PROTOCOL NO. RP3128-1601

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

PROTOCOL NUMBER:	RP3128-1601
TRIAL DRUG:	RP3128
SPONSOR:	**Rhizen Pharmaceuticals SA** Fritz-Courvoisier 40, Ch-2300 La Chaux-de-Fonds, Switzerland. Tel: +41 32 580 0113; +41 32 580 0175 Fax: +4132 967 95 96
PRINCIPAL INVESTIGATOR	[redacted]
SPONSOR'S MEDICAL EXPERT	[redacted]
VERSION	**Final, Version 3, Date: 27 December 2017**

Clinical Trial Protocol Statement of Compliance

The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Conference on Harmonisation and all applicable federal and local regulations

Protocol	Version	Date
3	Final	27 December 2017

The information provided in this document is strictly confidential and is available for review to investigator(s) and to the appropriate Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and National regulatory authority.

Protocol Amendment history

Amendment #/date	Reference to section	Summary	Rationale
Amendment 1, 16 Sept 2016	**Section 3.4** Safety Review Committee	An independent respirologist will be part of the SRC in POC, and will be responsible for reviewing the POC safety data.	As advised by the Ethics Committee
	Section 3.8 Subject discontinuation criteria	Subject discontinuation criteria and Dose escalation stopping rule updated.	
	Section 6.2 Screening and Appendix	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 cognitive function.	
	Section 6.6 Allergen Challenge	Allergen challenge procedure and safety measures are added to the study protocol	
	Section 7.3 Causality assessment	Reference to re-challenge is removed from definition of causality assessment	
	-	Correction of typo errors.	-

Amendment 2, 22 March 2017	**Contact information**	Change in Principal Investigator of the study **Dr. Peter Couroux** has taken over the responsibility of PI from Dr. Philip Matthew.	Administrative change
	Section 3.2.2 Part 2: Multiple Ascending dose	In line with protocol, the doses of MAD is updated to **RP3128 25 mg, 100 mg** and **400 mg,** considering the safety and PK profile of RP3128 in SAD.	In SAD, a single doses of RP3128 starting from 25 mg to 400 mg were found to be safe and well tolerated without any DLT. Considering of safety and exposure of drug, doses 25 mg, 100 mg, and 400 mg that allows 4-X increment of doses during escalation, are considered appropriate for MAD.
	Section 3.2.2 Part 2: Multiple Ascending dose	The dose of POC is updated to **RP3128 400 mg.**	Assuming 400 mg is the maximum tolerated dose in MAD, the dose is proposed for POC.
	Section 3.7 Expected duration of subject participation	The expected duration of subject participation in the study is revised to: • SAD: **up to 61 days** including screening period. • MAD: **up to 76 days** including screening period. • POC: **up to 112** days including screening and washout period.	Duration of expected subject participation is increased due to increased screening period from 30 days to 45 days in SAD; 28 days to 60 days in MAD and POC to facilitate the recruitment of the subjects in the study.
	Section 4.1 Inclusion criteria	**Inclusion criteria #6 is updated to:** Participant is able to procreate and agrees to use one of the accepted contraceptive regimens during the study; and **for at least 4** months after the last drug administration.	Duration of contraception is changed in line with the half-life of the drug that may extend up to 50 hrs.
	Section 4.2 Exclusion criteria	**Exclusion criteria #8 is updated to:** Subjects who have received any investigational drug within **2 months (60 days) or within 5 half-lives (for small molecule) or until the expected PD effect has returned to baseline** (for biologics) from screening in any clinical trial (whichever is longer) or drugs that directly or indirectly inhibit calcineurin, monoamine oxidase inhibitors, tricyclic antidepressants and anti-convulsants, or who are on extended follow-up;	Considering the safety of RP3128 in SAD, the eligibility criteria is revised to facilitate screening and the recruitment of the subjects in the study.
	Section 5.3 Prohibited medication	Some study specific restrictions are updated as below • Drugs directly or indirectly inhibits calcineurin, monoamine oxidase inhibitors, tricyclic antidepressants or anti-convulsants from **2 months** from screening. • Other investigational drug treatments from **2 months** from screening.	Considering the safety of RP3128 in SAD, the eligibility criteria is revised to facilitate screening and the recruitment of the subjects in the study.

	Section 5.4 Study Specific restrictions	Some study specific restrictions are updated as below. • Subjects will remain seated or ambulatory (will not be allowed to lie down) for the first 4 hrs following drug administration during confinement. **However, in case of AEs or to complete protocol mandated study assessments, subjects may be placed in appropriate position.** • Subjects should abstain from **strenuous exercise 72 hours** prior to each study visit and should not engage in strenuous activity at any time during the confinement. • Subjects will be expected to use an acceptable contraceptive regimen from the first administration of the study drug, during the study, and **until at least 4 months after the last drug administration**. • **One condom** will be provided to subjects upon departure from the clinical site for the first period of the study.	Protocol clarification
	Section 5.5 Procedures for monitoring subject compliance	Procedures for monitoring subject compliance using subject diary is updated. Telephonic call is removed from the MAD part.	Protocol clarification. In MAD, the two visits (on day 12 and Day 13) are added between Day 11 and Day 15, therefore telephonic calls are removed from MAD part.
	Section 6.2 Screening	Screening procedure is updated as below. Screening assessments will be performed **≤ 45 days** prior to initiation of treatment and **≤ 60 days** in MAD/POC; and informed consent will be obtained prior to initiating any study procedures. The eligibility will be confirmed by PI/designee on Day 1. Screening will be performed over multiple visits if required.	Considering the safety of RP3128 in SAD, the eligibility criteria is revised to facilitate screening and the recruitment of the subjects in the study.
	Section 6.2 (Screening) **EEG**	EEG time points is updated. An EEG will be performed in the subject **if clinically indicated** in case of any symptom as required by neurologist.	Considering the safety/PK of RP3128 in SAD in healthy volunteers and role of EEG in diagnosing neurological condition, the EEG is proposed to be done "**as clinically indicated**" instead of at "**pre-defined"** time points.
	Section 6.3: Lab investigations	Amount of blood volume is revised to **258.9 ml** (Approx. 260 ml)	Requirement is revised based on the blood collection for additional PK and Biomarker.
	Section 6.6 Allergen challenge	Procedure of allergen challenge are updated.	Procedure of allergen challenge are updated in line with the CRO's SOPs.

	Section 6.9 Ambulatory visits	Additional ambulatory visits are added in MAD: Ambulatory visits on Day 9, **Day 10**, Day 11, **Day 12**, **Day 13** and Day 15.	Additional time points are considered to complete delineation of PK profile of the drug.
	Schedule of assessment	Schedule of assessments are updated as above and to clarify the protocol related changes.	Protocol clarification.
	-	Correction of typo errors.	-
Amendment 3, 8 November 2017	Section 5.2 Concomitant medication	The language of concomitant medication is updated to clarify the use of short acting inhaled b-2 agonist in Part 3 (POC)	Protocol clarification
	Section 6.2 Screening procedure	Asthma action plan is referenced in the protocol	Protocol clarification
	Contact information	[redacted] is changed to [redacted] Sponsor's contact numbers are updated.	Administrative change
	Section 7.5 SAE reporting	The following sentence is updated The Sponsor **or designee** will be responsible for evaluating the events for expedited reporting, processing of events and for reporting it to the Health Canada and other regulatory agencies in accordance with the Health Canada / ICH Guidance Document.	Administrative change
Amendment 4, 27 December 2017	Section 6.2 ECG	Interpretation of triplicate ECG is clarified as below. Investigator's discretion will be used for interpretation of findings on triplicate ECGs (including determination of cardiac intervals), if the results are inconsistent/inconclusive.	Protocol clarification
	Contact information	Information on sponsor representative is updated.	Administrative change

Clinical Trial Protocol Approval Page

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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PROTOCOL NUMBER: RP3128-1601

TRIAL DRUG: RP3128

IND NUMBER: -

[redacted]

Principal Investigator **Signature** **Date**

[redacted]

Sponsor's Medical Expert **Signature** **Date**

RP3128-1601

Protocol Acceptance Form

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

PROTOCOL NUMBER:	RP3128-1601
TRIAL DRUG:	RP3128
IND NUMBER:	
FINAL:	Version 3, Dated 27 December 2017

[redacted]

Principal Investigator **Signature** **Date**

PROTOCOL SYNOPSIS

Protocol no.	RP3128-1601
Study Title	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.
Sponsor	Rhizen Pharmaceuticals SA, Switzerland
Study Sites & Enrollment	Single centre study in 56 healthy volunteers (HV) and 12 mild asthmatics. • Part 1 (SAD)-32 HV • Part 2 (MAD)-24 HV • Part 3 (POC)-12 mild asthmatics Enrollment is expected in approximately 8 months
Study Rationale	Ion-channels are known to control flow of physiologically important ions in and out of cells and play an important role in cell functions. Calcium Release Activated Calcium (CRAC) channels constitute major pathway for Ca^{++} influx in immune cells. The channels are known to be specific to Ca^{++} entry in immune cells. The CRAC channel regulated Ca^{++} entry, that in turn regulate the production and secretion of key pro-inflammatory cytokines such as IL-2, TNF-α, IL-4, IL-5 etc. The CRAC channel pathway is proven to be essential for the adaptive immune responses in humans. CRAC channel modulators therefore offer disease-modifying properties. Therapeutic applications include inflammatory disease conditions (e.g. asthma, rheumatoid arthritis, allergy, IBD, immunodeficiency, chronic obstructive pulmonary disease). RP3128, a CRAC channel modulator developed by Rhizen Pharmaceuticals SA, has demonstrated efficacy in pre-clinical models representative of various immunological disorders. This is a first-in Human (FIH) study to evaluate the safety, tolerability and pharmacokinetics of single and multiple ascending dose(s) of RP3128 in HV and to evaluate the effect on late phase asthmatic response to allergen challenge in patients with mild asthma.
Study Objectives	**Primary Objectives:** • Part 1 (SAD) - to investigate the safety and tolerability of single ascending oral doses of RP3128 in 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. • Part 3 (POC) - to evaluate allergen induced late phase asthmatic response (LAR) as measured by maximal percent decrease in the forced expiratory volume 1 second (FEV_1) and area under the effect curve (AUEC) from baseline (pre-allergen challenge) to the period beginning 3 hrs and ending 8 hrs after allergen challenge at the highest identified dose of RP3128.

	Secondary Objectives:
	• **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 daily, at three dose levels in HV.
	  • To evaluate ex-vivo effect of RP3128 on various biomarkers (Th1, Th2 and Th17 cytokines) following Lipopolysaccharide (LPS) or CD3/CD28 stimulation.
	• **Part 3 (POC) -**
	  • To evaluate the allergen induced early phase asthmatic response (EAR) as measured by maximal percent decrease in the FEV_1 and AUEC from baseline (pre-allergen challenge) to the first 3 hrs after allergen challenge at the highest identified dose of RP3128.
	  • Absolute count, percentage differential count of sputum eosinophils and neutrophils at approximately 8 and 24 hrs after allergen challenge in RP3128.
	  • FeNO change from baseline (pre-challenge) compared to 3, 8 and 24 hrs post-allergen challenge.

Efficacy Endpoints	**Primary end point(s):**
	• SAD: Adverse Events (AEs), clinical laboratory tests, vital signs, physical examination and 12 lead ECG after a single dose.
	• MAD: AEs, clinical laboratory tests, vital signs, physical examination and 12 lead ECG after multiple doses.
	• POC: Maximal percentage decrease from pre-allergen challenge in FEV_1 during 3 hrs to 8 hrs post allergen challenge.
	
	Secondary end point(s):
	• **SAD:**
	  - PK parameters including C_{max}, AUC_{0-t}, AUC_{0-inf}, T_{max}, $t_{½}$ and K_{el}
	• **MAD:**
	  - PK parameters including C_{max}, AUC_{0-t}, AUC_{0-inf}, T_{max}, $t_{½}$ and K_{el}
	  - Levels of various biomarkers (Th1, Th2 and Th17 cytokines) following LPS or CD3/CD28 stimulation.
	• **POC:**
	  - Maximal percentage decrease from pre-allergen challenge in FEV_1 during 0 to 3 hrs post allergen challenge.
	  - Post allergen challenge $AUEC_{0-3h}$, $AUEC_{3-8h}$
	  - Change in FeNo (Pre-challenge to 3, 8 and 24 hrs post allergen challenge)
	  - Absolute and percentage (%) differential counts of eosinophils and neutrophils at 8 and 24 hrs post allergen challenge.

Study design	This is a single-centre, randomized, double-blind, placebo controlled three-part study to evaluate the safety, tolerability and pharmacokinetics of single and repeat doses of RP3128 and to evaluate the effect on Late Phase Asthmatic Response (LAR) to allergen challenge in patients with mild asthma **SAD/MAD:**

This is a single-centre, randomized, double-blind, placebo controlled study except first cohort of SAD. There will be 5 cohorts in SAD and 3 cohorts in MAD. In the first part of the study (Part 1, SAD), single dose of RP3128/placebo will be administered on Day 1. In the second part (Part 2, MAD), multiple doses of RP3128/placebo will be administered once a day from Day 1 to Day 7.

In both SAD and MAD, the cohorts will be dosed sequentially so that a minimum of 8 days is allowed between dose of previous cohort and the initiation of next cohort. Progression to the next higher dose will occur 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).

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)
[$] Actual doses administered may change based on emerging safety, tolerability and PK data.
[$$] In case of safety concern, additional subjects may be added to cohort for safety assessment as per the decision of SRC.

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

[$] Actual doses administered may change based on emerging safety, tolerability and PK data.
[$$] In case of safety concern, additional subjects may be added to cohort for safety assessment as per the decision of SRC.

POC (allergen challenge):

This is a randomized, placebo-controlled, double blind, two period, cross-over, proof-of-concept study in male and female of non-child bearing potential with history of mild asthma. A total 12 patients will be randomized to receive RP3128/placebo in two treatment periods. The highest identified dose of RP3128 400 mg in Part 2 (MAD) will be considered for POC. Patients will receive RP3128 or placebo for 14 days (Day 1 to Day 14) in both periods. Allergen challenge will be performed on Day 14 in both periods. Treatment period will be separated by a

	washout period of at least 14 days (may vary depending on emerging safety, tolerability and PK data from SAD/MAD.
Dose Escalation Procedure	The dose escalation decisions in Part 1 and Part 2 will be made by the Safety Review Committee (SRC). After completion of each cohort, the SRC will review safety, tolerability and PK data of RP3128/placebo to confirm the dose limiting toxicity (DLT) of the existing dose, determination of Maximum Tolerated Dose (MTD), and make a decision to escalate to the next dose level. • Subjects who have completed 4-days safety follow up in SAD (Subjects visiting on day 5) and 7-days safety follow up in MAD (Subject visiting Day 15) will be considered for safety review. The subjects withdrawn after 48 hrs of safety follow up due to non-safety reasons will be considered for dose escalation decisions. The reason for withdrawal of such patients will be appropriately documented. • Safety data includes medical history, vitals, physical examination, hematology and biochemistry, ECG, AE, SAE and adverse events of special interest (pregnancy, overdose) and DLT throughout 4-days (SAD) and 7-days (MAD) from the last dose of study drug. PK data through 48 hours after the last dose will be considered for dose escalation. • Blinded data will be used (except for cohort 1) for dose escalation procedure. Limited unblinding of the SRC is allowed at the time of dose-escalation review to improve the accuracy of safety-related decisions. If un-blinding of data is required during the review, the timings of un-blinding and reason for un-blinding will be documented. • The data from at least 3 subjects (Cohort S1), 5 subjects (Cohort S2 and S3), 7 subjects (Cohort S4 and S5) in SAD part; and 7 patients in all three cohorts (Cohort M1-M3) in MAD part will be required for safety review. • The data will be subjected to a QC review prior to the dose. Progression to next higher dose will only occur if previous dose level is deemed to be safe and well tolerated by SRC. • Depending on the nature and the timing of the toxicities encountered and the pharmacokinetic data from dosing of RP3128, planned dose escalation may be modified to include the repetition of a dose based on the results of the safety and tolerability review, or if further characterization of the safety profile at that dose is required. Alternative dose (intermediate dose level or a lower increment) can also be done by SRC. • Section 3.8 will be used as an example for the determination of the MTD. In case of any criteria that meeting cohort termination criteria, the ongoing dose will be defined as ***the dose exceeding MTD***; No further dose escalation will be done thereafter. ***The previous dose level will be considered as the MTD*** and will be considered for the next part of the study as decided by the SRC. • If the MTD is not reached after completing the planned sequential groups, highest dose will be considered an optimal dose. No additional groups will be included.
Eligibility Criteria	**Inclusion Criteria** Subjects must meet all of the inclusion criteria to be considered eligible for study: 1. Male and non-childbearing female subjects aged 18 to 45 years (SAD/MAD) and male and non-childbearing female patients with mild asthma aged 18 to 65 years (POC);

	2. Healthy subjects as determined by pre-study medical history, vitals, physical examination and 12-lead ECG, and clinical laboratory tests within the normal reference ranges or clinically acceptable to investigator. 3. Body mass index (BMI) between 18.0 and 30.0 kg/m^2 inclusive, weight ≥50 kg; 4. Female subjects should be of non-child bearing potential, either surgically sterile or postmenopausal. Women should have either a history of no menses for at least 12 months or have documented bilateral oophorectomy with or without hysterectomy and have a documented serum FSH level ≥ 40 mIU/mL. 5. Non-smokers or ex-smokers being defined as someone who completely stopped smoking cigarettes for at least 6 months with history of less than a 10-pack year, before day 1 of the study; 6. A male subject must meet the following criteria: i. Participant is able to procreate and agrees to use one of the accepted contraceptive regimens during the study; and for at least 4 months after the last drug administration. An acceptable method of contraception includes one of the following: • Abstinence from heterosexual intercourse • Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository • Highly effective contraception should be used by the female partner as defined in **Appendix F**. ii. Participant is unable to procreate; defined as surgically sterile (i.e. has undergone a vasectomy at least 6 months prior to the first administration of the study drug), is required to use condom in order to prevent delivery of the drug via seminal fluid. 7. Willingness to adhere to the protocol requirements as evidenced by the informed consent form (ICF) duly read, signed and dated by the subject; able to comply with protocol requirements and or study procedure; 8. Negative screen for drugs of abuse and alcohol at screening and on admission, judged by the investigator and/or designee. **Additionally, for Part 3: POC** 9. Pre- bronchodilator FEV_1 of > 70% (adjusted for age, sex and race) 10. Steroid naïve subjects with history of mild asthma for the last 6 months that satisfy the Global Initiative for Asthma (GINA) definition of asthma, but otherwise healthy. 11. Positive methacholine with the provocative concentration of methacholine resulting in a 20 % fall in FEV_1 (PC_{20} methacholine) of equal or less than 8 mg/ mL at screening. 12. Documented allergy to at least one common allergen (house dust mite, pollen allergens or cat dander) as confirmed by the skin prick test wheal ≥ 3mm than the negative control in diameter. Historical data up to 1 year can be used. 13. Early asthmatic response (EAR) (FEV_1 fall of ≥ 20%, 0 to 60 minutes after allergen challenge) and LAR (FEV_1 fall of ≥ 15%, 3 to 8 hrs after allergen challenge. 14. Able to provide an acceptable sputum sample which is suitable for analysis.
	Exclusion Criteria 1. Subjects with evidence or history of clinically significant hematological, renal, endocrine, pulmonary (excluding mild asthma in Part 3), gastrointestinal,

	cardiovascular, hepatic, neurologic, or allergic disease (excluding subjects for Part 3) (including drug allergies) at the time of screening; 2. History or presence of significant gastrointestinal, liver or kidney disease, or any other conditions known to interfere with the absorption, distribution, metabolism or excretion of drugs or known to potentiate or predispose to undesired effects. 3. History of tuberculosis and/or a positive Tuberculin Skin Test and/or QuantiFeron- TB®-Gold test. 4. Suicidal tendency, history of or disposition to seizures, state of confusion, clinically relevant psychiatric diseases. 5. Use of any immunotherapy within 3 months prior to screening. 6. History of serious adverse reaction, severe hypersensitivity or allergy to any drug/drug substance (except house dust mite, pollen allergens or cat dander allergy in asthmatics) or in any other circumstance (e.g. anaphylaxis); 7. Clinically significant abnormalities in physical examination and/or in laboratory test results (including hematology and chemistry panels, urinalysis) as assessed by the Investigator; 8. Subjects who have received any investigational drug within 2 months (60 days) or within 5 half-lives (for small molecule) or until the expected PD effect has returned to baseline (for biologics) from screening in any clinical trial (whichever is longer) or drugs that directly or indirectly inhibit calcineurin, monoamine oxidase inhibitors, tricyclic antidepressants and anti-convulsants or who are on extended follow-up; 9. Current diagnosis of active epilepsy or any active seizure disorder requiring chronic therapy with anti-epileptic drug(s); 10. Abnormal liver function (ALT >1.5 X upper limit of normal (ULN) or bilirubin >1.5 X ULN. 11. Positive screen on hepatitis-B surface antigen (HBsAg), antibodies to the hepatitis C (HCV) or antibodies to the human immunodeficiency virus (HIV) 1,2; 12. Presence of out-of-range cardiac interval (PR < 110 msec, PR > 220 msec, QRS < 60 msec, QRS >119 msec and QTcB >450 msec (female) >430 msec (male) on the screening ECG or other clinically significant ECG abnormalities. 13. Maintenance therapy with any drug or significant history of drug dependency or alcohol abuse (> 3 units of alcohol per day, intake of excessive alcohol, acute or chronic) at screening. 14. Subject who have received the drugs metabolized by CYP2C19 enzyme (e.g. omeprazole, lansoprazole, pantoprazole) within 7 days or 5 half-lives (whichever is longer) prior to dosing or who are on treatment; 15. Concomitant disease or condition that could interfere with the conduct of the study, or for which the treatment could interfere with the conduct of the study, or that would in the opinion of investigator pose an unacceptable risk to the subject in this study, including but not limited to cancer, alcoholism, drug dependency or abuse or psychiatric disease. 16. Receipt or donation of 50 mL or more of blood in the previous 28 days before day 1 of this study. 17. Receipt or donation of 500 mL or more of blood/blood product (Canadian Blood Services, Hema-Quebec, clinical studies, etc.) in the previous 56 days before day 1 of this study. 18. Tattoo application 4 weeks prior to screening.

	Additionally, for Part 3: POC 19. Use of nasal/inhaled/oral corticosteroids, intra ophthalmic corticosteroids, nasal, inhaled or intra ophthalmic cromolyn sodium or nedocromil, leukotriene receptor antagonists (e.g. zafirlukast, pranlukast, montelukast) and 5-lipoxygenase inhibitors (e.g. zileuton) within 6 weeks prior to screening; 20. Patients on long acting beta agonists (LABA) (e.g. salmeterol, formeterol) and long acting anticholinergics (tiotropium) within 6 weeks prior to screening. Use of short acting β 2 agonists (salbutamol) is allowed if clinically warranted. 21. History of life threatening asthma, defined as asthma episode that required intubation or was associated with hyperpnoea, respiratory arrest and/or hypoxia. 22. Patient with respiratory tract infection (e.g. common cold, influenza, sinusitis) or symptomatic with allergic rhinitis (e.g. hay fever) requiring treatment within 2 weeks prior to dosing.
Expected duration of participation	• SAD: up to 61 days including screening period. • MAD: up to 76 days including screening period. • POC: up to 112 days including screening and washout period.
Study procedure	This study will be conducted sequentially in three parts as SAD, MAD and POC. Unless otherwise stated in this protocol, [redacted]perating procedures (SOPs) will be followed during this study. For all study subjects, the different parts of this study are summarized in **Appendix B** for Part 1, **Appendix C** for Part 2 and **Appendix D** for Part 3. **In house stay** SAD: In-house stay from Day -1 (afternoon) to Day 3 (morning); discharge after safety assessment on Day 3. MAD: In-house stay from Day -1 (afternoon) to Day 8 (morning); discharge after safety assessment on Day 8. POC: In house stay from Day 13 to Day 15; discharged on Day 15 after allergen challenge. During in-house stay, subjects will have restricted activity and will be taking diet as specified by investigator. Subjects should not take concomitant medications unless specified in their treatment. **Ambulatory visits** SAD: Ambulatory visits Day 5, Day 8 and Day 15. MAD: Ambulatory visits on Day 9, Day 10, Day 11, Day 12, Day 13 and Day 15. POC: Ambulatory visits on Day 1, Day 3, Day 7 and Day 11 in both periods and Day 50. ***All visits should occur on the protocol specified time***. Complete listings of the assessments will be performed at each visit during the trial treatment as specified in **Appendix B, C and D**. The study drug should be administered at the clinic under supervision of investigator/designee.
Drug administration	Depending on the cohort, subject will be dispensed single dose of RP3128/placebo by pharmacy staff during SAD part of study. Subject specific doses will be dispensed during MAD and POC part of study. RP3128/placebo capsules will be administered orally in the morning with approximately 240 mL (8 fluid ounces) of water at room temperature by the subject.

	Subjects will be required to start fasting at least 10 hrs before drug administration. Fasting will continue for at least 4 hrs following drug administration, after which a standardized lunch will be served during the confinement period. Subjects should follow fasting requirements for home dosing/ambulatory visits during POC.
Sample size	This trial will enroll up to 56 HV (32 in SAD and 24 in MAD) and 12 mild asthmatics in POC. Number of subjects to be enrolled in this study is in line with standard phase I studies and is considered sufficient to provide descriptive information on the pharmacokinetics, pharmacodynamics, safety and tolerability of RP3128 while minimizing exposure to humans. The actual number of dose cohorts will depend upon the emerging safety data.
Statistical analysis	**Analysis Populations** Safety Population: This population will include all subjects who are randomized and receive a dose of study drug. There will be separate safety populations each for SAD, MAD and POC parts. PK Population: All subjects in Safety population with sufficient concentration-time data to determine the PK parameters will be included in the PK population Evaluable Population: All subjects in Safety population for POC part who have at least one post dose efficacy measurement without important protocol deviations will be included in the Evaluable population. **Safety Analyses** All safety data will be included in the subject data listings. Summary tables will be based upon the safety population. Classification of AEs will be performed by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.1 or higher. AE listings will be presented by subject, system organ class, and preferred term. The incidence of all reported AEs and SAEs will be tabulated. In addition, summary tables for AE will be presented by severity and drug relationship. For laboratory data, a list of clinically significant abnormal values will be presented. **Exploratory Analyses** The exploratory analyses will be performed in Part 2. Exploratory parameter (Th1, Th2 and Th17 cytokines) levels will be compared between RP3128 and placebo using appropriate analysis of variance models and summarized using descriptive statistics. **Efficacy Analyses** The efficacy analysis will be performed in Part 3. All subjects who receive at least one dose of RP3128 or placebo and have at least one post dose efficacy measurement without important protocol deviations will be included. The details of efficacy analysis will be presented in statistical analysis plan (SAP). **Pharmacokinetic Analyses** Subjects who provide evaluable data will be included in the pharmacokinetic and statistical analysis. The following PK parameters will be derived: C_{max}, AUC_{0-t}, AUC_{0-inf}, T_{max}, $t_{½}$ and K_{el} and estimated by non-compartmental analysis method by using a suitable software. These variables will be summarized by n, mean, standard deviation, median, minimum, and maximum by dose. The geometric means will also be presented for AUC and C_{max}.

CONTACT INFORMATION	
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PRINCIPAL INVESTIGATOR &STUDY SITE	[redacted]
SPONSOR REPRESENTATIVE	[redacted]
SPONSOR'S MEDICAL EXPERT & MEDICAL MONITOR AND SAE CONTACT	[redacted]
SCREENING AND CLINICAL FACILITY	[redacted]
SCREENING FACILITY	
CLINICAL LABORATORY	
BIOANALYTICAL LABORATORY	

List of Abbreviations

AE	Adverse Events
ALP	Alkaline Phosphatase
ALT (SGOT)	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
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_{last}	Area Under the Concentration Time Curve at Last Dose
AUC_{0-inf}	Area Under the Curve from Zero extrapolated to infinite time
AUEC	Area Under Effect Curve
BSA	Bovine Serum Albumin
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CD3/28	Cluster of Differentiation 3 / 28
CNS	Central Nervous System
C_{max}	Peak Drug Concentration
CPU	Clinical Pharmacology Unit
CRAC	Calcium Release Activated Calcium Channel
CRF	Case Report Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP2C19	Cytochrome P450 2C19
EAR	Early Phase Asthmatic Response
EC50	The Dose of a Drug That Is Pharmacologically Effective for A 50% Response in A Biological System
ECG	Electrocardiogram
ECHO	Echocardiography
EEG	Electro Encephalo Gram
FDA	Food and Drug Administration
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume, 1 second
FIH	First in Human
FSH	Follicular Stimulating Hormone
GCP	Good Clinical Practices
GGT	Gamma Glutamyl Transpeptidase
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface Antigen
HbA1c	Glycated Hemoglobin
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HED	Human Equivalent Dose
HIV	Human Immune Deficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
HV	Healthy Volunteers
hrs	Hours
IB	Investigator Brochure
IC50	Half Maximal Inhibitory Concentration
ICH	International Conference On Harmonization
ICF	Informed Consent
IEC	Independent Ethics Committee
IL	Interleukin

IMP	Investigational Medicinal Product
IFNγ	Interferon gamma
ISF	Investigator Site File
IUD	Intrauterine Device
K_{el}	Elimination Rate
LABA	Long acting Beta Agonists
LAR	Late Phase Asthmatic Response
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LLN	Lower Limit of Normal
LPS	Lipopolysaccharide
MAD	Multiple Ascending Dose
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCT	Methacholine Challenge Test
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Authority
MMSE	Mini Mental State Examination
MTD	Maximum Tolerated Dose
MRI	Magnetic resonance imaging
NOAEL	No-Observed-Adverse Effect Level
n	Number
NSAID	Non-Steroidal Anti Inflammatory Drug
OTC	Over the Counter
PD	Pharmacodynamics
PDGF	Platelet Derived Growth Factor
PI	Principal Investigator
PK	Pharmacokinetics
PO	Per Oral
POC	Proof of Concept
PP	Per Protocol
PT/INR	Prothrombin Time/International Normalized Ratio
PVP	Poly Vinyl Pyrolidone
QA	Quality Assurance
QD	Quaque die
QTcB	Bazett's (QTc) Formulas
SAD	Single Ascending Dose
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SDV	Source Document Verification
SCID	Severe Combined Immunodeficiency
SOP	Standard Operating Procedures
SPT	Skin Prick Testing
SRC	Safety Review Committee
$t_{1/2}$	Elimination Half Life
TB	Tuberculosis
TH1/TH2/TH17	T Helper 1 / 2 / 17 Cells
t_{max}	Time at Which Maximum Concentration Is Achieved
TNCB	2-chloro-1,3,5-trinitrobenzene
TNF α	Tumor Necrosis Factor
TSH	Thyroid Stimulating Harmone
ULN	Upper Limit of Normal
WHO	World Health Organization
λ_z	Terminal Rate Constant

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1 INTRODUCTION

1.1 Background

Calcium release-activated calcium (CRAC) channels belong to the class of store-operated channels (SOC) that are present on the plasma membrane of non-excitable cells (lymphocytes and mast cells) and mediate immune responses[1]. Activation of CRAC channels via depletion of endoplasmic reticulum stores results in alteration in calcineurin/ NFAT-dependent expression of several cytokines including interleukin-2 (IL-2). While calcineurin inhibitors are potent immunosuppressive agents, they are limited by nephrotoxicity and neurotoxicity. Because localization of the CRAC channels is restricted to non-excitable cells, inhibition of calcium influx by altering CRAC channel activity is expected to be an effective strategy for the treatment of autoimmune and inflammatory diseases devoid of side effects. Furthermore, studies in subjects with non-functional CRAC channels suggest that inhibition of this target both safe and efficacious.

Abnormal CRAC channel activity is associated with several diseases including asthma, rheumatoid arthritis, thrombosis, cancer, severe combined immunodeficiency (SCID), and inflammatory bowel disease[2].The contribution of CRAC channels to asthma stems for several studies in pre-clinical models wherein these channels have been shown to regulate mast cell activation and subsequent downstream effects[3]. Drugs targeting CRAC channels could therefore be of immense clinical benefit.

1.2 RP3128

RP3128 (N- (6- (5- cyclopropyl -3 - (trifluoromethyl) - 1H-pyrazol – 1 -yl) pyridin- 3 - yl) - 2 methylbenzamide) is a potent and orally available inhibitor of Calcium release activated calcium (CRAC) channels. Chemically, RP3128 is a pyridyl substituted benzamide.

1.3 Summary of RP3128 Preclinical Evaluations

1.3.1 In Vivo Activity

RP3128 in a potent inhibitor of CRAC channels, blocking thapsigargin (TG) induced calcium influx, antigen-induced cytokine production, and NFAT driven promoter activity in leukocytes. RP3128 also inhibits lung IL-4 and airway eosinophil infiltration in animal models of asthma. Summary of pre-clinical findings are outlined below[4]:

Study	Procedure outline	Results	Conclusion
Thapsigargin induced calcium influx	Blockade of CRAC channel in presence of 1 μM thapsigargin	IC_{50} in Jurkat = 40.53 nM IC_{50} in Monocytes = 370.4 nM IC_{50} in B-cells = 3789 nM IC_{50} in T-cells = 45.26 nM	High selectivity towards T-lymphocytes

Mast cell degranulation	RBL-2H3 cells were treated with vehicle or RP3128 followed by antigen activation.	IgE induced IC50 = 21.60 nM TG induced IC50 = 225.8 nM	Potent inhibition of mast cell degranulation
CRAC channel electrophysiology	Patch clamp was conducted on tight cell whole cell configuration in Jurkat cells. ICRAC was measured on cells treated with vehicle or RP3128.	IC50 in Jurkat = 0.103 µM	Potent inhibition of CRAC channel currents
PHA + PMA induced IL-2 release in Jurkat cells	Cells were treated with vehicle of compound followed by induction with PHA + PMA for 24 h. Supernatant was collected and IL-2 were estimated by ELISA.	IC50 for IL-2 release in Jurkat = 57.46 nM	Inhibition of CRAC channel mediated IL-2 secretion
PHA + PMA or Con A + PMA induced cytokine secretion in isolated human T-cells	Cells were treated with vehicle of compound followed by induction with ConA + PMA for 24 h for PHA + PMA for 48 h. Supernatant was collected and cytokines were estimated by ELISA.	TNFα IC50= 364.6 nM IFNγ IC50= 541.6 nM IL-2 IC50= 543.8 nM IL-10 IC50= 34.19 nM	Potent inhibition of pro-inflammatory cytokine release from T-cells
NFAT dephosphorylation in transfected HEK293 cells	Cells were incubated with RP3128 or vehicle for 24 and stimulated with PMA + Ionomycin.	Dose-dependent inhibition	Potent inhibition of NFAT dephosphorylation
fMLP induced elastase exocytosis	Neutrophils were isolated from healthy donor blood, treated with RP3128 or vehicle followed by induction using fMLP. Labeled-elastase substrate was added to estimate the amount	Dose-dependent inhibition	Inhibition of neutrophil functionality
fMLP induced Neutrophil migration	Neutrophils were isolated from healthy donor blood, treated with RP3128 or vehicle followed by induction using fMLP in migration plates. Cells were stained by crystal violet to estimate migration.	Dose-dependent inhibition	Inhibition of neutrophil functionality
PHA + PMA or ConA + PMA induced	Cells were treated with vehicle of compound followed by induction with	TNFα IC50= 35.77nM IFNγ IC50= 185.7 nM IL-2 IC50= 57.37 nM	Potent inhibition of Th1, Th2,

cytokine secretion in isolated human PBMCs	ConA + PMA for 24 h for PHA + PMA for 48 h.	IL-17 IC50= 56.63 nM IL-4 IC50= 327.8 nM IL-5 IC50=233.6 nM	and Th17 cytokines in isolated cell systems
PHA + PMA or ConA + PMA induced cytokine secretion in human whole blood	Cells were treated with vehicle of compound followed by induction with ConA + PMA for 24 h for PHA + PMA for 48 h. Supernatant was collected and cytokines were estimated by ELISA.	TNFα IC50= 350.3 nM IFNγ IC50= 665.0nM IL-2 IC50= 69.4 nM IL-17 IC50= 319.7 nM IL-4 IC50= 372.8 nM IL-5 IC50= 186.9 nM	Potent inhibition of Th1, Th2, and Th17 cytokines in human whole blood

1.3.2 In Vitro Activity

Translation of in vitro activity to in vivo efficacy was assessed in animal models relevant to respiratory disorders, rheumatoid arthritis, psoriasis, and Inflammatory Bowel Disease (IBD) [5].

Study	Procedure outline	Results	Conclusion
Delayed type hypersensitivity (DTH)	RP3128 Dose = 10 mg/kg/p.o. Methylated BSA induced foot paw DTH in mice (Single dose study)	Reduced paw thickness by 40%	Therapeutic potential in immuno-inflammatory disorders. Efficacy equivalent to cyclosporine (10 mg/kg/ip)
Contact hypersensitivity	RP3128 Dose = 0.3, 1, 3 and 10 mg/kg/p.o. Topical application of 2-chloro-1,3,5-trinitrobenzene (TNCB) to mice ear pinnae (Single dose study)	ED50 = 1.28 mg/kg/p.o.	Therapeutic potential in immuno-inflammatory disorders. Consistent with DTH.
DNFB induced DTH	RP3128 Dose = 3, 10 and 30 mg/kg/p.o. DNFB sensitization (D0, D1) followed by TNCB challenge (D5) on mice ear pinnae.	ED50 = 7.95 mg/kg/QD/p.o.	Potent inhibition of T-cell mediated inflammatory response. Inhibition equivalent to dexamethasone

	Ear thickness measured on D7. RP3128 administered D2 to D7		(10 mg/kg/QD/p.o)
Imiquimod induced psoriasis	RP3128 = 25 mg/kg/QD/p.o. Positive control = Cortisone acetate = 0.25 mg/kg/QD/p.o.	Significant reduction macroscopic score (Day 10) as well as in back skin Epidermal thickness (37%) upon H & E staining similar to cortisone	Reduced psoriatic symptom compared to un-treated group.
Collagen induced arthritis	RP3128 Dose = 7.5, 15, 30, 60 mg/kg/p.o. Collagen sensitization and challenge followed by therapeutic dosing in Male DBA/1OlaHsd Mice	Dose dependent inhibition of arthritis at doses 15 mg/kg/QD/p.o. and 60 mg/kg/QD/p.o.	Potent in vivo anti-arthritic activity. Better efficacy compared to methotrexate (2 mg/kg/QD/p.o.)
Inflammatory bowel disease (IBD)	Single dose TNBS induced in rat with RP3128 at 50 mg/kg/QD/p.o. (7 days).	Significantly reduced colonic weight and thickness along with reduction in ulcer length.	Potent inhibitor of ulcerative colitis. Disease score comparable to prednisolone (10 mg/kg/QD/p.o.)
LPS induced pulmonary neutrophilia	RP3128 Dose = 0.3, 1, 3, 10 mg/kg LPS (1 mg/kg/it) challenged rats. Lung BALF collected after 6 h. TLC and DLC estimated.	ED50 = 0.52 mg/kg/PO (Single dose study)	Therapeutic role in neutrophil-mediated inflammation
LPS induced TNFα in blood	RP3128 Dose = 3, 10, 30 mg/kg/p.o. LPS (1 mg/kg/it) challenged Wistar rat. Blood collected after 2 h. TNFα estimated by ELISA	Dose dependent inhibition of TNFα after TPS administration	Therapeutic role in inflammation
In vivo mast cell degranulation	RP3128 Dose = 0.1, 1, 3, 10 mg/kg/p.o. IgE induced in blood (mice) RP3128 Dose = 10 mg/kg/p.o.	Dose dependent reduction in IgE induced histamine with ED50 0.64 mg/kg/QD/p.o. of	Potential therapeutic role in histamine mediated inflammations and allergic asthma

	Ovalbumin induced in BALF (guinea pig)	Significant reduction in histamine level in BALF (guinea pig)	
Ovalbumin induced eosinophilia	RP3128 Dose = 0.1, 1, 3, 10 mg/kg/p.o. Ovalbumin sensitization in guinea pigs followed by therapeutic dosing of RP3128. TLC and DLC to estimate eosinophil count	ED50 = 0.6 mg/kg/QD/p.o.	Therapeutic potential in asthma
Citric Acid-induced Cough Reflex	RP3128 Dose = 3 mg/kg/p.o. Citric acid aerosol inhalation in plethysmograph chamber in ovalbumin sensitized guinea pigs	Significant reduction in cough reflex, 2 h after administration RP3128	Potential anti-tussive role for RP3128.
Exhaled NO and IHC in asthma	RP3128 Dose = 3 mg/kg/p.o. IHC was performed along with estimation of exhaled NO in ovalbumin sensitized guinea pigs	Significantly reduced exhaled NO along with mast cell and eosinophil infiltration in lung tissues	Potent effect on symptomatic markers.
Cytokines in serum and BALF	RP3128 Dose = 3 mg/kg/p.o. BALF and serum from Ovalbumin sensitized guinea pigs were determined by ELISA to estimate cytokines	IL-4, IL-3 and TNFα were inhibited However, IL-5 was unaffected.	Potent effect on downstream pharmacodynamic markers in vivo

1.3.3 Toxicology

In 28-days toxicological investigations in Wistar rat at doses 50, 150, and 500 mg/kg. RP3128 caused dose-dependent reductions in body weight at 150 mg/kg/day and above that was most pronounced at Days 4 and 7. Dose levels were therefore adjusted to 25, 75, and 200 mg/kg. After the dose level changes, body weights trended toward control levels.

CNS-related clinical signs, and reduced food consumption and early mortality were observed at 150 mg/kg/day RP3128 and above with changes more severe in female animals compared to male animals. In addition, RP3128-related changes in hematology parameters included increased reticulocytes and erythrocyte distribution width with slight reductions in red cell counts at 150 mg/kg/day and above. RP3128-related changes in clinical chemistry

parameters included increased cholesterol at 50/25 mg/kg/day and above. Based on these results, the no-observed-adverse-effect level (NOAEL) was considered to be 50/25 mg/kg/day. On day 1, an exposure (AUC_{0-24h}) of 93.0 µg.hr/mL in males and 100.0 µg.hr/mL in females was observed. On day 28, the exposures (AUC_{0-48h}) in males was 275.0 µg.hr/mL and 289.0 µg.hr/mL.

In 28-days toxicological investigations in Cynomogus monkeys[5] at doses 5, 25, and 150 mg/kg, RP3128-related clinical signs included significant signs associated with CNS abnormalities (tremors, decreased activity, incoordination, hunched posture, and dilated pupils) at 150 mg/kg that necessitated the reduction in dose to 75 mg/kg. Beside the significant CNS-related clinical signs (observed in 3 females) at 150 mg/kg, effects seen in the 150/75 mg/kg included reduced body weight, and increases in cholesterol. At 25 mg/kg/day, RP3128 caused in non-adverse elevation of cholesterol.

Based on these results, the no-observed-adverse-effect level (NOAEL) was considered to be 25 mg/kg/day while the no observed effect level (NOEL) was 5 mg/kg/day. The NOAEL dose 25 mg/kg/day had an exposure (AUC_{0-24h}) of 64.40 µg.hr/mL for males and 78.5 µg.hr/mL for females on day 1. On day 28 the exposure (AUC_{0-48h}) for males was 53.50 µg.hr/mL and 154.00 µg.hr/mL.

1.4 Rationale

1.4.1 Rationale for the Trial

Calcium Release Activated Calcium (CRAC) channels constitute major pathway for Ca++ influx in immune cells. The CRAC channel regulated Ca++ entry, in turn mediates the production and secretion of key pro-inflammatory cytokines such as IL-2, TNF-α, IL-4, IL-5 etc. and is proven to be essential for adaptive immune responses in humans.

Abnormal CRAC channel activity is associated with several diseases including asthma, rheumatoid arthritis, thrombosis, cancer, severe combined immunodeficiency (SCID), and inflammatory bowel disease. The contribution of CRAC channels to asthma and other inflammatory diseases stems for several studies in pre-clinical models wherein these channels have been shown to regulate mast cell/cytokine activation and subsequent downstream effects. Drugs targeting CRAC channels could therefore be of immense clinical benefit.

RP3128 has demonstrated efficacy in pre-clinical in vitro and in vivo models relevant to respiratory disorders, rheumatoid arthritis, psoriasis, and Inflammatory Bowel Disease (IBD). In cell based assay, RP3128 demonstrated dose dependent inhibition of immune cell functionality and reduction of delayed type hypersensitivity and contact hypersensitivity. RP3128 demonstrated efficacy in a range of in vivo models representative of various inflammatory diseases[6] (e.g. Imiquimod induced psoriasis. Collagen induced arthritis. Inflammatory bowel disease (IBD), LPS induced pulmonary neutrophilia. LPS induced TNFα in blood, In vivo mast cell degranulation. Ovalbumin induced eosinophilia. Citric Acid- induced Cough Reflex, Exhaled NO and IHC in asthma and Cytokines in serum and BALF. Based on these efficacy results, it is expected that RP3128 would be a good drug

candidate to be investigated in clinical studies in patients with in various inflammatory and airway diseases.

Therefore, this Phase I study is planned to evaluate the safety tolerability of RP3128 in SAD and MAD study and evaluate clinical efficacy in POC study.

1.4.2 Rationale for the Starting Dose

The relevant species following the conduct of 28 day toxicology studies was determined to be rat. For selection of the starting dose an mg/kg approach was used based on the FDA Guidance[7]. A safety factor of 1/10 of the HED (Human Equivalent Dose) was considered to be appropriate to determine the starting dose for human. Based on the NOAEL obtained in the relevant species (Wistar Rat), the starting dose was determined to be 25 mg. The highest dose administered will be decided on the basis of observed safety and PK data obtained during human dose escalation.

2 TRIAL OBJECTIVES

2.1 Primary Objectives:

- **Part 1 (SAD):** To investigate the safety and tolerability of single ascending oral doses of RP3128 in 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.
- **Part 3 (POC):** To evaluate allergen induced late phase asthmatic response (LAR) as measured by maximal percent decrease in the forced expiratory volume 1 second (FEV_1) and area under the effect curve (AUEC) from baseline (pre-allergen challenge) to the period beginning 3 hrs and ending 8 hrs after allergen challenge at the highest identified dose of RP3128.

2.2 Secondary Objectives:

- **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.
  - To evaluate ex-vivo effect of RP3128 on various biomarkers (Th1, Th2 and Th17 cytokines) following LPS or CD3/CD28 stimulation.
- **Part 3 (POC)**
  - To evaluate the allergen induced early phase asthmatic response (EAR) as measured by maximal percent decrease in the FEV_1 and AUEC from baseline

(pre-allergen challenge) to the first 3 hrs after allergen challenge at the highest identified dose of RP3128.
- Absolute count, percentage differential count of sputum eosinophils and neutrophils at approximately 8 and 24 hrs after allergen challenge in RP3128.
- FeNO change from baseline (pre-challenge) compared to 3, 8 and 24 hrs post-allergen challenge.

3 TRIAL DESIGN

3.1 Trial endpoints

3.1.1 Primary endpoint

- SAD: Adverse Events (AEs), clinical laboratory tests, vital signs, physical examination and 12 lead ECG after a single dose
- MAD: AEs, clinical laboratory tests, vital signs, physical examination and 12 lead ECG after multiple doses.
- POC: Maximal percentage decrease from pre-allergen challenge in FEV_1 during 3 hrs to 8 hrs post allergen challenge.

3.1.2 Secondary end points

- SAD:
  - PK parameters including C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, T_{max}, $t_{½}$ and K_{el}
- MAD:
  - PK parameters including C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, T_{max}, $t_{½}$ and K_{el}
  - Levels of various biomarkers (Th1, Th2 and Th17 cytokines) following LPS or CD3/CD28 stimulation.
- POC:
  - Maximal percentage decrease from pre-allergen challenge in FEV1 during 0 to 3 hrs post allergen challenge.
  - Post allergen challenge $AUEC_{0\text{-}3h}$, $AUEC_{3\text{-}8h}$
  - Change in FeNo (Pre-challenge to 3, 8 and 24 hrs post allergen challenge)
  - Absolute and percentage (%) differential counts of eosinophils and neutrophils at 8 and 24 hrs post allergen challenge.

3.2 Design of trial

This study is an integrated, single centre, Phase I/IIa protocol divided into three parts; a SAD (Part 1) and a MAD (Part 2) studies in HV and a proof-of-concept study in subjects with mild asthma (Part 3). All subjects will receive RP3128 or matching placebo as per part of the study described below. The Investigator will have overall responsibility for any safety and tolerability decisions. Details of study measurements and assessments are included in **Appendix B** (Part 1), **Appendix C** (Part 2) and **Appendix D** (Part 3).

3.2.1 Part 1: Single Ascending Dose (SAD)

This is a randomized, double-blind (except first cohort), placebo controlled SAD study in 32 HV to evaluate the safety, tolerability and pharmacokinetics of single dose of RP3128.

In each cohort, subject will receive a single oral dose of RP3128/placebo. Within each cohort, 2 sentinel subjects will be dosed first for safety assessment. Safety and tolerability data up to 24 hrs will be reviewed along with any observation up to 36 hrs by the investigator prior to dosing the remaining subjects at that dose level. The remainder of the cohort will be dosed sequentially at least 48 hrs after confirming safety and tolerability of sentinel cohort.

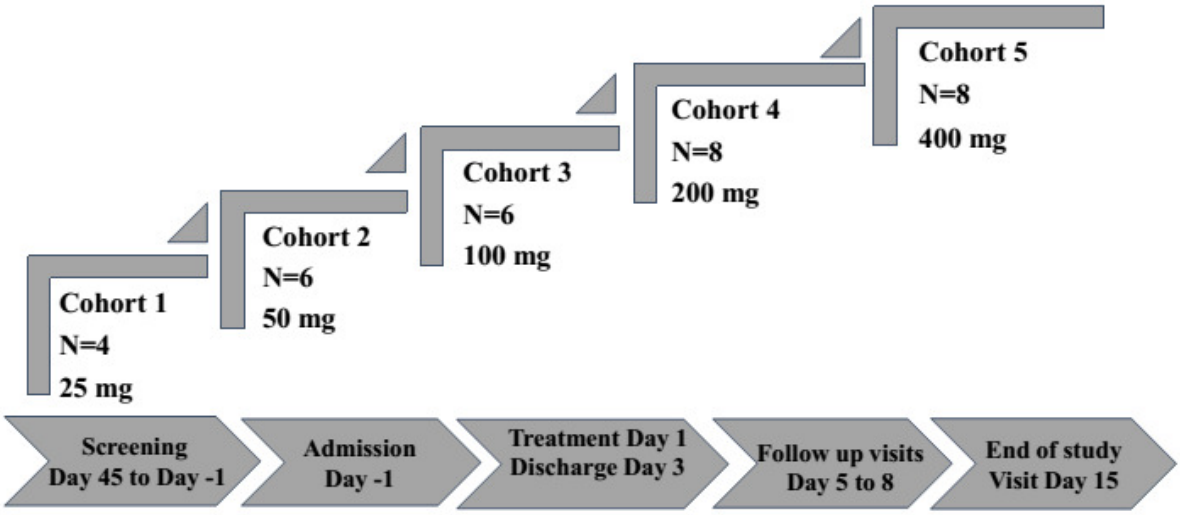
The cohorts will be dosed sequentially so that a minimum of 8 days is allowed between the dosing of ongoing cohort and the next cohort, only after confirming safety, tolerability and PK of existing dose by the Safety Review Committee (SRC). In case of safety concern, additional subjects may be added to cohort for safety assessment as per the decision of SRC. The details of dose escalation cohorts are given in Table 1

Table 1 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)
[$] Actual doses administered may change based on emerging safety, tolerability and PK data.
[$$]In case of safety concern, additional subjects may be added to cohort for safety assessment as per the decision of SRC

Figure 1 Study design and Dose escalation for Part 1 (SAD)



3.2.2 Part 2: Multiple Ascending Dose

This is a randomized, double-blind, placebo controlled MAD study in 24 HV to evaluate the safety, tolerability and pharmacokinetics of repeat doses of RP3128. The selection of daily doses of RP3128 for Part 2 are anticipated to be the maximum well tolerated dose selected from Part 1.

In each cohort, subject will receive once a day, oral dose of study drug/placebo in ratio of 3:1 from Day 1 to Day 7. Within each cohort, 2 sentinel subjects will be dosed first for safety assessment. Safety and tolerability data up to 24 hrs following the first dose will be reviewed along with any observation up to 36 hrs by the investigator prior to dosing the remaining subjects at that dose level. The remainder of the cohort will be dosed sequentially at least 48 hrs after confirming safety and tolerability of sentinel cohort.

If the dose selected for Part 2 is not well tolerated on repeat dosing, the dose may be reduced or given as divided doses. Refer Table 2

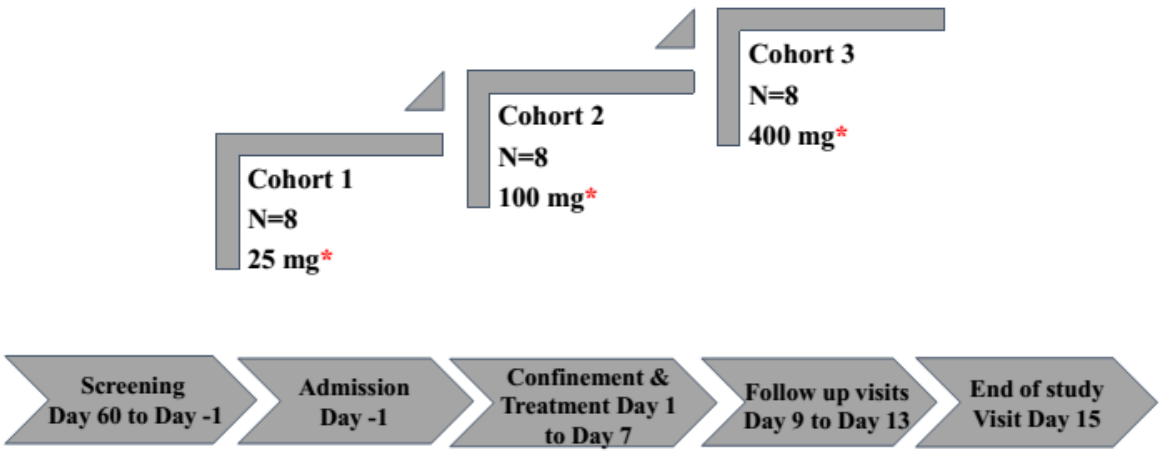
Table 2 Dose escalation strategy for Part 2 (MAD)

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

[$] Actual doses administered may change based on emerging safety, tolerability and PK data.
[$$] In case of safety concern, additional subjects may be added to cohort for safety assessment as per the decision of SRC.

The cohorts will be dosed sequentially so that a minimum of 8 days is allowed between last dose of ongoing cohort and first dose of next cohort, only after confirming safety, tolerability and PK of existing dose. Progressing to the next dose level will only occur if previous dose level is deemed to be safe and well tolerated by the SRC.

Figure 2 Study design and Dose escalation for Part 2 (MAD)



*Dose may change depending on emerging safety data.

3.2.3 Part 3: POC (n=12)

This is a randomized, double-blind, cross-over, placebo controlled, proof-of-concept study in 12 patients with mild asthma to evaluate the effect of RP3128 on late phase asthmatic response to allergen challenge.

Mild asthmatic patients will be randomized to receive RP3128/ placebo in the ratio of 1:1. Each subject will receive single oral dose of RP3128/placebo once a day for 14 days from Day 1 to Day 14 in both treatment periods. The selection of daily doses of RP3128 for Part 3 are anticipated to be the maximum well tolerated dose selected from Part 2. The treatment periods will be separated by a washout period of 14 days. The washout period may vary depending on the safety, tolerability and PK data from the SAD/MAD part. The selection of daily doses of RP3128 for Part 3 are anticipated to be the maximum well tolerated dose selected from Part 2. If the dose selected for Part 3 is not well tolerated on repeat dosing, the dose may be reduced or given as divided doses (Table 3**)**

Table 3 Dosing strategy for Part 3 (POC)

	Period 1	**Period 2**	**Number of Subjects**
Sequence 1	RP3128 400 mg[$]	Placebo	6
Sequence 2	Placebo	RP3128 400 mg[$]	6
Total			12

[$] Actual doses will be based on emerging safety, tolerability and PK data from Part 2.

3.3 Dose escalation procedure

The dose escalation decisions in Part 1 and Part 2 will be made by the Safety Review Committee (SRC). After completion of each cohort, the SRC will review safety, tolerability and PK data of RP3128/placebo to confirm the dose limiting toxicity (DLT) of the existing dose, determination of Maximum Tolerated Dose (MTD), and make a decision to escalate to the next dose level.

- Subjects who have completed 4-days safety follow up in SAD (Subjects visiting on day 5) and 7-days safety follow up in MAD (Subject visiting Day 15) will be considered for safety review. The subjects withdrawn after 48 hrs of safety follow up due to non-safety reasons will be considered for dose escalation decisions. The reason for withdrawal of such patients will be appropriately documented.
- Safety data includes medical history, vitals, physical examination, hematology and biochemistry, ECG, AE, SAE and adverse events of special interest (pregnancy, overdose) and DLT throughout 4-days (SAD) and 7-days (MAD) from the last dose of study drug. PK data through 48 hours after the last dose will be considered for dose escalation.
- Blinded data will be used (except for cohort 1) for dose escalation procedure. Limited unblinding of the SRC is allowed at the time of dose-escalation review to improve the

accuracy of safety-related decisions. If un-blinding of data is required during the review, the timings of un-blinding and reason for un-blinding will be documented.

- The data from at least 3 subjects (Cohort S1), 5 subjects (Cohort S2 and S3), 7 subjects (Cohort S4 and S5) in SAD part; and 7 patients in all three cohorts (Cohort M1-M3) in MAD part will be required for safety review.
- The data will be subjected to a QC review prior to the dose. Progression to next higher dose will only occur if previous dose level is deemed to be safe and well tolerated by SRC.
- Depending on the nature and the timing of the toxicities encountered and the pharmacokinetic data from dosing of RP3128, planned dose escalation may be modified to include the repetition of a dose based on the results of the safety and tolerability review, or if further characterization of the safety profile at that dose is required. Alternative dose (intermediate dose level or a lower increment) can also be done by SRC.
- Section 3.8 will be used as an example for the determination of the MTD. In case of any criteria that meeting cohort termination criteria, the ongoing dose will be defined as ***the dose exceeding MTD***; No further dose escalation will be done thereafter. ***The previous dose level will be considered as the MTD*** and will be considered for the next part of the study as decided by the SRC.
- If the MTD is not reached after completing the planned sequential groups, highest dose will be considered an optimal dose. No additional groups will be included.
- The further details of dose escalation will be covered in the Safety Management Plan.

3.4 Safety Review Committee

The SRC will be constituted by the sponsor in consultation with the Investigator and will consist of Study Investigator, Sponsor Representative, Sponsor's Medical monitor, Safety physician, Neurologist, PK/PD expert and a Statistician. In addition, an independent respirologist will be part of the SRC in POC, and will be responsible for reviewing the POC safety data. The SRC will meet and review the blinded safety and PK data at the end of each cohort and as required by the sponsor/investigator to assess the safety and tolerability of study drug. The further details of SRC charter will be covered in Safety Management Plan.

3.5 Randomization and Blinding.

This is a double blind randomized, placebo controlled study. A simple randomization will be used. After confirmation of eligibility, subjects will be assigned a subject number in the order in which they are randomized in the study. A separate randomization schedule will be used for study Part 1, 2 and 3 as indicated in the tables above.

The study will be double blinded except for first dose level in SAD part. All study personnel including investigators and study nurses will remain blinded to the treatment allocation except the pharmacy department, statisticians preparing the randomization, the bioanalytical assay group, study monitor reviewing pharmacy procedure and drug dispensing; and QA auditor. ***Limited unblinding of the SRC is allowed at the time of dose-escalation review to improve the accuracy of safety-related decisions.*** The treatment allocation codes corresponding to each subject randomized in trial will be sealed in envelopes and maintained safely in the pharmacy department. In the event of a medical emergency, when management

of subject condition requires knowledge of trial medication, the sealed code-break envelope provided may be opened by personnel authorized by the investigator. The date on which code was broken along with details of person responsible must be documented.

3.6 Investigational Medicinal Product

3.6.1 Dosage form and Strengths

Investigational Product	Dosage form and strength	Manufacturer
RP3128	25 mg, 100 mg and 200 mg capsules	Wuxi Apptec (Shanghai) Co. Ltd

Additional information can be found in the current RP3128 Investigator Brochure.

Rhizen Pharmaceuticals SA will be responsible for ensuring that the IMP is manufactured in accordance with applicable Good Manufacturing Practice regulations and requirements. All labels for the study drug will meet applicable requirements of the protocol.

3.6.2 Labelling, Packaging and supply

The IMPs (RP3128 and matching placebo) will be bulk supplied by Rhizen Pharmaceuticals, SA in high density polyethylene (HDPE) containers to investigational site. The IMP will be packed and labeled by Rhizen Pharmaceuticals, SA as per the GMP regulations and requirements. All labels for the study drug will meet applicable requirements. The Rhizen pharmaceuticals will supply the study drug to the clinical site.

3.6.3 Preparation and Administration of Investigational Products

RP3128/placebo will be available as 30 capsules per bottle. The inactive ingredients used are Croscarmellose Sodium, Microcrystalline cellulose, PVP VA64, Magnesium Stearate, Sodium Lauryl sulfate and purified water.

Depending on the cohort, subject will be dispensed single dose of RP3128/placebo by pharmacy staff during SAD part of study. Subject specific doses will be dispensed during MAD and POC part of study. RP3128/placebo capsules will be administered orally in the morning with approximately 240 mL (8 fluid ounces) of water at room temperature by the subject. The capsule must be swallowed whole and must not be chewed or broken. RP3128/placebo capsules should NOT be crushed/opened or chewed.

Subjects will be required to start fasting at least 10 hrs before drug administration. Fasting will continue for at least 4 hrs following drug administration, after which a standardized lunch will be served during the confinement period. Subjects should follow fasting requirements for home dosing/ambulatory visits during POC.

Food and fluid intake other than water will be controlled for each housing period and for all subjects. Drinking water will be permitted *ad libitum* with the exception of one-hour prior to and one-hour following drug administration. Subjects will be instructed to follow the same for home dosing.

If a dose of RP3128/placebo is missed, it should be taken as soon as possible the same day. If it is missed for the entire day, it should not be replaced. If vomiting occurs, no attempt should be made to replace the vomited dose. In Part 3 (POC), study drug compliance will be evaluated at each visit using diary card. Missed doses should be documented.

Administration of study drug will be staggered between subjects for the purpose of accurate sampling time.

3.6.4 Storage and Handling

The clinical site will maintain an inventory record of the investigational products received, stored in a secure restricted area, and dispensed. Investigational products will be provided to study subjects only.

Upon completion or termination of the study, the unused investigational products will be stored and kept for the same period of time as the reserve samples in their original containers. This includes containers of investigational products that were partially used as well as unopened supplies that were never dispensed.

3.6.5 Accountability of Investigational Products

The PI (or designee) is responsible for accountability of all used and unused trial drug supplies at the site. The study monitor will verify receipt of investigational product at the site during monitoring visit(s), and will conduct an inventory of remaining clinical trial supplies at the site close-out visit. All trial drug inventories must be made available for inspection by the monitor, sponsor representatives and regulatory agency inspectors upon request. At the end of the trial, a "Drug accountability Form" will be completed by the site and will accompany the clinical trial supplies that will be returned or destroyed according to local institutional policy.

3.6.6 Precautions and Risks Associated with Investigational Products

RP3128 is under development for potential beneficial effects on cellular immune function and cellular trafficking. Anticipated risks associated with inhibition of CRAC channel, based on the pre-clinical experience and the drugs of similar profile, and guidance on the management thereof are outlined below.

CNS abnormality:

- RP3128 may cause CNS abnormalities (tremors, decreased activity, un-coordination, hunched posture, and dilated pupils, seizures, disturbed consciousness, or speech disorders), however pathogenesis of these CNS abnormalities is not still completely understood. It has therefore been suggested that in case of subject developing these symptoms, an electroencephalogram (EEG)/MRI (as required) as performed as part of evaluation, if required.
- Most of the CNS abnormality have been reported at the high doses of drug. Therefore, the first step in the treatment of symptoms is to discontinue the study drug and corrections of the symptoms including correction of electrolyte abnormality and control of hypertension if present.

Infection:

- Subject may be at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections due to immunosuppression. Subjects with current, active, or latent infection must be excluded from early phase studies (subjects with latent tuberculosis, hepatitis B and C, and HIV should be excluded from these trials).
- Any infection that occurs in the middle of an early phase study should be treated at the discretion of the Investigator and the subject should be referred for additional clinical evaluation as appropriate.

Respiratory irritation:

- In the event of acute asthma or acute upper or lower airway irritation, the subjects should be advised to use a short acting β-2 agonist and seek medical advice as soon as possible.

Drug Interactions

- Concomitant administration of drugs directly or indirectly inhibits calcineurin, monoamine oxidase inhibitors, tricyclic antidepressants and anti-convulsants, are not recommended to use with the study drug. Subjects who are on these treatments should be excluded from the study.
- Concomitant anti-asthma treatment (e.g. Salmeterol, formeterol, tiotropium, inhaled corticosteroid, montelukast) are not recommended to use with the study drug and should be discontinued prior to study treatment. Short acting inhaled β-2 agonist can be administered according to individual's need.
- Based on pre-clinical experience with RP3128, subjects who have received the drugs metabolized by CYP2C19 enzyme (e.g. omeprazole, lansoprazole, pantoprazole) within 7 days of dosing or who are on treatment) should be excluded from the study or these drugs should be withdrawn 7 days or 5- half-life (whichever is longer) prior to treatment initiation.

3.7 The expected duration of subject participation and follow-up

The expected duration of subject participation in the study is:

- SAD: up to 61 days including screening period.
- MAD: up to 76 days including screening period.
- POC: up to 112 days including screening and washout period.

The follow up assessments are detailed in **Appendix B** for part 1 and **Appendix C** for part 2 and **Appendix D** for part 3**.** In case of drug related SAE/AE, the subjects will be followed till the resolution/stabilization of the AE or 30 days after the last study dose, whichever is earlier.

3.8 Study/Cohort Stopping and Subject discontinuation criteria

The occurrence of any of the following criteria will serve as the basis for placing the **study/cohort on hold**, pending a thorough safety review by the SRC. Following a full safety review, a decision will be made to resume or terminate the study/cohort by the SRC.

- Two (2) or more treatment-related AE, CTCAE Grade 3 or higher;
- Two (2) or more subjects experience a serious adverse event (SAE);
- Two (2) or more subjects experience the same AE (from the list below):
  - Neurological symptoms (tremors, decreased activity, un-coordination, hunched posture, and dilated pupils, seizures, disturbed consciousness, or speech disorders)
  - Severe systemic infection or opportunistic infection that requires treatment (e.g., sepsis, mycoses, pneumonia);
  - Nausea, vomiting, diarrhea, or anorexia, CTCAE Grade 3 or higher;
  - Clinical significant weight reduction
  - A relative decline in FEV1; > 15% from baseline, confirmed by repeated measurement;

3.8.1 Cohort Stopping criteria

Cohort will be terminated if emerging safety findings confirm increased risk to remaining subjects or significantly altered risk-benefit assessment; examples include but are not limited to the following:

- Predefined exposure limit [Cmax-9.68 μg/ml and AUC_{0-48} - 275μg.hr/ml] has been reached.
- Drug related severe adverse events of the same character in 50% or more subjects, as assessed by the SRC.
- Occurrence of multiple clinically significant severe adverse events, which are judged by the investigator to be causally related to RP3128; examples include but are not limited to the following:
  - Two or more subjects have asymptomatic, QTc interval ≥ 500 msec OR increase in interval ≥ 60 msec above baseline. Finding should be persisting for at least 5 minutes on repeated ECGs.
  - Two or more subjects develop an increase in resting supine blood pressure to above 180 mmHg or diastolic blood pressure above 110 mmHg for at least 10 minutes.
  - Two or more subjects have hepatic toxicity defined as one or more of: Confirmed (within 48 hrs) increase of > 3X ULN of either ALT or AST, or > 2X ULN for bilirubin or ALP.
  - One or more subjects have hepatic toxicity defined as one or more of: have ALT ≥ 3X ULN and bilirubin ≥ 2X ULN in the absence of significant increase in ALP where no other reason can be found to explain the combination of increases (e.g. elevated serum ALP indicating cholestasis, viral hepatitis, another drug (e.g. erythromycin).
  - One or more subjects experience a drug related SAE or a drug-related clinically significant non-serious AE as assessed by the SRC.
- Other findings that at the discretion of the SRC indicate that further dose escalation should be stopped.

In case of cohort termination, ongoing dose level will be defined as the dose exceeding MTD; No further dose escalation will be done thereafter. The previous dose level will be

considered as the MTD and will be considered for the next part of the study as decided by the SRC.

3.8.2 Study Stopping criteria

The study will be terminated if emerging safety findings confirm increased risk to remaining subjects or significantly altered risk-benefit assessment; examples include but are not limited to the following:

- New toxicological or pharmacological findings that significantly alter the risk-benefit assessment or more SAEs of similar nature which in the opinion of the investigator, are the result of RP3128 and risk of placing remaining subjects at risk.
- Occurrence of multiple clinically significant severe adverse events, which are judged by the investigator to be causally related to RP3128; examples include but are not limited to the following:
  - Two or more subjects have asymptomatic, QTc interval ≥ 500 msec OR increase in interval ≥ 60 msec above baseline. Finding should be persisting for at least 5 minutes on repeated ECGs.
  - One or more subject have ALT ≥ 3X ULN and bilirubin ≥ 2X ULN in the absence of significant increase in ALP where no other reason can be found to explain the combination of increases (e.g. elevated serum ALP indicating cholestasis, viral hepatitis, another drug (e.g. erythromycin).
- The sponsor may also decide to discontinue the study if it becomes apparent that subject enrollment is unsatisfactory with respect to Good clinical practice.

It should be made clear that these are guidelines only, SRC can make an exception, if justified. However, when such an exception is made, the reasons for it should be clearly documented. Refer **Appendix E** for **Algorithm to be used decision making for dose escalation.**

3.8.3 Subject discontinuation criteria

- Development of a serious (≥ grade 3) adverse event related to the trial medication or intolerable AE which necessitates discontinuation.
- If the Subject's partner becomes pregnant
- Any relevant deterioration in the health of the subject (AEs, vital signs, ECG, laboratory parameters)
- Clinically relevant QT or QTcB interval prolongation
- Clinically relevant change in liver or renal parameters
- Clinically relevant change in vital signs if technical failure can be excluded and result is confirmed by at least 1 additional measurement.
- In opinion of Investigator, continued participation is not in the best interest of subject.
- Protocol deviation/violation that in the opinion of sponsor warrants discontinuation from study.
- Subject experiences an allergic reaction/anaphylaxis to study drug.

- Subject requires concomitant medication that may interfere the PK of study drug
- Subject experiences emesis within 10 hrs of dosing.
- Lost to follow-up
- Termination or discontinuation of the study by the Sponsor.

In case of premature discontinuation, the reason and cause must be documented. Subjects discontinued from the study at any stage will be considered for safety analysis. For withdrawn subject, the end of study safety assessment must be completed at the time of early termination. Subjects who are prematurely withdrawn from the study for reasons other than safety may be replaced as advise by the SRC by an equal number of newly enrolled subjects, unless the SRC deems it unnecessary based on duration of the follow-up completed or cohort size already enrolled.

4 SELECTION AND WITHDRAWAL of SUBJECTS

4.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to be eligible for study:

1. Male and non-childbearing female subjects aged 18 to 45 years (SAD/MAD) and male and non-childbearing female patients with mild asthma aged 18 to 65 years (POC);
2. Healthy subjects as determined by pre-study medical history, vitals, physical examination and 12-lead ECG, and clinical laboratory tests within the normal reference ranges or clinically acceptable to investigator.
3. Body mass index (BMI) between 18.0 and 30.0 kg/m^2 inclusive, weight ≥50 kg;
4. Female subjects should be of non-child bearing potential, either surgically sterile or postmenopausal. Women should have either a history of no menses for at least 12 months or have documented bilateral oophorectomy with or without hysterectomy and have a documented serum FSH level ≥ 40 mIU/mL.
5. Non-smokers or ex-smokers being defined as someone who completely stopped smoking cigarettes for at least 6 months with history of less than 10-pack year, before day 1 of this study;
6. A male subject must meet the following criteria:
    i. Participant is able to procreate and agrees to use one of the accepted contraceptive regimens during the study; and for at least 4 months after the last drug administration. An acceptable method of contraception includes one of the following:
        - Abstinence from heterosexual intercourse
        - Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
        - Highly effective contraception should be used by the female partner as defined in **Appendix F**.
    ii. Participant is unable to procreate; defined as surgically sterile (i.e. has undergone a vasectomy at least 6 months prior to the first administration of the study drug), is required to use condom in order to prevent delivery of the drug via seminal fluid.

7. Willingness to adhere to the protocol requirements as evidenced by the informed consent form (ICF) duly read, signed and dated by the subject; Able to comply with protocol requirements and or study procedures;
8. Negative screen for drugs of abuse and alcohol at screening and on admission, judged by the investigator and/or designee.

Additionally, for part 3 (POC):

9. Pre- bronchodilator FEV_1 of > 70% (adjusted for age, sex and race)
10. Steroid naïve subjects with history of mild asthma for the last 6 months that satisfy the Global Initiative for Asthma (GINA) definition of asthma, but otherwise healthy.
11. Positive methacholine with the provocative concentration of methacholine resulting in a 20 % fall in FEV_1 (PC_{20} methacholine) of equal or less than 8 mg/ ml at screening.
12. Documented allergy to at least one common allergen (house dust mite, pollen allergens or cat dander) as confirmed by the skin prick test wheal ≥ 3mm that the negative control in diameter. Historical data up to 1 year can be used
13. Early asthmatic response (EAR) (FEV_1 fall of ≥20%, 0 to 60 minutes after allergen challenge) and LAR (FEV_1 fall of ≥15%, 3 to 8 hrs after allergen challenge.
14. Able to provide an acceptable sputum sample which is suitable for analysis.

4.2 Exclusion Criteria

1. Subjects with evidence or history of clinically significant hematological, renal, endocrine, pulmonary (excluding mild asthma in part 3), gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (excluding subjects for part 3) (including drug allergies) at the time of screening;
2. History or presence of significant gastrointestinal, liver or kidney disease, or any other conditions known to interfere with the absorption, distribution, metabolism or excretion of drugs or known to potentiate or predispose to undesired effects
3. History of tuberculosis and/or a positive Tuberculin Skin Test and /or QuantiFeron- TB®-Gold test.
4. Suicidal tendency, history of or disposition to seizures, state of confusion, clinically relevant psychiatric diseases.
5. Use of any immunotherapy within 3 months prior to screening
6. History of serious adverse reaction, severe hypersensitivity or allergy to any drug/drug substance (except house dust mite, pollen allergens or cat dander allergy in asthmatics) or in any other circumstance (e.g. anaphylaxis);
7. Clinically significant abnormalities in physical examination and/or in laboratory test results (including hematology and chemistry panels, urinalysis) as assessed by the Investigator;
8. Subjects who have received any investigational drug within 2 months (60 days) or within 5 half-lives (for small molecule) or until the expected PD effect has returned to baseline (for biologics) from screening in any clinical trial (whichever is longer) or drugs that directly or indirectly inhibit calcineurin, monoamine oxidase inhibitors, tricyclic antidepressants and anti-convulsants, or who are on extended follow-up;
9. Current diagnosis of active epilepsy or any active seizure disorder requiring chronic therapy with anti-epileptic drug(s);

10. Abnormal liver function (ALT >1.5 X upper limit of normal (ULN) or bilirubin >1.5 X ULN.
11. Positive screen on hepatitis-B surface antigen (HBsAg), antibodies to the hepatitis C (HCV) or antibodies to the human immunodeficiency virus (HIV) 1 and 2;
12. Presence of out-of-range cardiac interval (PR < 110 msec, PR > 220 msec, QRS < 60 msec, QRS >119 msec and QTcB >450 msec (female) >430 msec (male) on the screening ECG or other clinically significant ECG abnormalities
13. Maintenance therapy with any drug or significant history of drug dependency or alcohol abuse (> 3 units of alcohol per day, intake of excessive alcohol, acute or chronic) at screening.
14. Subject who have received the drugs metabolized by CYP2C19 enzyme (e.g. omeprazole, lansoprazole, pantoprazole) within 7 days or 5 half-lives of dosing (whichever is longer) prior to dosing or who are on treatment;
15. Concomitant disease or condition that could interfere with the conduct of the study, or for which the treatment could interfere with the conduct of the study, or that would in the opinion of investigator pose an unacceptable risk to the subject in this study, including but not limited to cancer, alcoholism, drug dependency or abuse or psychiatric disease.
16. Receipt or donation of 50 mL or more of blood in the previous 28 days before day 1 of this study
17. Receipt or donation of 500 mL or more of blood (Canadian Blood Services, Hema-Quebec, clinical studies, etc.) in the previous 56 days before day 1 of this study
18. Tattoo application 4 weeks prior to screening

Additionally, for part 3: POC

19. Use of nasal/inhaled/oral corticosteroids, intra ophthalmic corticosteroids, nasal, inhaled or intra ophthalmic cromolyn sodium or nedocromil, leukotriene receptor antagonists (e.g. zafirlukast, pranlukast, montelukast) and 5- lipoxygenase inhibitors (zileuton) within 6 weeks prior to screening;
20. Patients on LABA (e.g. salmeterol, formeterol) and long acting anticholinergics (e.g. tiotropium) within 6 weeks prior to screening. Use of short acting β2 agonists (salbutamol) is allowed if clinically warranted;
21. History of life threatening asthma, defined as asthma episode that required intubation or was associated with hyperpnoea, respiratory arrest and/ hypoxia.
22. Patients with respiratory tract infections (e.g. common cold, influenza, sinusitis) or symptomatic with allergic rhinitis (e.g. hay fever), requiring treatment within 2 weeks prior to dosing.

4.3 Subject Withdrawal from Trial Treatment

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

- Irreversible or intolerable toxicity or abnormal laboratory values related to drug toxicity
- Consent withdrawal
- Pregnancy
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (at the investigator's discretion)
- Non-compliance by patient
- Discontinuation of the study by the Sponsor

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

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

5 TREATMENT OF SUBJECTS

5.1 Administration of RP3128

SAD

A single dose of RP3128 or matching placebo will be self-administered orally by the subject on Day 1. The dose will depend on cohort of the subject.
Cohort S1: A single dose of 25 mg RP3128 (n=3) or matching placebo (n=1) on Day 1.
Cohort S2: A single dose of 50 mg RP3128 (n=4) or matching placebo (n=2) on Day 1.
Cohort S3: A single dose of 100 mg RP3128 (n=4) or matching placebo (n=2) on Day 1.
Cohort S4: A single dose of 200 mg RP3128 (n=6) or matching placebo (n=2) on Day 1.
Cohort S5: A single dose of 400 mg RP3128 (n=6) or matching placebo (n=2) on Day 1.

If the MTD is not reached after completing the planned sequential groups, highest dose will be considered an optimal dose. No additional groups will be included.

MAD

Multiple doses of RP3128/ matching placebo will be self-administered orally by the subject on Day 1 to Day 7. The dose levels of Cohort M1 to M3 will be determined after evaluation of the safety, tolerability and PK results of SAD and MAD (when applicable) cohorts. MAD may start during SAD part but only when enough PK and safety data are available.
The dose will depend on cohort of the subject.
Cohort M1: RP3128 25 mg (n=6) or matching placebo (n=2) once a day from Day 1 to 7.
Cohort M2: RP3128 100 mg (n=6) or matching placebo (n=2) once a day from Day 1 to 7.
Cohort M3: RP3128 400 mg (n=6) or matching placebo (n=2) once a day from Day 1 to 7.

If the MTD is not reached after completing the planned sequential groups, highest dose will be considered an optimal dose. No additional groups will be included.

POC:
Multiple doses of RP3128/ matching placebo will be self-administered orally by the subject on Day 1 to Day 14 (Period 1 and Period 2). The POC dose will be determined after evaluation of the safety, tolerability and PK results of MAD cohorts.

5.2 Concomitant Medications

As a general rule, no concomitant medication will be permitted, ***with exception of medication to treat AEs and short acting inhaled β-2 agonist (can be administered according to individual's need in Part 3)****, unless the rationale for the exception is discussed with PI/medical monitor and clearly documented.* As a result, subjects will be instructed not to take any additional medications during the course of the study without prior consultation with the research team except *short acting inhaled β-2 agonist in Part 3*. At each visit, the subject will be asked about any new medications he/she is taking or has taken after the start of the study drug.

5.3 Prohibited Medications

The following treatments are prohibited while on clinical trial:

- RP3128 demonstrated moderate inhibition of CYP2C19 enzymes. Therefore, all calcium channel blockers and drugs metabolized through CYP2C19 are withheld 7 days or 5 half-lives (whichever is longer) prior to dosing, these drugs include but are not limited to
  - Antiplatelet agents: clopidogrel
  - Anticonvulsants: mephenytoin, phenytoin, primidone, mephenytoin,
  - Antidepressants: amitriptyline, citalopram, S-citalopram, clomipramine, imipramine, fluoxetine, escitalopram, moclobemide, trimipramine, sertraline
  - Antineoplastic drugs: cyclophosphamide
  - Antiretroviral/antifungal drugs: nelfinavir, voriconazole
  - Proton pump inhibitors: lansoprazole, omeprazole, pantoprazole
  - Miscellaneous drugs: diazepam, progesterone, propranolol, R-warfarin, proguanil, malarone, carisoprodol and flunitrzaepam.
- Drugs directly or indirectly inhibits calcineurin, monoamine oxidase inhibitors, tricyclic antidepressants or anti-convulsants from 2 months from screening.
- Anti-asthma treatment (e.g. Salmeterol, formeterol, tiotropium, inhaled corticosteroid, montelukast) from 6 weeks from screening. Short acting inhaled β-2 agonist can be administered according to individual need in Part 3.
- Other investigational drug treatments from 2 months from screening.

Discontinuation of subject who received concomitant/prohibited medication will be taken by the PI in consultation with Medical Monitor on case to case basis. If administration of any above listed drug should become necessary for any reason during the course of the study, the Investigator will record the details of the drug, the dose and the time of administration in the case report form (CRF).

5.4 Study-Specific Restrictions

- Subjects will be requested to abstain from alcohol for 72 hrs prior to each dosing and during each treatment period. Throughout the study, in case of any doubt about alcohol consumption, a test for alcohol may be performed to confirm the Investigator's judgment.
- Only non- or ex-smokers will be allowed in this study.
- Subjects will be requested to avoid food or beverages containing xanthines (i.e. tea, coffee, cola drinks, or chocolate), broccoli, spinach, or lettuce for 72 hrs prior to each dosing and during each treatment period.
- Subjects will be instructed to avoid food or beverages containing grapefruit and/or pomelo for 7 days prior to the first dosing and during the study.
- Subjects will remain seated or ambulatory (will not be allowed to lie down) for the first 4 hrs following drug administration during confinement. However, in case of AEs or to complete protocol mandated study assessments, subjects may be placed in appropriate position.
- Subjects should abstain from strenuous exercise 72 hours prior to each study visit and should not engage in strenuous activity at any time during the confinement.
- Standardized meals will be provided to you during confinement
- No food will be permitted from 10 hrs prior to dosing with the study drug, until at least 4 hrs following dosing.
- Herbal preparations/medications are not allowed throughout the trial (e.g. St. John’s wort and Grape fruit juice). Subjects should stop using these herbal medications at least 14 days prior to screening and throughout the study.
- Use of NSAIDs (except acetaminophen) from screening and throughout the study.
- OTC drugs including vitamins for 48 hrs prior to screening and throughout the study. Acetaminophen up to a maximum of 2g/day can be permitted for pain relief if required during the study.
- Males who are sexually active will be made aware of the possible male-mediated foetal toxicity associated with RP3128. Subjects will be expected to use an acceptable contraceptive regimen from the first administration of the study drug, during the study, and until at least 4 months after the last drug administration. (**Refer Appendix F**)
- Tattoo application 4 weeks prior to screening and during study period.
- One condom will be provided to subjects upon departure from the clinical site for the first period of the study. In addition to the use of condoms, subjects will be informed that it is strongly recommended that their female partner uses one of the two methods listed below:
  - Systemic contraceptives (birth control pills, injectable/ implantable/ insertable hormonal birth control products, transdermal patch)
  - Intrauterine device

All study specific restrictions are applicable till end of Study (EOS) unless stated otherwise.

5.5 Procedures for monitoring subject compliance

Subject must take study drug at the study site during in-house stay and on ambulatory visit. The following measures will be employed to ensure treatment compliance:

- Administration of study drug will be observed and verified by a clinical staff member.
- A mouth and hand check of all subjects will be carried out by a clinical staff member to ensure that all capsules and water have been swallowed.
- Additionally, investigator/designee will record the missed doses and determine the treatment compliance at each visit before dispensing new medication to the study subject.
- In Part 3, diary card will be reviewed at each visit to ensure treatment compliance. Following points will be considered as part of treatment compliance and subject will be trained on this.
    - Date and time of each administered dose
    - Number of capsules consumed from the prescribed bottle/vial.
    - Volume of water consumed during dosing
    - Confirmation that the subject fasted 10 hours prior to dosing until 4 hours post dose.
    - Confirmation that the subject adhered to the water restriction from 1 hour pre-dose to 1 hour post dose,
    - Confirmation that the dosing was complete-no lost capsules and no vomiting
    - Documentation of any changes in health
    - Use of any concomitant medication
- In Part 1 and 3, telephone assessments for adverse events and concomitant medications are performed prior to the EOS visit and as required by physician.

6 TRIAL ASSESSMENT AND TREATMENT

6.1 Overview

This study will be conducted sequentially in three parts as SAD, MAD and POC. Unless stated otherwise in this protocol, [redacted] standard operating procedures (SOPs) will be followed during this study. For all study subjects, the different parts of this study are summarized in **Appendix B** for Part 1, **Appendix C** for Part 2 and **Appendix D** for Part 3. The list of assessments for the study are indicated with an "X" when the assessments have to be performed. Any deviation from protocol procedures should be noted in the Case Report Forms (CRFs) and the Sponsor should be notified.

6.2 Screening

The screening assessments will be performed ≤ 45 days prior to initiation of treatment in SAD part and ≤ 60 days in MAD/POC; and informed consent will be obtained prior to initiating any study procedures. The subjects will be assigned a specific screening number and screening will include past medical history, demographics, detailed physical examination, vital signs, clinical laboratory investigations, 12 lead ECG, drug and alcohol screen, pregnancy test (female). Reasonable efforts should be made to determine all relevant treatments received by the subject within 6 weeks before first dose of treatment. The

eligibility will be confirmed by PI/designee on Day 1. Screening will be performed over multiple visits if required. In POC, asthma action plan (AAP) will be discussed with each subject during screening and will be reminded at subsequent visits.

- **Medical history**

A detailed medical history will be taken which include present history, past history, allergy, family history, surgical history, concomitant medication and prior medication (in last 8 weeks); and other medical history at screening and abbreviated history will be taken at all subsequent visits.

- **Vital signs**

At screening, vital signs (temperature, systolic and diastolic blood pressure, respiratory rate and pulse rate) will be assessed in the supine position after the subject has rested for at least three minutes. Blood pressure and pulse will be assessed again after three minutes in the standing position. Subjects should be excluded if their standing vital signs (relative to supine) show findings which, in the opinion of the Investigator, are associated with clinical manifestation of postural hypotension (i.e., absence of any other cause).

At other time points, vital signs (temperature, systolic and diastolic blood pressure, respiratory rate and pulse rate) will be measured in supine position after subject has rested for 3 min. 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.

- **Physical Examination**

A complete physical examination will include the examination of 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.

- **12 Lead Electrocardiogram**

A standard 12-lead ECG will be performed with the subject in a supine position. Interpretation of the tracing must be made by the investigator and documented on the ECG section of the CRF and kept in the source documents at the study site. Single ECG measurements will be done, unless stated otherwise. Triplicate ECGs will be performed on screening, Day 1 (pre-dose) and done only for confirmation of abnormalities detected in the single ECG measurement performed on subsequent visits. Investigator's discretion will be used for interpretation of findings on triplicate ECGs (including determination of cardiac intervals), if the results are inconsistent/inconclusive. The following parameters will be recorded: rhythm, ventricular rate, PR interval, QRS duration, QT and QTcB. All ECG's will be performed on local equipment.

- **Electroencephalogram (EEG)**

An EEG will be performed with the subject if clinically indicated in case of any symptom as required by neurologist. Interpretation of the tracing will be made by a qualified physician and will be documented in the EEG section of the CRF and kept in the source documents at the study site. Additional Neurological Tests: Test such as CT scan and /or MRI or other Neurological tests may be performed at the discretion of the Investigator as indicated.

- **Cognitive test**

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

Note: Following window for study assessments would be applicable for all three parts of study.

- ECG: +/- 15 minutes of the scheduled time.
- Pre-dose procedures: within 2 hours of dosing.

6.3 Laboratory Investigations

Laboratory investigations include Clinical chemistry, hematology, serum electrolyte, coagulation, urine analysis, serological tests (HIV, HBsAg, HCV), Tuberculin test/QuantiFeron-TB ®-Gold test, pregnancy test (female), drug screening and alcohol screening to be performed in specified times. Blood drawn for these tests will be specified in informed consent form (ICF).

Urinary screening will be carried for opiates, methadone, cocaine, amphetamine, cannabinoids, barbiturates, and benzodiazepines. Rescreening will be performed on admission on day 1. Alcohol will be tested using alcohol breath test.

The investigations will be performed at central laboratory. Details of the laboratory parameters are summarized in **Appendix A.** Amount of blood to be collected during screening and during the study are detailed below.

Table 4 Blood volume - Part 1 (SAD)

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Safety			
Clinical chemistry	5	6	30
Hematology	4	6	24
Coagulation	2.7	6	16.2
Serology	5	1	5
Pharmacokinetics			
RP3128	4	14	56
Total*			131.2

*Sample volumes are based on direct venipuncture; where a cannula is used an extra 1 ml will be drawn and discarded.

Table 5 Blood volume – Part 2 (MAD)

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Safety			
Clinical chemistry	5	7	35
Hematology	4	7	28
Coagulation	2.7	7	18.9
Serology	5	1	5
Pharmacokinetics			
RP3128	4	28	112
Biomarkers			
Biomarkers	20	3	60
Total*			258.9 (Approx. 260 mL)

*Sample volumes are based on direct venipuncture; where a cannula is used an extra 1 ml will be drawn and discarded.

Table 6 Blood volume -Part 3 (POC)

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Safety			
Clinical chemistry	5	4	20
Hematology	4	4	16
Coagulation	2.7	4	10.8

Serology	5	1	5
Pharmacokinetics			
RP3128	4	10	40
Total* (for each period)			91.8
Total (Period 1+ period 2)			178.6

*Sample volumes are based on direct venipuncture; where a cannula is used an extra 1 mL will be drawn and discarded.

6.4 Correlative Biomarkers

No biomarkers will be assessed in SAD. In MAD, blood biomarkers (Th1, Th2 and Th17 cytokines) will be measured following LPS or CD3/CD 28 stimulation. Blood samples will be collected at baseline (Day 1, pre-dose), and Day 7 (pre-dose and 4 hrs post dose). See laboratory manual for biomarker processing instructions.

6.5 Spirometry

In Part 3 (POC), FEV_1 will be performed at screening, pre-dose on Day 1, Day 7, and Day 14 (pre-dose and post allergen challenge as per the allergen challenge procedures) and Day 15 (pre discharge). FeNo will be performed at screening, Day 14 (pre-dose, 3 hrs, 8 hrs and 24 hrs post allergen challenge). The detailed technique of spirometry and instructions will be covered in [redacted] Operational Manual/SOPs.

6.6 Allergen challenge

In Part 3 (POC), inhalation allergen challenge will be performed at screening and on Day 14 approximately 1 hr post dose.

Allergen Challenge Process

A methacholine challenge test (MCT) will be performed during the screening phase of the study in those subjects who have met all of other eligibility criteria. The MCT will be performed on different screening days by the two minute tidal breathing dosing protocol that is recommended by the American and Canadian Thoracic Societies.

Subjects who successfully complete the MCT and who continue to meet the eligibility criteria will return to the clinic the next day (up to approximately a week later) to undergo the multi-skin prick sensitivity test with concentrations of cat or house dust mite or pollen allergen extracts. The allergen concentrations for both skin prick testing and allergen challenge are noted in the [redacted]

The allergen selected for the multi-skin prick sensitivity test and allergen challenge will be at the investigators discretion based on the subjects' medical history and the results of the skin prick test (SPT) performed at the screening visit. A positive control and a negative control will also be administered. The wheal diameter will be measured in two perpendicular directions 15 to 20 minutes after application and the mean wheal diameter will be determined for each dilution. Skin sensitivity will be defined as the lowest allergen

concentration that produces a wheal that is at least 3 mm in diameter or greater than the negative control.

The allergen challenge test will be performed similarly to the MCT as described in the manual. The first allergen concentration to be administered will be determined based on the results from the MCT and allergy SPT titrations performed at screening. The concentration of the allergen PC_{20} will then be predicted from the previous methacholine challenge PC_{20} and the skin sensitivity using the following logarithmic formula:

Log_{10} (Allergen PC_{20}) = 0.69 log_{10} (MCT PC_{20} x skin sensitivity) + 0.11 (r = 0.85).

(This formula may be subject to modification and is dependent on the allergen PC_{20} estimated in subjects).

Following the allergen PC_{20} prediction, subjects will first inhale 2 mL of diluent saline for a period of 2 minutes by tidal breathing and the FEV_1 will be measured about 30 ± 2.5 and 90 ± 2.5 seconds post inhalation. The higher of the 2 FEV_1 measurements will be used as the diluent baseline value. The first dose of allergen administered will be 3 doubling doses below that predicted to induce a 20% fall in PC_{20}. Subjects will be administered the allergen at an output of ~ 0.13 mL/min for a period of 2 minutes by tidal breathing using the appropriate nebulizer. At 10 ± 1 minutes post inhalation, the FEV_1 will be measured at two separate times 60 ± 2.5 seconds apart and the highest value will be compared to the baseline value. If the FEV_1 has dropped < 20% from baseline, the next allergen concentration 2 fold greater than previous concentration will be delivered and the FEV_1 will be similarly measured. This process will continue until there is at least a 20% drop in the FEV_1. If the FEV_1 has fallen between 15% and 20% from the pre-allergen baseline, the FEV_1 will be repeated 20 ± 2.5minutes after inhalation. When a drop in FEV_1 of at least 20% compared to baseline has been achieved the challenge will be terminated.

The FEV_1 will be measured at 30, 60, 90, 120 and 180 ± 15 minutes post allergen exposure to evaluate the early asthmatic response. The FEV_1 will be measured every hour ± 15 minutes thereafter until 8 hours ± 1 hour post allergen challenge.

The allergen challenge procedure will be performed by a respiratory therapist or other qualified medical personnel and the subject will be under observation for the duration of this test. If the subject develops symptoms of bronchospasm such as chest tightness or shortness of breath, examinations will be performed and salbutamol will be administered as necessary. Subjects will not leave the site until the investigator is satisfied that it is safe to do so.

The detailed technique of allergen challenge and procedure will be covered in [redacted] Operational Manual/SOPs.

6.7 Sputum Analysis

In Part 3 (POC), sputum will be analysed for absolute count, percentage differential count of sputum eosinophils and neutrophils. Sputum will be induced post allergen at screening

and Day 14 (8 hrs and 24 hrs after allergen challenge). The detailed technique of sputum collection and analysis will be covered in [redacted]

6.8 In house stay

SAD: In-house stay from Day -1 (afternoon) to Day 3 (mornings); discharge after safety assessment on Day 3.
MAD: In-house stay from Day -1 (afternoon) to Day 8 (mornings); discharge after safety assessment on Day 8.
POC: In house stay from Day 13 to Day 15; discharged on Day 15 after allergen challenge.
During in-house stay, subjects will have restricted activity and will be taking diet as specified by investigator. Subjects should not take concomitant medications unless specified in their treatment.
The diary card will be issued at the time of discharge (Day 1) during Part 3 (POC). Subjects will be trained on completion of diary during the in-house stay. Subjects will also be trained on capturing missed doses in diary.

6.9 Ambulatory visits

SAD: Ambulatory visits day 5, day 8 and day 15.
MAD: Ambulatory visits on Day 9, Day 10, Day 11, Day 12, Day 13 and Day 15.
POC: Ambulatory visits on Day 1, Day 3, Day 7 and Day 11 in both periods and Day 50.

All visits should occur on the protocol specified time. Complete listings of the assessments will be performed at each visit during the trial treatment as specified in **Appendix B, C and D**. The study drug should be administered at the clinic under supervision of Investigator/designee. In Part 3, the diary card will be reviewed for patient compliance, missed dosed/overdose at each ambulatory visit and at the time of admission.

6.10 End of Study Visit

Subject will be on treatment as specified in protocol unless discontinued in between due to unacceptable toxicity or decision to discontinue treatment by subject or study investigator. End of Study evaluations will be performed on each subject as specified in **Appendix B , C and D**. Subjects who discontinued the treatment due to adverse event will be followed till the resolution/stabilization of adverse event or for 30 days following the last study dose, whichever is the earlier. Withdrawn subjects will have End of Study evaluations performed as specified in protocol.

7 SAFETY ASSESSMENT

7.1 Definition of AE

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 (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

A suspected adverse reaction (SAR) is any AE for which there is a reasonable possibility that the study treatment caused the adverse event. ‘Reasonable possibility’ means there is

evidence to suggest a causal relationship between the study treatment and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a study treatment.

An AE may be:

- A new illness,
- Worsening of a concomitant illness or a baseline event,
- An effect of the study treatment; it could be an abnormal laboratory value as well as a significant shift from baseline within normal range which the Principal Investigator or medical qualified designate considers to be clinically important.
- Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the treatment period. Planned surgical measures permitted by the clinical study protocol and the conditions(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions),
- Is a congenital anomaly or birth defect,
- Is an important medical event defined as an event that does not fit one of the other outcomes, but may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of other outcome. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders), or seizure/convulsion that does not result in hospitalization. The development of drug dependence or drug abuse would be other examples of important medical events.

7.2 Severity assessment

All adverse events will be graded according to the Common Toxicity Criteria Adverse Events (**CTCAE Version 4.03**). If CTC-AE grading does not exist for an adverse event, severity assessment will be performed according to the following definitions:

Mild: Causing no limitation of usual activities; the subject may experience transient slight discomfort.

Moderate: Causing some limitation of usual activities; the subject may experience annoying discomfort.

Severe: Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

Every effort will be made to obtain an adequate evaluation of the severity.

7.3 Causality Assessment

The principal investigator or a medical qualified designate will determine the relationship of any adverse event to the Investigation Product according to the following criteria:

TERM	DEFINITION
Reasonable Possibility	A temporal relationship exists between the AE onset and administration of the investigational product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or adverse event profile of the investigational product.
No Reasonable Possibility	Evidence exists that the adverse event has an etiology other than the investigational product. For SAEs, an alternative causality must be provided (e.g. pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

7.4 Routine Reporting

For the purposes of this study, the period of observation of adverse events for each subject extends from the pretrial evaluation until the end-of-study safety assessments. During this period, all adverse events spontaneously reported by the subject, observed by the clinical staff or elicited by general questioning will be recorded on an information sheet and reported in the CRF.

If necessary, every effort will be made to obtain an adequate follow-up of the subjects. Should any subject choose to withdraw early from the study, they will be advised of the safety precautions to be taken.

Subjects will be questioned on their health status at the beginning of the treatment period and before departure from the clinical site. Open-ended questions will be asked.

7.5 Serious Adverse Event Reporting

The Investigator will notify any SAE to the sponsor, without regard to causality, within 24 hrs after becoming aware of its occurrence.

The initial SAE report must be as complete as possible, including details of the current illness and SAE, and an assessment of the causal relationship between the event and the investigational product.

The notification, in English, should be directed to the following sponsor representative:

[redacted]

[redacted]5

An SAE will be considered “unexpected” if the AE is not listed in the Investigator brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the Investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the investigational product, but are not specifically mentioned as occurring with the particular product under investigation.

[redacted] will report any serious unexpected related adverse events to the IRB based on the IRB’s guidelines/requirements. The event will be reported within 15 calendar days of the investigator or staff becoming aware of the event.

The Sponsor or designee will be responsible for evaluating the events for expedited reporting, processing of events and for reporting it to the Health Canada and other regulatory agencies in accordance with the Health Canada / ICH Guidance Document.

During a clinical trial conducted in Canada, it is required to inform Health Canada of any serious, unexpected adverse drug reaction that has occurred inside or outside Canada:

- Where it is neither fatal nor life-threatening, within 15 days after becoming aware of the information;
- Where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information; and
- Within 8 days after having informed Health Canada of the ADR, submit as complete a report as possible which includes an assessment of the importance and implication of any findings.

If reports of any new and unexpected adverse events become available to the sponsor during the clinical study (related or not to the present study), the sponsor has to advise [redacted] through its Clinical Investigator, of those events.

7.6 Protocol-Defined Events of Special Interest

The following are events of special interest, and will need to be reported expeditiously.

7.6.1 Pregnancy, Abortion, Birth Defects/Congenital Anomalies:

Female subjects who are not of child-bearing potential who have a negative pregnancy test are eligible for the study.

During the course of the trial, all female subjects or partner of male subject must contact the treating investigator immediately if they suspect that they may be pregnant. If an investigator suspects that a female subjects or partner of male subject may be pregnant after the subject has been receiving trial drug(s), the trial drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the trial drug(s) must be immediately and permanently stopped, the subject must be discontinued from the trial, and the investigator must notify the Sponsor Representative as soon as possible. If a subject becomes pregnant while enrolled in the trial, a Pregnancy Form should be completed and sent by fax/email to the Sponsor.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

7.6.2 RP3128 Overdose

Both intentional (misuse/abuse) and unintentional (accidental) overdose must be reported in the CRF. Symptomatic unintentional and intentional overdose must be reported as AE in the CRF. Any accidental overdose with the trial treatment that is symptomatic, fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within 24 hrs) using the corresponding screens in the CRF, and following the same process described for SAE reporting. Intentional overdose should be reported as an SAE irrespective of seriousness criteria.

Summary of reporting requirements for overdose.

Type of overdose	Document in CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional (accidental)	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

8. PHARMACOKINETIC ASSESSMENTS

8.1 Collection of pharmacokinetic samples

A 4 ml of blood samples will be collected at each time points described in **Appendix B**, **Appendix C** and **Appendix D**. Depending up on the PK of previous cohorts, the time points for subsequent cohorts will be adjusted or changed at discretion of SRC. The procedures will be documented appropriately. The detail procedure related with blood sample collection, numbering, processing and shipment will be outlined in pharmacokinetic manual.

The time and date of collection of each sample will be recorded in CRF. The samples will be collected stored at -60^0 C to -80^0 C and shipped to North East bioanalytical laboratory,

USA for analysis. Details of methods used for measurement of drug concentrations will be described in bioanalytical report.

8.2 Pharmacokinetic analyses

The PK analyses of plasma concentration data will be done using statistical software SAS 9.1 or higher. The actual sampling times will be used in PK parameter calculations.

The following PK parameters will be determined for RP3128 from plasma concentration data.

- Maximum plasma concentration (C_{max})
- Time to C_{max} (T_{max})
- Terminal half-life ($t_{½}$)

- Area under the plasma concentration time curve from zero until the last measurable time point (AUC_{0-t})
- Area under the plasma concentration time curve from zero extrapolated to infinite time (AUC_{0-inf})
- Elimination rate constant (K_{el})

Plasma remaining after completion of the determination of parent drug (RP3128) may be used for exploratory assessment of metabolites. Given the exploratory nature of the work, the analytical method used for those assessments will not be validated. As such, the results from this exploratory analysis will not be included in the clinical study report.

9. EFFICACY ASSESSMENTS

Efficacy will be evaluated in part 3 of the study. Efficacy assessment will be measurement of sputum neutrophils, eosinophils, FEV1 and FeNo from pre allergen challenge to post allergen challenge. Details of assessment time points are included in **Appendix D**.

10. STATISTICAL CONSIDERATIONS

10.1 General Considerations

This section described the statistical methods to be used to analyze the safety and efficacy parameters. These methods may be revised as required by the protocol. The final analysis plan will be documented in a formal statistical analysis plan (SAP) that must be finalized before database lock. The SAP will include details on how variables will be derived, how missing data will be handled, and how censoring procedures will be applied to time to event related variables as well as the details on statistical methods to be used for safety and efficacy analyses. The final clinical study report will discuss deviations from the SAP, if any.

10.2 Determination of Sample Size

This trial will enroll up to 56 HV (32 in SAD and 24 in MAD) and 12 mild asthmatics in POC. Number of subjects to be enrolled in this study is in line with standard phase I studies and is considered sufficient to provide descriptive information on the pharmacokinetics,

pharmacodynamics, safety and tolerability of RP3128 while minimizing exposure to humans. The actual number of dose cohorts will depend upon the emerging safety data.

Analysis Populations

Safety Population: This population will include all subjects who are randomized and receive a dose of study drug. There will be separate safety populations each for SAD, MAD and POC parts.

PK Population: All subjects in Safety population with sufficient concentration-time data to determine the PK parameters will be included in the PK population

Evaluable Population: All subjects in Safety population for POC part who have at least one post dose efficacy measurement without important protocol deviations will be included in the Evaluable population.

10.3 Statistical Analyses

All statistical analyses will be performed using SAS 9.1or higher.

10.3.1 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics for continuous variables, and frequencies and percentages for categorical variables.

10.3.2 Safety Analyses

All safety data will be included in the subject data listings. Summary tables will be based upon the safety population. Classification of AEs will be performed by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.1 or higher.

AE listings will be presented by subject, system organ class, and preferred term.
The incidence of all reported AEs and SAEs will be tabulated. In addition, summary tables for AE will be presented by severity and drug relationship.

For laboratory data, a list of clinically significant abnormal values will be presented.

10.3.3 Exploratory Analyses

The exploratory and will be performed in part 2. Exploratory parameter (Th1, Th2 and Th17 cytokines) levels will be compared between RP3128 and placebo using appropriate analysis of variance models and summarized using descriptive statistics.

10.3.4 Efficacy Analyses

The efficacy analysis will be performed in part 3. All subjects who receive at least one dose of RP3128 or placebo and have at least one post dose efficacy measurement without important protocol deviations will be included. The details of efficacy analysis will be presented in Statistical analysis plan.

10.3.5 Pharmacokinetic Analyses

Subjects who provide evaluable data will be included in the pharmacokinetic and statistical analysis.

The following PK parameters will be derived: C_{max}, AUC_{0-t}, AUC_{0-inf}, T_{max}, $t_{½}$ and K_{el} and estimated by non-compartmental analysis method by using a suitable software.

These variables will be summarized by n, mean, standard deviation, median, minimum, and maximum by dose. The geometric means will also be presented for AUC and C_{max}.

11 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

11.1 IEC/IRB Approval

This protocol and the ICF will be submitted to an IRB prior to initiation of the study and the study will not start until the Board has approved the documents. Notification of the Board's approval will be appended to the study report.

11.2 Ethical conduct of the study

This study will be conducted in compliance with the study protocol, the ethical principles that have their origins in the Declaration of Helsinki, the ICH Guideline E6 for GCP, the FDA GCP Code of Federal Regulations (CFR) Title 21 (part 56), the Directive 2001/20/EC (Europe) and the Tri-Council Policy Statement (Canada).

11.3 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to trial initiation. If required, the Sponsor will also ensure that the implementation of substantial amendment to the protocol and other relevant trial documents happen only after approval by the relevant regulatory authorities.
Safety updates for RP3128will be prepared by the Sponsor or its representative as required, for submission to the relevant regulatory authority.

11.4 Insurance and Indemnity

Details of insurance and/or indemnity will be contained within the written agreement between the PI or site and the Sponsor.

11.5 Informed Consent

Before inclusion in the study, each prospective subject will be given a full explanation of the purpose of the study, the procedures to be carried out and the potential hazards. Once this essential information is provided to the subject and once the investigator or designee has the conviction that the subject understands the implications of participating in the study, the subjects will be required to read, sign and date a properly executed written informed consent form in compliance with the U.S. Code of Federal Regulations (Title 21, Part 50) prior to enrollment. Subjects will be assured that they may withdraw from the study at any time without jeopardizing their medical care. They will be given a copy of their informed consent form.

If an amended or revised ICF is introduced during the study, each subject's further consent should be obtained.

11.6 Confidentiality

11.6.1 Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with by Canadian Information Protection and Electronic Documentation Act (PIPEDA) and Ontario Personal Health Information Protection Act (PHIPA), the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and national data protection laws, as applicable. HIPAA regulations require that, in order to participate in the trial, a patient must sign an authorization from the trial that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this trial;
- Who will have access to that information and why;
- Who will use or disclose that information;
- The information collected about the research trial will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the trial;
- Whether the authorization contains an expiration date; and
- The rights of a research patient to revoke his or her authorization.

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled trial period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR, it is a requirement that the investigator and institution permit authorized representatives of Sponsor, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of trial-related procedures and data.

11.6.2 Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the site database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub-investigator, the site shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

12 RECORD RETENTION AND DOCUMENTATION OF THE TRIAL

12.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor. All amendments require review and approval of Rhizen Pharmaceutical and the Principal Investigator supporting the trial. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the investigator's facility for the board's approval.
Amendments specifically involving change to trial design, risk to patient, increase to dosing or exposure, subject number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB at the Investigator's facility.

The amendment will be submitted formally to the Health Canada and IRB as applicable; specifically when an increase to dosing or patient exposure and/or subject number has been proposed; or, when the addition or removal of an Investigator is necessitated.
Items requiring a protocol amendment with IRB and/or Health Canada approval include, but are not limited to, the following:

- Change to trial design
- Risk to patient
- Increase to dose or patient exposure to drug
- Subject number increase
- Addition or removal of tests and / or procedures
- Addition/removal of a new Investigator
- It should be further noted that, if an amendment to the protocol substantially alters the trial design or the potential risks to the patients, their consent to continue participation in the trial should be obtained.

12.2 Documentation Required to Initiate Trial

Before the trial may begin, documentation required by Health Canada will be provided by the Sponsor. Documents at a minimum required to begin a trial in the Canada include, but are not limited to: a signature-authorized protocol and contract; a copy of the official IRB approval of the trial and the IRB members list; current Curricula Vita for the principal investigator and any associate investigator(s) who will be involved in the trial; indication of appropriate accreditation for any laboratories to be used in the trial and a copy of the normal ranges for tests to be performed by that laboratory; original Form FDA 1572 (Statement of Investigator), appropriately completed and signed; a copy of the IRB-approved consent form containing permission for audit by representatives of Sponsor, the IRB, and the FDA; financial disclosure forms for all investigators listed on Form FDA 1572; site qualification reports, where applicable; verification of Principal Investigator acceptability from local and/or national debarment list(s).

13 DATA HANDLING AND RECORD KEEPING

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated trial duties and should ensure that all persons assisting in the conduct of the trial are informed of their obligations. All persons authorized to make entries and/or corrections on the CRFs are to be included on this document. All entries in the patient's CRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the patient's CRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The PI and trial staff are responsible for maintaining a comprehensive and centralized filing system (Site Trial File/SSF or ISF) of all trial-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF/SSF must consist of those documents that individually or collectively permit evaluation of the conduct of the trial and the quality of the data produced. The ISF/SSF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP and 21 CFR Part 312.57,including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed CRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the trial drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain PI name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the CRF must be maintained and be readily available.

All essential documents and records will be maintained [redacted] for a period of 25 years. These documents may be retained for a longer period if required by the applicable regulatory requirement(s) (FDA CFR 312.57 (C)) or if needed by the sponsor.

13.1 Data Collection

The data will be captured in an electronic Case Record Form (eCRF). The eCRF is clinical trials data management tool that provides investigational sites a standardized and validated, remote, electronic data capture system for the collection of clinical trial data. All data requested on the CRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done this will be documented as protocol deviations in the eCRF. Additional data entry requires will be described in the study specific eCRF Completion Guidelines. For any data entry errors made, the error(s) will be queried for clarification and must be corrected. Any changes made to the original entry will be documented via the database audit trail.

The principal investigator will electronically sign and date each subject's eCRF attesting to his/her responsibility for the quality of all data included therein, and that the data represent a complete and accurate record of each subject's participation in the study.

Source data will be entered into an OmniComm EDC database, which will be used for collection of data to support tables and listings for the final study report. Appropriately trained and designated individuals will be given access to the database and will perform entry of the data from the source. Clinical data management will be performed in accordance with applicable standards. Data cleaning procedures will be performed with the objective of removing errors and inconsistencies in the data which would otherwise impact on the analysis and reporting objectives, or the credibility of the Clinical Study Report. Adverse events, medical history and concomitant medications will be coded using industry standard dictionaries (MedDRA and WHO Drug).

13.2 Trial Monitoring, Auditing, and Inspecting

The sponsor or its representative may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. [redacted] will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

13.3 Quality Assurance and Quality Control

[redacted] site shall be required to have Standard Operating Procedures (SOP's) to define and ensure quality assurance/control processes for trial conduct, data generation & collection, recording of data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

All parts of the bioanalytical phase of the study and all its documentation will be subject to inspection by the quality assurance unit of the bioanalytical facility to ensure that the data are generated, documented and reported in compliance with the protocol and applicable requirements as outlined in the Health Canada and OECD Principles of GLP.

14 DISCLOSURE AND PUBLICATION POLICY

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the trial. Results from the trial will be published/presented as per the Sponsor's publication strategy or shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions.

15 REFERENCES

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7. US FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. http://www.fda.gov/downloads/Drugs/.../Guidance/UCM078932.pdf

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, 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	**-45 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. The screening assessments will be performed ≤ 45 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 3, 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, 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 (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 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: 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 hr) 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 investigators. A window of +/-1 Day will be used for this call.
15. Window for study assessments: ECG: +/- 15 minutes of the scheduled time; Pre-dose procedures: within 2 hours of dosing.

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 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). 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.

Appendix D : Part 3 (POC) -Schedule of Events

Study Day	**Screening**	**Assessment period (Period 1 & 2)**							**EOS**
		Ambulatory visits				**Admission**	**Confinement**	**Discharge**	**Follow up[22]**
Study Day	**-60 to -1**	**1**	**3**	**7**	**11**	**Day 13**	**Day 14**	**Day 15**	**Day 50 (±2)**
Confinement[1]	-	-	-	-	-	X	X	-	-
Ambulatory visits[2]	-	X	X	X	X	-	-	-	X
Informed consent[3]	X	-	-	-	-	-	-	-	-
Medical history[4]	X	X	X	X	X	X	-	-	X
Demographics[5]	X	-	-	-	-	-	-	-	-
Physical examination[6]	X	-	-	X	-	X	X	X	X
Vital signs[7]	X	X	X	X	X	X	X	X	X
Eligibility assessment	X	X	-	-	-	X	-		-
12-lead ECG[8]	X	X	-	X	-	X	X	X	X
Clinical laboratory[9]	X	X		-	-	X	-	X	X
Drug and alcohol screen[10]	X	X	-	-	-	X	-	-	-
Tuberculin test / QuantiFeron- TB ®-Gold test	X	-	-	-	-	-	-	-	-
HBsAg, HCV, HIV	X	-	-	-	-	-	-	-	-
Asthma Action plan	X	X	X	X	X	X	X	X	X
Randomization	-	X	-	-	-	-	-	-	-
Pregnancy test[11]	X	-	-	-	-	-	-	-	-
Spirometry[12]	X	X	-	X	-	-	X	X	X
FeNo[13]	X	-	-	-	-	-	X	X	-
Allergen Challenge[14]	X	-	-	-	-	-	X	-	-
Methacholine challenge	X	-	-	-	-	-	-	-	-
Skin prick test	X	-	-	-	-	-	-	-	-
Sputum analysis[15]	X	-	-	-	-	-	X	X	-
Study drug dispensing	-	X	X	X	X	X	X	-	-
Drug administration[16]	-	X	X	X	X	X	X	-	-
PK sampling: blood[17]	-		-	-	-	-	X	X	-
Issue of Diary card[18]	-	**X**	-	-	-	-	-	-	-
Diary card review[19]	-		X	X	X	X	-	-	-
Adverse events[20]	X	X	X	X	X	X	X	X	X

Conc. medication	X	X	X	X	X	X	X	X	X
Wash out[21]	-	-	-	-	-	-	-	-	-

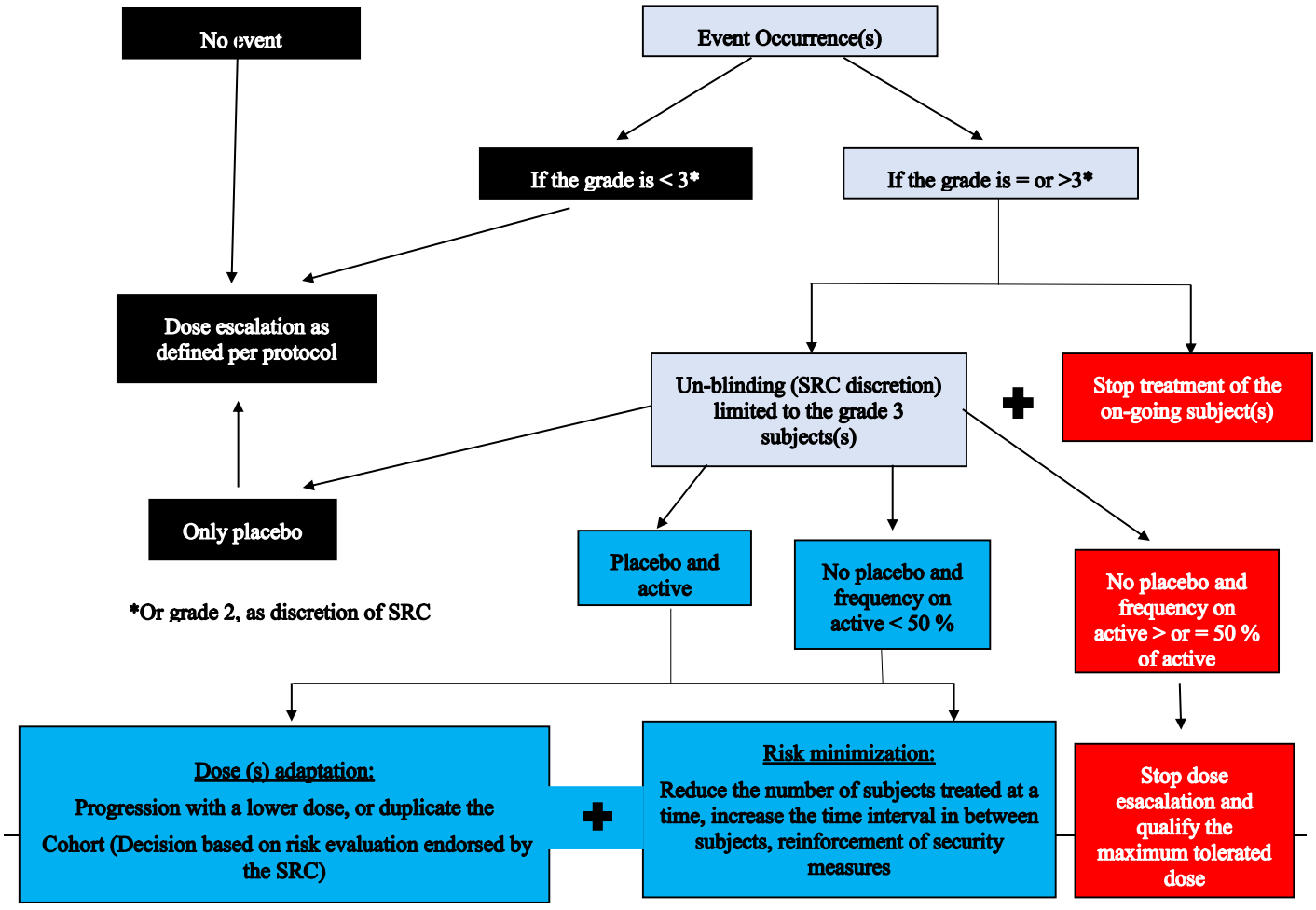
Foot note:

1. CPU confinement: Subjects will enter the CPU on Day 13 and will be discharged on day 15 after safety assessment in both periods.
2. Ambulatory visit: Day 1, Day 3, Day 7 and Day 11 in both periods; and Day 50 (EOS).
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 7, Day 13, day 14, Day 15 in both periods; and Day 50 (EOS). 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 (pre-dose, 30 min, 1, 2, 4 and 6 hrs post dose), Day 3, Day 7, Day 11, Day 13, Day 14, day 15 in both periods and Day 50 (EOS). 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 (Triplicate ECG will be performed at screening and single ECG on other time points): on screening, Day 1 (pre-dose, 30 min, 1 and 6 hrs post dose), Day 7, Day 13, Day 14 (pre-dose) and Day 15 in both periods and Day 50 (EOS). 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. Investigator's discretion will be used for interpretation of findings (including determination of cardiac intervals), if the results are inconsistent/inconclusive.
9. Laboratory assessment: Screening, Day 1, Day 13 (at admission), Day 15 (at discharge) in both periods; and Day 50 (EOS). Clinical chemistry, haematology, 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. Pregnancy test: β-HCG will be conducted in serum at screening in all women of non-child bearing potential; UPT will be performed at later time points in case of suspected pregnancy.
12. FEV1 will be performed at screening, pre-dose on Day 1, day 7, and Day 14 (pre-dose and post allergen challenge as per the procedures) and Day 15 (pre discharge) in both periods; and Day 50 (EOS).
13. FeNo: Screening, Day 14 (pre-dose, 3hrs, 8 hrs and 24 hrs post allergen challenge).
14. Allergen challenge will be performed on screening and Day 14 approximately 1 hr. post dose in both periods
15. Sputum analysis include absolute count, percentage differential count of sputum eosinophils and neutrophils. Sputum will be induced post allergen at screening and Day 14 (8 hrs and 24 hrs after allergen challenge).
16. In both periods, study drug (RP3128/placebo) will be administered once a day from Day 1 to Day 14 in both periods. On Day 1, Day 3, Day 7 and Day 11 the study drug will be administered at the CPU. On Day 2, Day 4, Day 5, Day 6, Day 8, Day 9 and Day 10, drug will be administered at home.
17. PK time points: Day 14 (Pre-dose, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0 and 24.0 hr post dose) in both periods. Window period for sample collection will be outlined in pharmacokinetic manual.
18. Issue of diary card: The diary card will be issued at the time of discharge on Day 1. Subjects will be trained on completion of diary on Day 1. Subjects will also be trained on capturing missed doses in diary.
19. Review of diary card: The diary card will be reviewed for patient compliance, missed dosed/overdose at each ambulatory visit and at the time of admission on Day 13.
20. In all subjects, telephone assessments for adverse events and concomitant medications are performed 3 days prior to the EOS visit and as required by investigator. A window of +/-2 Day will be used for this call. 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.
21. The treatment periods will be separated by washout period of 14 days.
22. End of study (EOS) evaluation at Day 50 will occur 5 days (+/- 2) after Day 15 of period 2.
23. Window for study assessments: ECG: +/- 15 minutes of the scheduled time; Pre-dose procedures: within 2 hours of dosing.

Appendix E : Algorithm for Decision Making For Dose Escalation



Appendix F : Contraceptive Guidelines and Pregnancy

The highly effective contraception is defined as either:

1. **True abstinence:** When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
2. **Sterilization:** have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to dosing. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
3. Use of a combination of any two of the following (a+b):

   a) Placement of an intrauterine device (IUD).

   b) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

The following are **acceptable** forms of contraception by female partners:

- Oral contraception, injected or implanted hormonal methods ((birth control pills, injectable/ implantable/ insertable hormonal birth control products, transdermal patch).
- Placement of an intrauterine device (IUD).

Fertile Males:

Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment; and additional 4 months after stopping treatment and should not father a child during the study for safety reason.

A condom is also required to be used by vasectomized men in order to prevent delivery of the drug via seminal fluid.

Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to Rhizen Pharmaceuticals SA within 24 hrs of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to Rhizen Pharmaceuticals SA. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Rhizen Pharmaceuticals SA study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.