA	NA	NA
Geometric CV%	xx.x	xx.x	xx.x	NA	NA	NA

N=Number of subjects with derivable PK parameter.

<Dose Level> = RP3128 25 mg, 50 mg, 100 mg, 200 mg, 400 mg

Programming Notes: Geometric mean shall be calculated for all PK parameters except T_{max}, $t_{1/2}$ and K_{el}. T_{max} will only have n, median, min, max provided.

X will be assigned as 1, 2, 3…. as per each RP3128 dose level.

Table 14.2.1.2.1.X.M RP3128 – Summary of PK parameters (MAD) – Day 1
PK Population
<Dose Level>

Cohort/Subject	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	T_{max} (h)	$T_{1/2}$ (h)
xxxx	xxx	xxx	xxx	xxx
xxxx	xxx	xxx	xxx	xxx
Statistics				
N	xx	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x	xxx.x
SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx
CV (%)	xx.x	xx.x	xx.x	xx.x
Minimum	xxx	x.x	x.x	x.x
Median	xxx.x	xx.x	xx.x	xx.x
Maximum	xxx	x.x	x.x	x.x
Geo Mean[1]	xxx.x	xxx.x	NA	NA
Geometric CV%	xx.x	xx.x	NA	NA

N=Number of subjects with derivable PK parameter.

[1]: Geo Mean: Geometric means are based on the arithmetic means of ln-transformed values

Programming Note: <Dose Level> = RP3128 25mg, 100mg, and 400mg.

X will be assigned as 1, 2, and 3 as per each RP3128 dose level.

Table 14.2.1.2.2.X.M RP3128 – Summary of C_{trough} (MAD)
PK Population
<Dose Level>

Cohort/Subject	C_{trough} (ng/mL)		
	Day 3	Day 5	Day 7
xxxx	xxx	xxx	xxx
xxxx	xxx	xxx	xxx
Statistics			
N	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x
SD	xxx.xx	xxx.xx	xxx.xx
CV (%)	xx.x	xx.x	xx.x
Minimum	xxx	xxx	x.x
Median	xxx.x	xxx.x	xx.x
Maximum	xxx	xxx	x.x
Geo Mean[1]	xxx.x	xxx.x	xxx.x
Geometric CV%	xx.x	xx.x	xx.x

N=Number of subjects with derivable PK parameter.

[1]: Geo Mean: Geometric means are based on the arithmetic means of ln-transformed values

Programming Note: <Dose Level> = RP3128 25mg, 100mg, and 400mg.

X will be assigned as 1, 2, and 3 as per each RP3128 dose level.

Table 14.2.1.2.3.X.M RP3128 – Summary of PK parameters (MAD) – Day 7
PK Population
<Dose Level>

Cohort/Subject	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{0-24} (ng·h/mL)	Cav (ng/mL)	Degree of Fluctuation	Swing	T_{max} (h)	$T_{1/2}$ (h)
xxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
xxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Statistics								
N	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
CV (%)	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xxx	xxx	x.x	xxx	xxx	x.x	x.x	x.x
Median	xxx.x	xxx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xxx	xxx	x.x	x.x	x.x	x.x	x.x	x.x
Geo Mean[1]	xxx.x	xxx.x	xxx.x	xxx.x	NA	NA	NA	NA
Geometric CV%	xx.x	xx.x	xx.x	xx.x	NA	NA	NA	NA

N=Number of subjects with derivable PK parameter.

[1]: Geo Mean: Geometric means are based on the arithmetic means of ln-transformed values

Programming Note: <Dose Level> = RP3128 25mg, 100mg, and 400mg

X will be assigned as 1, 2, and 3 as per each RP3128 dose level.

Table 14.2.2.X.1.M Summary of Cytokines <expression value>: Change from Baseline (MAD)

Safety Population

		Treatment	
Visit and Time Point	Statistic	Placebo (N=xx)	RP3128 (N=xx)
Baseline (Day 1, Pre-dose)			
	n	Xx	Xx
	Mean ± SD	xx.x ± x.xx	xx.x ± x.xx
	Median	xx.x	xx.x
	Min, Max	xx , xx	xx , xx
Day 7 (Pre-dose)			
	n	xx	Xx
	Mean ± SD	xx.x ± x.xx	xx.x ± x.xx
	Median	xx.x	xx.x
	Min, Max	xx , xx	xx , xx
Change from Baseline [1]			
	n	xx	Xx
	Mean ± SD	xx.x ± x.xx	xx.x ± x.xx
	Median	xx.x	xx.x
	Min, Max	xx , xx	xx , xx
	Paired t-test	x.xx	x.xx
Day 7 (4 hr Post-dose)			
Change from Baseline [1]			
Change from Baseline [2]			

Note: 1 Baseline set at Day 1 pre-dose;
2 baseline set at Day 7 pre-dose
Data source: Listings 16.2.6.1

Programming note: Replace <expression value> with Th1, Th2, and Th17 and X will be assigned as 1, 2, and 3 for expression Th1, Th2 and Th17 respectively

Table 14.2.2.X.2.M ANCOVA Results of Cytokine <expression value> Change from Baseline to Day 7 (Pre-dose/Post-dose)/ Difference between Pre-dose and Post-dose on Day 7 (MAD)

Safety Population

					Difference between RP3128 to Placebo				
Item	Treatment	n	LSMeans	Std Err	LSMeans	Std Err	95%-confidence Interval	P-value Treatment	P-value Baseline
CFB Day 7 (Pre-dose)	Overall	xxx						x.xxxx	x.xxxx
	Placebo	xxx	x.xxx	x.xxx					
	RP3128	xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx, x.xxx	x.xxxx	
CFB[1] Day 7 (4 hr Post-dose)	Overall	xxx						x.xxxx	x.xxxx
	Placebo	xxx	x.xxx	x.xxx					
	RP3128	xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx, x.xxx	x.xxxx	
CFB[2] Day 7(4 hr Post dose)	…								

Note: 1 Baseline set at Day 1 pre-dose
2 Baseline set at Day 7 pre-dose
LSMeans: Least square means; Std Err: Standard error
LSMeans, Std Err, 95% confidence intervals and p-values are based on an ANCOVA with change from baseline as dependent variable, visit and treatment as fixed effect and baseline as covariate. P-values are from two-sided test at 5%-level.

Data source: Listings 16.2.6.1

Programming note: Replace <expression value> with Th1, Th2, and Th17 and X will be assigned as 1, 2, and 3 for expression Th1, Th2 and Th17 respectively

Table 14.3.1.1.S/M Treatment-Emergent Adverse Events – Overall Summary (SAD/MAD)
Safety Population

	Treatment at Onset of Adverse Event						
	Pooled Placebo (N=xx)	RP3128 25 mg (N=xx)	RP3128 50 mg (N=xx)	RP3128 100 mg (N=xx)	RP3128 200 mg (N=xx)	RP3128 400 mg (N=xx)	RP3128 Overall (N=xx)
Number (%) of Subjects with TEAE	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Number (%) of Subjects with Serious TEAE	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Number (%) of Subjects with Severe TEAE	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Number (%) of Subjects with Related TEAE	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Number (%) of Subjects with Study Discontinued due to TEAE	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]

Notes: A treatment-emergent adverse event (TEAE) is an AE, which starts or worsens after treatment with the study drug.
An AE is considered to be related if it is reasonably related to study treatment.
Summaries are presented as: number of subjects (percentage of subjects) [number of events]

Table 14.3.1.2.S/M Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (SAD/MAD)
Safety Population

System Organ Class/ Preferred Term	Treatment at Onset of Adverse Event						
	Pooled Placebo (N=xx)	RP3128 25 mg (N=xx)	RP3128 50 mg (N=xx)	RP3128 100 mg (N=xx)	RP3128 200 mg (N=xx)	RP3128 400 mg (N=xx)	RP3128 Overall (N=xx)
Any System Organ Class							
Any Event	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Cardiac Disorders	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Any Event	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Bradycardia	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…							

Notes: A treatment-emergent adverse event (TEAE) is an AE, which starts or worsens after treatment with the study drug.
For each row category, a subject with two or more adverse events in that category is counted only once.
Summaries are presented as: number of subjects (percentage of subjects) [number of events]

Table 14.3.1.3.S/M Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity (SAD/MAD)
Safety Population

		Treatment at Onset of Adverse Event						
System Organ Class/ Preferred Term	Maximum Intensity	Pooled Placebo (N=xx)	RP3128 25 mg (N=xx)	RP3128 50 mg (N=xx)	RP3128 100 mg (N=xx)	RP3128 200 mg (N=xx)	RP3128 400 mg (N=xx)	RP3128 Overall (N=xx)
Any System Organ Class								
Any Event	Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cardiac Disorders								
Any Event	Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…								

Notes: A treatment-emergent adverse event (TEAE) is an AE which starts or worsens after treatment with the study drug.
For each row category, a subject with two or more adverse events in that category is counted only once at the maximum severity level.
Summaries are presented as: number of subjects (percentage of subjects)

Table 14.3.1.4.S/M Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Relationship (SAD/MAD)
Safety Population

		Treatment at Onset of Adverse Event						
System Organ Class/ Preferred Term	Maximum Relationship	Pooled Placebo (N=xx)	RP3128 25 mg (N=xx)	RP3128 50 mg (N=xx)	RP3128 100 mg (N=xx)	RP3128 200 mg (N=xx)	RP3128 400 mg (N=xx)	RP3128 Overall (N=xx)
Any System Organ Class								
Any Event	No Reasonable Possibility	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Reasonable Possibility	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cardiac Disorders								
Any Event	No Reasonable Possibility	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Reasonable Possibility	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…								

Notes: A treatment-emergent adverse event (TEAE) is an AE which starts or worsens after treatment with the study drug.
For each row category, a subject with two or more adverse events in that category is counted only once at the maximum relationship level.
Summaries are presented as: number of subjects (percentage of subjects)

Table 14.3.3.1.X.S/M Summary of <laboratory Panel> (SAD/MAD)

Safety Population

Example of quantitative data:

Parameter (unit)		Statistic	Pooled Placebo (N=xx)	RP3128 25 mg (N=xx)	RP3128 50 mg (N=xx)	RP3128 100 mg (N=xx)	RP3128 200 mg (N=xx)	RP3128 400 mg (N=xx)
Albumin (g/L)	Baseline*							
		Summary Statistics						
		n	xx	xx	xx	xx	xx	Xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Minimum	xx	xx	xx	xx	xx	Xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
		Maximum	xx	xx	xx	xx	xx	xx
		Relation to Reference Range, n (%)						
		n	n	n	n	n	n	n
		Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Low	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		High	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Day X		…					
	CFB on Day X		…					
…..								

Note: CFB = Change from Baseline

*Baseline is defined as the last observation prior to dosing on Day 1.

<Laboratory Panel> = Hematology, Chemistry, Urinalysis

Programming Note: X will be assigned as 1, 2, and 3 as per laboratory panels. Day X will depends on SAD or MAD;
Relation to Reference Range will be summarized for raw data only, not for change-from-baseline values

Example of qualitative data:

Parameter (unit)	Visit		Pooled Placebo (N=xx)	RP3128 25 mg (N=xx)	RP3128 50 mg (N=xx)	RP3128 100 mg (N=xx)	RP3128 200 mg (N=xx)	RP3128 400 mg (N=xx)
Urine Protein (G/L)	Baseline*							
		Frequency, n (%)						
		n	n	n	n	n	n	n
		Category 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Category 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Relation to Reference Range, n (%)						
		n	n	n	n	n	n	n
		Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Abnormal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Day X		…					
	Follow-up or ET		…					
….								

*Baseline is defined as the last observation prior to dosing on Day 1.
Notes: Percentages are calculated based on the number of subjects in the Safety population per treatment group.
<Laboratory Panel> = Hematology, Chemistry, Urinalysis

Programming Note: X will be assigned as 1, 2, 3 as per laboratory panels.

Table 14.3.3.2.X.S/M <Laboratory Panel>: Shift Table from Baseline to End of Treatment Results (SAD/MAD)
Safety Population

			Baseline (n=xx)*			
Laboratory Parameter (unit)	Study Day [Treatment]	Parameter	Low	Normal	High/Abnormal[#]	Total
Parameter 1 (unit)	Day 3/8 [Placebo]	Low	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		High	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Day 3/8 [RP3128 25 mg]	….	…			
		….	…			
….						

Note: Doses are Total Daily Dose.

Notes: *Baseline is defined as the last observation prior to dosing on Day 1.

[#] For categorical assays, abnormal results are counted under the "High/Abnormal" column ('Low' column is 'N/A')

Note: Percentages are calculated based on the number of subjects in the Safety population per treatment group.

Note: <Laboratory Panel> = Hematology, Chemistry, Urinalysis

Programming Note: Table will continue for other lab parameters. X will be assigned as 1, 2, 3 as per laboratory panels. For SAD, Day 3 will be used to compare with Baseline. For MAD, Day 8 will be used.

Table 14.3.4.X.S/M Summary of Vital Signs Data by Treatment, Visit and Time Point (SAD/MAD)
Safety Population

<Vital Signs Parameter (unit)>

Time Point/ Visit (Day)	Statistic	Pooled Placebo (N=xx)	RP3128 25 mg (N=xx)	RP3128 50 mg (N=xx)	RP3128 100 mg (N=xx)	RP3128 200 mg (N=xx)	RP3128 400 mg (N=xx)
Baseline*							
	n	xx	xx	xx	xx	xx	Xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Minimum	xx	xx	xx	xx	xx	Xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx	xx	xx	Xx
0.5h Day 1							
0.5h Day 1 CFB							
…							

*Baseline is defined as the last observation prior to the dose on Day 1.

Note: CFB = Change from Baseline

<Vital Signs Parameter (unit)> = Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Heart Rate (bpm), Respiratory Rate (breaths/min), Oral Temperature (°C)

Programming Note: Table also includes all days and time points except screening and check-in.

X will be assigned as 1, 2, 3, 4 and 5 as per vital sign parameters (unit).

Table 14.3.4.6.S/M Summary of Weight Data by Treatment and Time Point (SAD/MAD)
Safety Population

Time Point	Statistic	Pooled Placebo (N=xx)	RP3128 25 mg (N=xx)	RP3128 50 mg (N=xx)	RP3128 100 mg (N=xx)	RP3128 200 mg (N=xx)	RP3128 400 mg (N=xx)
Check-in (Baseline)							
	n	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Minimum	xx	xx	xx	xx	xx	xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx	xx	xx	xx
Day 3/4							
Day 3/4 CFB							
Day 8							
Day 8 CFB							
Day 15							
Day 15 CFB							

*Baseline is defined as the last observation prior to the dose on Check-in.

Note: CFB = Change from Baseline

Programming Note: For SAD, Day 3 will be applied. For MAD, Day 4 will be applied.

Table 14.3.5.1.S/M Summary of Overall ECG Interpretation (SAD/MAD)
Safety Population

	Pooled Placebo (N=xx)	RP3128 25 mg (N=xx)	RP3128 50 mg (N=xx)	RP3128 100 mg (N=xx)	RP3128 200 mg (N=xx)	RP3128 200 mg (N=xx)
Baseline						
n	xx	xx	xx	xx	xx	Xx
Normal, n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, Not Clinically Significant, n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, Clinically Significant, n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing, n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…						
Follow-up or ET						
n	xx	xx	xx	xx	xx	Xx
Normal, n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, Not Clinically Significant, n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, Clinically Significant, n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing, n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are calculated based on the number of subjects in the Safety population per treatment group.

Programming Note: Table also includes time points and visits listed in the section 9.5

Table 14.3.5.X.S/M Summary of ECG Continuous Data (SAD/MAD)
Safety Population
<ECG Parameter (unit)>

Time Point/ Statistic	Pooled Placebo (N=xx)	RP3128 20 mg (N=xx)	RP3128 60 mg (N=xx)	RP3128 120 mg (N=xx)	RP3128 240 mg (N=xx)
Baseline*					
n	xx	xx	xx	xx	Xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Minimum	xx	xx	xx	xx	Xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	Xx
5 min					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
…	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	xx
5 min CFB					
…					

CFB = Change from Baseline
Note: *Baseline is defined as the last observation prior to the dose.

<ECG Parameter (unit)> = Ventricular Rate (bpm), PR interval (msec), QRS duration (msec), QT Interval (msec), QTcB Interval (msec)

Programming Note: Table also includes time points and visits listed in the section 9.5

X will be 2, 3, 4, 5 and 6 for VR, PR, QRS, QT and QTcB.

Table 14.3.6.1.S/M Summary of Mini-Mental State Examination (SAD/MAD)
Safety Population

Visit/Statistic	Pooled Placebo (N=xx)	RP3128 25 mg (N=xx)	RP3128 50 mg (N=xx)	RP3128 100 mg (N=xx)	RP3128 200 mg (N=xx)	RP3128 400 mg (N=xx)
Baseline*						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Minimum	xx	xx	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	xx	xx
Day 3/8						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
…	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	xx	xx
Day 3/8 CFB						
…						

CFB = Change from Baseline
Note: *Baseline is defined as the observation from screening.

Programming Note: Day 3 will be used for SAD and Day 8 will be used for MAD.

Listing 16.1.7.S/M Randomization Scheme and Code (SAD/MAD)
Randomized Population

Randomization Number	Cohort/Treatment	Age* (years)	Date of Randomization	Sex
xxxx	1/Placebo	30	DDMONYYYY	F
….				

*Age at Informed Consent

Listing 16.2.1.S/M Subject Disposition and Completion/Discontinuation (SAD/MAD)
Randomized Population

Cohort/ Treatment	Subject	Completed Study	Date of Study Completion or Early Discontinuation / Date of last Contact	Date of dosing	Reason for Study Discontinuation*
1/Placebo	xxxx	Yes	DDMONYYYY/ DDMONYYYY	DDMONYYYY	xxxxxxxxxxx
…					

*A corresponding AE number will be displayed if Reason for Treatment Discontinuation or Reason for Study Discontinuation is "Adverse Event".

Listing 16.2.2.S/M Protocol Deviations (SAD/MAD)
Safety Population

Cohort/ Treatment	Subject	Start Date of deviation	Visit/Day	Description of Protocol Deviation	Classification	Category
1/Placebo	xxxx	DDMONYYYY	xxxx	Xxxxxxx	Major/Minor	Procedures/Assessments Outside Protocol Window
….						

Listing 16.2.3.S/M Exclusions from Analysis Populations (SAD/MAD)
Randomized Population

Cohort/ Treatment	Subject	Excluded from Safety Population	Reason for Exclusion from the Safety Population	Excluded from PK Population	Reason for Exclusion from the PK Population
1/Placebo	xxxx	No	Xxxxxxx	Yes	Xxxxxxx
…					

Listing 16.2.4.S/M Demographics and Informed Consent at Screening (SAD/MAD)
Safety Population

Cohort/ Treatment	Subject	Informed Consent Date	Sex	Date of Birth	Age* (years)	Race	Ethnicity	Height (cm)	Weight (kg)	BMI (kg/m^2)
1/Placebo	xxxx	DDMONYYYY	x	DDMONYYYY	xx	xxxxx	xxxxx	xxx	xx	xx
…										

*Age at Informed Consent

Listing 16.2.5.1.S/M Study Drug Administration and Compliance (SAD/MAD)
Safety Population

Cohort/ Treatment	Subject	Visit/Day	Study Drug Administered?	Route of Administration	Dose/Unit	Start date	Start time/End time	Treatment Comment
1/Placebo	xxxx	Day 1	Yes	Oral	xx/mg	DDMONYYYY	HH:MM/HH:MM	xxxxxxxxx
…								

Listing 16.2.5.2.S/M Pharmacokinetic Sample Collection Data (SAD/MAD)
Safety Population

Cohort/ Treatment	Subject	Dosing Date and Time	Date of Sample Collection	Scheduled Time Point (hr)	Elapsed Time* (hr)*	Actual Sample Collection Time (HH:MM)	Time Deviation** (min)	Plasma Concentration (ng/mL)
1/RP3128 20 mg	xxxx	DDMONYYYY HH:MM	DDMONYYYY	Pre-dose	-1.4	HH:MM	xx	xx
				0.083	0.083	HH:MM	xx	xx
				0.25	0.25	HH:MM	xx	xx
				0.5	0.51	HH:MM	xx	xx
				2	2.1	HH:MM	xx	xx
				6	6	HH:MM	xx	xx
				12	12	HH:MM	xx	xx
		….	….					
….								

*Difference between actual sample collection time and dosing time
**Difference actual collection and scheduled collection time (post treatment time points only)
Note: BLQ = Below the limit of quantification.

Note: HH:MM = Hours: Minutes

Listing 16.2.5.3.S Pharmacokinetic Parameters (SAD)
PK Population

Cohort/Treatment	Subject	Lower Time* (h)	Upper Time* (h)	Number of points used in K_{el} estimation	Adjusted R-Square	K_{el} (1/h)	$t_{1/2}$ (h)
1/RP3128 25 mg	xxxx	xxx	xxx	xxx	xxx	xxx	xxx
	…						

*Lower time and upper time are the lower and upper limits on time, respectively, for values to be included in the estimation of Kel.
Note: Minimum 3 points will be used to estimate Kel.

Listing 16.2.5.4.S/M Reasons Why Pharmacokinetic Parameters Could Not be Determined (SAD/MAD)

Cohort/Treatment	Subject	Pharmacokinetic Parameter (Units)	Original Value	Reason
1/RP3128 20 mg	xxxx	K_{el} (h)	xxx	Xxxxxxxxxx
	…			
……				

Listing 16.2.6.1: Cytokine assessment

Cohort/Treatment	Subject	Visit	Date	Time Point	Cytokine Test		
					Th1	Th2	Th17
1/Placebo	1001	Day 1	DDMMMYYYY	Pre-dose	xx	xx	xx
		Day 7	DDMMMYYYY	Pre-dose	xx	xx	xx
		Day 7	DDMMMYYYY	post-dose	xx	xx	xx
	……						
2/RP3128 25mg	xxxx						

Programming Note: the list of cytokine here is just an example, the final listing will show all cytokines available in the eCRF.

Listing 16.2.7.1.S/M Adverse Events (SAD/MAD)
Safety Population

Cohort/ Treatment	Subject	Visit	AE #	System Organ Class/ Preferred Term/ Verbatim Term	TEAE ?	Ongo -ing?	Start Date and Time/ Stop Date and Time/	Time from Dosing/ Duration (DD:HH:MM)*	Toxicity Grade (if applicable)	Severity/ Serious/ Relationship to Study Drug/ Outcome	Study Drug Action Taken/ Non-Drug Action Taken	Caused Study Discontinuation
			x	Gastrointestinal disorders/ Vomiting/ Vomiting	Y	Y	DDMONYYYY HH:MM	DD:HH:MM/ DD:HH:MM	2	Moderate/ No/ Related / Recovered/Resolved	Not Applicable/ None	
	…											

*DD:HH:MM = Days:Hours:Minutes

Listing 16.2.7.2.S/M Deaths, Other Serious and Significant Adverse Events Safety Population (SAD/MAD)

Cohort/ Treatment	Subject	System Organ Class/ Preferred Term/ Verbatim Term	Date and Time of Event/ Date and Time of Resolution	Severity/ Serious/ Relationship to Study Drug/ Outcome	Study Drug Action Taken/ Other Action Taken
1/Placebo	xxxx	Nervous system disorders/ Migraine/ Migraine	DDMONYYYY HH:MM/ DDMONYYYY HH:MM	Mild/ No/ Possibly Related/ Recovered/Resolved	Dose Not Changed/ ConMed Taken (CM # 1)
	…				

Programming Note: this listing will only be produced when any SAE has occurred during the study.

Listing 16.2.8.X.S/M <Laboratory Panel> (SAD/MAD)
Safety Population

Cohort/ Treatment	Subject	Visit/Day	Date of Sample Collection	Lab test (Unit)	Value	Reference Range Indicator	Normal Range	Completion Status
1/Placebo	xxxx	Screening	DDMONYYYY	Xxxxxxxxxxxxx (xxxx)	xx	High	xx - xxx	Yes
				Xxxxxxxxxxxxx (xxxx)	xx	Abnormal	Negative	Yes
	…							

<Laboratory Panel> = Hematology, Chemistry, Urinalysis
Note to programmer: X will be assigned as 1, 2, and 3 as per each laboratory panels.

Listing 16.2.8.X.S/M <Laboratory Panel>: Abnormal Results (SAD/MAD)
Safety Population

Cohort/Treatment	Subject	Visit/Day	Date/Time	Lab test (Unit)	Value	Reference	Normal	Significance[#]

						Range Indicator	Range	
1/Placebo	xxxx	Screening	DDMONYYYY HH:MM	xxxxxxx	x.x	Abnormal	Negative	NCS
		…..				High	xx-xxx	CS
…								

Note: #Significance: CS = Clinically Significant, NCS = Not Clinically Significant
<Laboratory Panel> = Hematology, Chemistry, Urinalysis
Note to programmer: X will be assigned as 4, 5, and 6 as per each laboratory panels.

Listing 16.2.8.7.S/M Viral Screen and TB Test at Screening (SAD/MAD)
Safety Population

Cohort/Treatment	Subject	Date and Time	Hepatitis B Surface Antigen	Hepatitis C Virus Antibody	HIV 1/2 Antibody	Tuberculin test /QuantiFeron-TB - Gold test
1/Placebo	xxxx	DDMONYYYY HH:MM	Negative	Negative	Non-Reactive	Negative
	…					

Listing 16.2.8.8.S/M Drug and Alcohol Screen (SAD/MAD)
Safety Population

Cohort/ Treatment	Subject	Visit	Collection Date	Opiates	Methadone	Cocaine	Amphetamine	Cannabinoids	Barbiturate	Benzodia-zepine	Alcohol Breath Test
1/Placebo	xxxx	Screening	DDMONYYYY	Negative	Negative	Positive	Negative	Negative	Negative	Negative	Negative
		Day -1	….								
	…..										

Listing 16.2.9.1.S/M Vital Signs (SAD/MAD)
Safety Population

Cohort/Treatment	Subject	Visit	Time Point	Position	Date	Time	SBP (mmHg)	DBP (mmHg)	HR (bpm)	RR (bpm)	Temp (ºC)	Weight (kg)
1/Placebo	xxxx	Screening		Supine	DDMONYYYY	HH:MM	xxx	xx	xx	xx	xx	xx
		Check-in Day -1			DDMONYYYY	HH:MM	xxx	xx	xx	xx	xx	xx
		Day 1	Pre-dose		DDMONYYYY	HH:MM	xxx	xx	xx	xx	xx	
			30 min		DDMONYYYY	HH:MM	xxx	xx	xx	xx	xx	
			1 hour		DDMONYYYY	HH:MM	xxx	xx	xx	xx	xx	
		Day 2										
		Follow-up or ET										
	….											
…….												

Note: SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HR = Heart Rate; RR = Respiration Rate; Temp = Oral Temperature; bpm = Beats per Minute or Breaths per Minute

Listing 16.2.10.1.S/M Electrocardiogram (ECG) (SAD/MAD)
Safety Population

Cohort/ Treatment	Subject	Visit	Time Point	Date and Time	Was the ECG Performed ?	ECG Overall Interpre-tation	VR (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTcB (msec)
1/Placebo	xxxx	Screening		DDMONYYYY HH:MM	Yes	Abnormal/NCS	xx	xxx	xx	xx	xxx
		Day 1	Pre-dose	DDMONYYYY HH:MM	No						
			15 min	DDMONYYYY HH:MM	Yes	Normal	xx	xxx	xx	xx	xxx
			30 min	DDMONYYYY HH:MM	NU						
			45 min	DDMONYYYY HH:MM	Yes	Normal	xx	xxx	xx	xx	xxx
			1 hour	DDMONYYYY HH:MM	Yes	Normal	xx	xxx	xx	xx	xxx
			….								
		Day 3		DDMONYYYY HH:MM	Yes	Normal	xx	xxx	xx	xx	xxx
		Follow-up or ET		DDMONYYYY HH:MM	Yes	Normal	xx	xxx	xx	xx	xxx/N
	….										
……											

Note: CFB: Change from baseline; NU: Not Useable; CS = Abnormal, Clinically Significant; NCS = Abnormal, Not Clinically Significant; VR = Ventricular Rate; PR=Pulse Rate.

Listing 16.2.10.2.S/M ECG: Abnormal Results – Listing (SAD/MAD)
Safety Population

Cohort/Treatment	Subject	Day	Time Point	Date and Time of ECG	ECG Abnormality	Clinically Significant
1/Placebo	xxxx	Day 1	Pre-dose	DDMONYYYY HH:MM	Sinus bradycardia otherwise normal ECG, physician comments transcribed as per monitor's request	No
	…					

Listing 16.2.11.S/M Mini-Mental State Examination (SAD/MAD)
Safety Population

Cohort/Treatment	Subject	Day	Date and Time	Score	Results
1/Placebo	xxxx	Screening	DDMONYYYY HH:MM	XX	Normal
	…				

Note: MMSE - Mini-Mental State Examination

Listing 16.2.12.S/M Medical History (SAD/MAD)
Safety Population

Cohort/ Treatment	Subject	MH #	Body System/ Preferred Term	Condition	Start Date	End Date	Ongoing
1/Placebo	xxxx	x	Xxxx/Xxxxx	Xxxxxx	DDMONYYYY	DDMONYYYY	No
…							

Listing 16.2.13.S/M Clinical Events (SAD/MAD)
Safety Population

Cohort/ Treatment/	Subject	Clinical Event	Planned time point	Start Date and Time	End Date and Time	Ongoing?
1/Placebo	xxxx	XXXXXX	Pre-dose	DDMONYYYY	DDMONYYYY	No
		XXXXXX	5 min	DDMONYYYY		Yes
	…					

Listing 16.2.14.S/M Prior and Concomitant Medications (SAD/MAD)
Safety Population

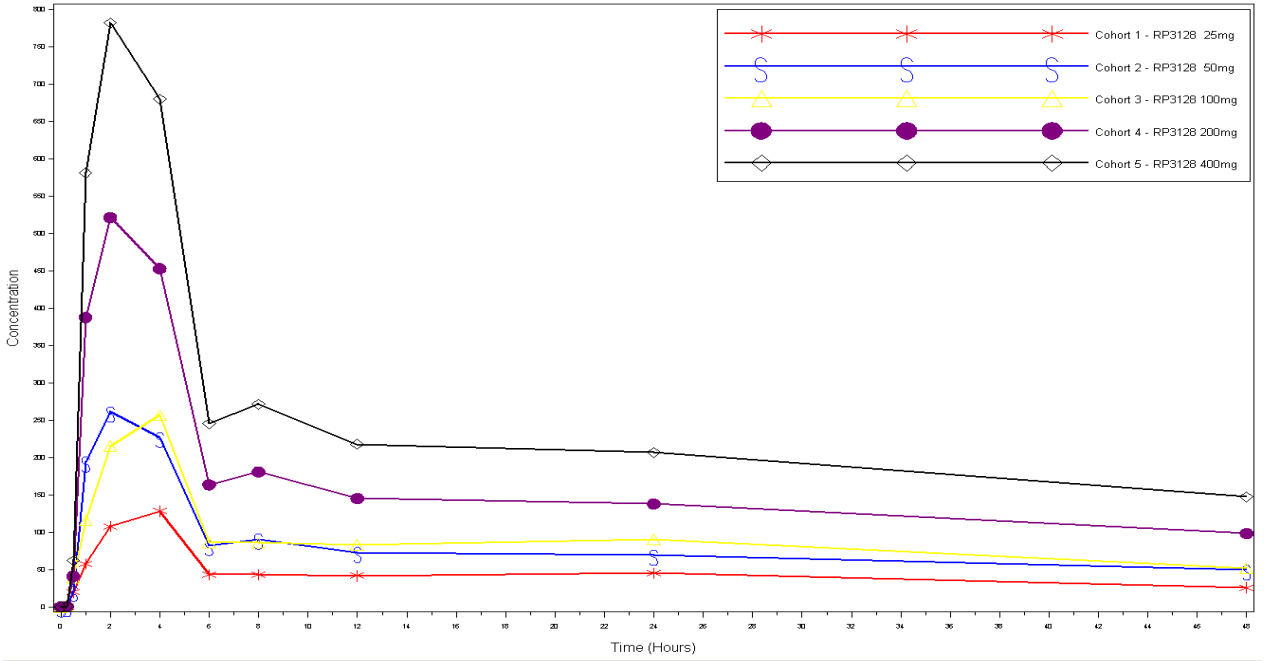
Cohort/ Treatment	Subject	Medication #	Drug Class/ Preferred Term/ Verbatim Term	Medication Information*	Start Date/Stop Date	Ongoing?	Indication	Administered for AE?	Administered for MH?
1/Placebo	xxxx	1	xxxx	xxx/ mg/ Once/ Oral	DDMONYYYY/ DDMONYYYY	No	Headache	Yes (AE # 4)	No
		2	xxxx	xxx/ mg/ Once/ Oral	DDMONYYYY	Yes	Xxxxx	No	Yes (MH #2)
…									

*Dose/Unit/Frequency/Route

Listing 16.2.15.M Electroencephalogram at Screening (MAD)
Safety Population

Cohort/ Treatment	Subject	EEG Test Date and Time	Results	Clinically Significant
1/Placebo	xxxx	DDMONYYYY HH:MM	Abnormal	No
	…			

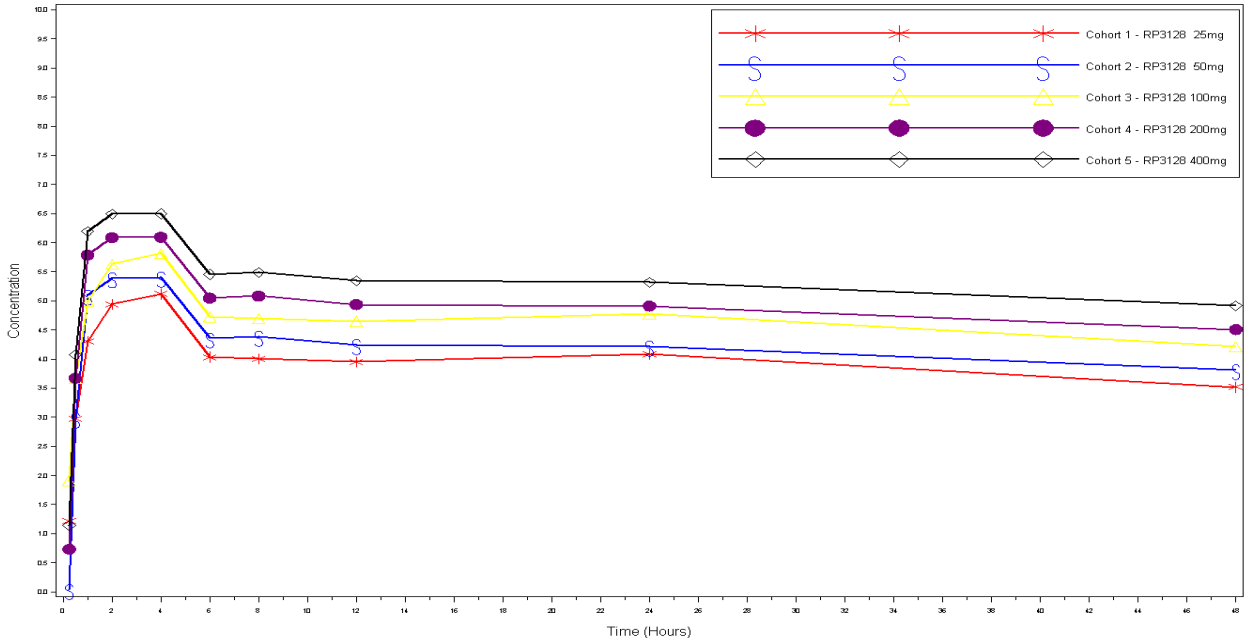
Figure 14.4.1.S/M – Mean Plasma RP3128 Concentrations – Linear Scale (SAD/MAD)
Safety Population



Programming Notes: Replace XX with corresponding dose of indicated cohort.

Figure 14.4.2.S/M – Mean Plasma RP3128 Concentrations – Semi-logarithmic Scale (SAD/MAD)

PK Population



Programming Notes: Replace XX with corresponding dose of indicated cohort.

Figure 14.4.3.X.S/M–Individual Plasma RP3128 Concentrations – Linear Scale (SAD/MAD)

(ZZ mg)
Safety Population

Programming Notes: Similar to 14.4.1 except graphs will represent individual subject graphs within each cohort. Increase value of X by 1 with each cohort. Replace ZZ with corresponding dose of indicated cohort.

Figure 14.4.4.X.S/M–Individual Plasma RP3128 Concentrations – Semi-logarithmic Scale (SAD/MAD)

(ZZ mg)
Safety Population

Programming Notes: Similar to 14.4.2 except graphs will represent individual subject graphs within each cohort. Increase value of X by 1 with each cohort. Replace ZZ with corresponding dose of indicated cohort.