CLINICAL STUDY PROTOCOL

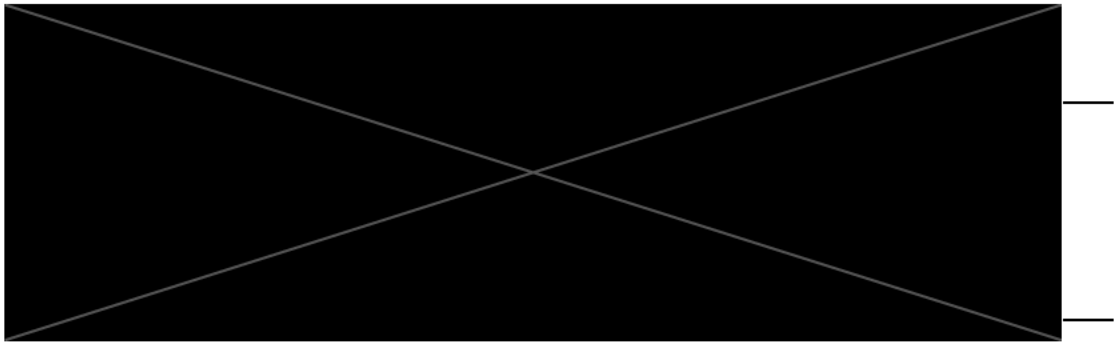
Title:	A Phase 2 study to evaluate the efficacy and safety of RPT193 in adults with moderate-to-severe T2-high asthma who are partially controlled on inhaled corticosteroid and long-acting beta 2 agonist therapy
Protocol number:	RPT193-03
Study phase:	Phase 2
Test product:	RPT193
Regulatory agency identifier number(s):	IND Number: 161880 EU CT Number: 2022-502854-16-00
Sponsor:	RAPT Therapeutics, Inc. 561 Eccles Avenue South San Francisco, CA 94080 United States
Protocol version and date:	Amendment 2– 12Sep2023

This study will be performed in compliance with the principles of Good Clinical Practice.

PROTOCOL SIGNATURE PAGE – SPONSOR

This protocol has been reviewed and approved by the representative listed below. Any modification of the protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

RAPT Therapeutics, Inc. representative:



Signature Date

PROTOCOL SIGNATURE PAGE – COORDINATING INVESTIGATOR

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH GCP), and applicable regional regulatory requirements.

Coordinating Investigator:

Print Name	Title
Institution	
Signature	Date

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

I have read this protocol, which has been agreed by RAPT Therapeutics, Inc. and given approval/favorable opinion by the IRB/IEC, and I agree that it contains all necessary details for my staff and me to conduct this study as described. I will provide copies of the protocol and any amendments to all study personnel under my supervision and provide access to all information provided by RAPT Therapeutics, Inc. or their specified designees. I will discuss the material with the study personnel to ensure that they are fully informed about the study.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from RAPT Therapeutics, Inc. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH GCP), and applicable regional regulatory requirements.

I agree to comply with the procedures described for data recording and reporting and to permit monitoring and auditing by RAPT Therapeutics, Inc., and inspection by the appropriate regulatory authorities.

I agree to make my subjects' study records available to RAPT Therapeutics, Inc. personnel, their representatives, and relevant regulatory authorities in order to verify data that I have entered into the electronic case report forms (eCRFs). I will retain the study-related essential documents until RAPT Therapeutics, Inc. indicates that they are no longer needed. I am aware of my responsibilities as an Investigator as provided by RAPT Therapeutics, Inc.

I understand that RAPT Therapeutics, Inc. may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to RAPT Therapeutics, Inc.

Investigator:

Print Name	Title
Institution	
Signature	Date

SERIOUS ADVERSE EVENT (SAE) AND ADVERSE EVENT OF CLINICAL INTEREST (AECI) CONTACT INFORMATION

In the event of an SAE/AECI, the Investigator will send a safety report form within 24 hours of becoming aware of the SAE/AECI to:

[redacted]

[redacted]

Email: [redacted]

PROTOCOL SYNOPSIS

Protocol Number: RPT193-03

Protocol Title: A Phase 2 study to evaluate the efficacy and safety of RPT193 in adults with moderate-to-severe T2-high asthma who are partially controlled on inhaled corticosteroid and long-acting beta 2 agonist therapy

Sponsor: RAPT Therapeutics, Inc.

Coordinating Investigator: TBD

Study Phase: 2

Study Sites: Approximately 40 sites in North America and Europe

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effect of 400 mg RPT193 compared with placebo on loss of asthma control (LOAC) in adults with T2-high partially controlled asthma on inhaled corticosteroid (ICS) plus long-acting beta 2 agonists (LABA) over 14 weeks	Proportion of subjects who satisfy any of the following LOAC criteria: • ≥ 30% reduction in morning peak expiratory flow (PEF) from baseline on 2 consecutive days • ≥ 6 additional reliever inhalations of short-acting beta 2 agonist (SABA) in a 24-hour period relative to baseline on 2 consecutive days • Increase by a factor of 4 or more in the most recent dose of ICS (or if ICS has been fully withdrawn, ≥ 50% of the prescribed ICS dose at baseline) • Exacerbation requiring systemic corticosteroids. • Exacerbation of asthma-related adverse events (AEs) that requires a hospitalization or emergency room visit
Secondary	
• To evaluate the safety and tolerability of RPT193 administered orally	• Frequency of treatment-emergent adverse events
• To evaluate the effect of RPT193 on time to a LOAC event(s)	• Time to a LOAC event
• To evaluate the effect of RPT193 on lung function in subjects with asthma	• Change in forced expiratory volume in 1 second (FEV1) at Day 99 (Week 14) and at each interval visit after treatment with RPT193 compared to baseline
• To evaluate the effect of RPT193 on asthma control	[redacted] • ange n PEF at Day 99 Wee 14 an at eac interval visit after treatment with RPT193 compared to baseline • Change in reliever bronchodilator use at Day 99 (Week 14) and at each interval visit after treatment with RPT193 compared to baseline • Change in fractional exhaled nitric oxide (FeNO) at Day 99 (Week 14) and at each interval visit after treatment with RPT193 compared to baseline
• To evaluate the effect of RPT193 [redacted]	• [redacted] Day 99 (Week 14) and at each interval visit after treatment with RPT193 compared to baseline

Exploratory	
• To evaluate the extent of sustained effect of RPT193 on lung function after 14 weeks of treatment	• Change in FEV1 from Day 99 to 140 (Weeks 14 to 20) • Change in FEV1 from Day 43 to 98 (Weeks 6 to 14)
• To evaluate the extent of sustained effect of RPT193 on asthma control after 14 weeks of treatment	• Change in [redacted] from Day 99 to 140 (Weeks 14 to 20) • Change in [redacted] from Day 43 to 98 (Weeks 6 to 14) • Proportion of subjects who are able to continue without inhaler therapy between Day 99 to 140 (Weeks 14 to 20) • Proportion of subjects with lower dose of ICS/LABA at Day 141 (Week 20) compared to baseline
• To evaluate the pharmacokinetics (PK) of RPT193 following administration of 400 mg of RPT193 administered orally once daily for 14 weeks to subjects with asthma	• PK parameters at Days 29, 43, 71, 99, and 113 (Weeks 4, 6, 10, 14, and 16)
• To evaluate the effect of RPT193 treatment on serum analytes, transcription in peripheral blood and peripheral immune populations and biomarkers associated with asthma	• Change in serum cytokines, chemokines, and other soluble analytes • Change in transcription in peripheral blood • Change in peripheral immune populations
• To evaluate the effects of RPT193 on nasal biomarkers	• Changes in the nasal transcriptome and nasal proteome

Study Design: Phase 2, randomized, multi-center, double-blind, placebo-controlled, parallel group, proof--of--concept study with RPT193 in subjects with T2-high, moderate-to-severe asthma who are partially controlled on medium or high doses of ICS in combination with LABA. Subjects who fulfill all the inclusion criteria and none of the exclusion criteria will be accepted into the study. After a screening period starting at Day -42, subjects will then receive standardized, inhaled therapy during a run-in- period of 4 weeks from Day -28 to Day -1. Thus, the Screening/run-in period will be no more than 6 weeks, and eligible subjects (n~100) will be randomized (1:1) on Baseline (Day 1) to receive RPT193 or placebo as oral tablet(s) daily from Baseline (Day 1) to Day 98 (Week 14).

All enrolled subjects will receive background inhaled therapy with ICS and LABA with management as follows:

- Period 1) during the screening and run-in period, potentially eligible subjects will begin standardized inhaled therapy with LABA and ICS from Day -28 to Day -1 at a dose commensurate with the subject's therapy at the initial Screening visit,
- Period 2) from Baseline (Day 1) through Day 42, subjects will receive RPT193 as adjunctive therapy to background ICS and LABA,
- Period 3) from Day 43 (Week 6) to Day 56, subjects will have LABA withdrawn and remain on medium- or high-dose ICS,
- Period 4) starting at Day 57 (Week 8), subjects will undergo a 2-to-3-week taper of ICS, and
- Period 5) starting at Day 78 (Week 11) (or Day 71 [Week 10] for those on medium-dose ICS and LABA at baseline), subjects will have a 3- (or 4-) week period of RPT193 monotherapy.

To explore the extent of sustained effect after treatment with RPT193, at the end-of-treatment visit at Day 99 (Week 14), subjects who have not satisfied any of the criteria for LOAC and have [redacted] and FEV1 >80% (consistent with being considered well-controlled) will enter into the 6-week follow-up period with re-initiation of background ICS and LABA therapy conditional upon any clinical or symptomatic evidence of worsening of asthma status (as advised in the Global Initiative for Asthma 2022 [GINA 2022] guidelines). At the end of the 6-week follow-up period, subjects will be reevaluated in terms of asthma control and be prescribed accordingly as per GINA 2022 guidelines and per Principal Investigator (PI) discretion.

At the end of treatment visit, sub ects who have not satisfied any of the criteria for LOAC and are not considered well-controlled with [redacted] and/or FEV1 < 80% predicted will re-initiate their individual, pre-screening inhaled therapy and enter the 6-week follow-up period. During the 6-week follow-up period, subjects will continue to be evaluated in terms of asthma control and be prescribed accordingly as per GINA 2022 guidelines and per PI discretion.

Study Duration: The maximum duration per subject is approximately 26 weeks, including up to 6 weeks for the screening/run-in periods, 14 weeks for the treatment period, and 6 weeks for the follow-up period.

The start of the study will be the date on which the first subject provides informed consent, and the end of the study will be the last subject's last assessment.

Planned Number of Subjects: Approximately 100 subjects will be enrolled 1:1 into 1 of 2 arms (RPT193 versus matched placebo).

Target Population:

Inclusion Criteria

1. Male or female (biologic sex) adult aged 18 to 75 years, inclusive, at the time of consent.
2. Physician diagnosis of asthma for ≥ 6 months based on GINA guidelines (GINA 2022).
3. Body mass index (BMI) ≥ 18 kg/m^2.
4. Pre-bronchodilator FEV1 of > 40% and < 80% at the Screening visit and > 40% and < 85% at the Baseline (Day 1) visit. The screening spirometry can be repeated once during the screening period at the discretion of the Investigator if it is nearly outside of eligibility criteria and in the Investigator's judgment there may be the potential for spirometry values aligned with eligibility based on subject's historic data.
5. Subjects with evidence of reversible airway obstruction, as defined by either of the following:
   a. ≥ 12% and 200 mL increase in FEV1 after administration of up to 4 inhalations (up to 400 µg) of albuterol during Screening, or documented history of a reversibility test that met these criteria within 12 months prior to Screening.
   b. Absolute relative change in FEV1 ≥12% and 200 mL over 2 measurements documented by repeat spirogram over the previous year and within 4 months after initiation of treatment with ICS with or without LABA (Wechsler 2019).
6. Subject has a history of at least 1 of either of the following in the past 12 months:
   a. Treatment with a systemic corticosteroid (either orally for ≥ 3 days or parenterally) OR
   b. Hospitalization or an emergency room visit for worsening asthma.
7. Medium- or high-dose equivalent ICS therapy (as defined by GINA 2022 guidelines) in combination with LABA at Screening with a stable dose in the 8 weeks prior to Screening and at the Baseline visit.
   Note: Subjects will receive standardized therapy equivalent to the dose of ICS the subject is taking at Screening.
8. [redacted]
9. Absolute eosinophil count ≥ 300/µL within the last 6 months prior to Screening OR FeNO ≥ 25 ppb at Screening.
10. Women of childbearing potential with a negative serum pregnancy test at Screening and negative urine pregnancy test at the Baseline (Day 1) visit.
11. For women of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method from at least 4 weeks prior to Baseline (Day 1) until at least 30 days after the last investigational product (IP) administration. Highly effective contraceptive methods include hormonal contraceptives (eg, combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s), tubal ligation or double barrier methods of contraception (eg, male condom with cervical cap, male condom with diaphragm, and male condom with contraceptive sponge) in conjunction with spermicide.
    Notes:
    a. A woman of nonchildbearing potential is defined as follows:
       i. Female subject who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).

ii. Female subject who has had a cessation of menses for at least 12 months prior to the Screening visit without an alternative medical cause, and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).

b. Subjects must have been on a stable regimen of hormonal contraceptives for at least 4 weeks prior to Baseline.

c. The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Baseline (Day 1) and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

d. For countries where double barrier methods are not accepted as highly effective contraception, then this option must not be considered.

12. Female subject agrees to not have egg retrieval during the study and for 30 days after the last IP administration.
13. For male subject involved in any sexual intercourse that could lead to pregnancy, subject must agree to use 1 of the highly effective contraceptive methods listed in Inclusion Criterion #11 from Baseline (Day 1) until at least 90 days after the last IP administration. If the female partner of a male subject uses any of the hormonal contraceptive methods listed above, this contraceptive method should be used by the female partner from at least 4 weeks before Baseline (Day 1) until at least 90 days after the last IP administration.
14. Male subject agrees not to donate sperm during the study and for 90 days after the last IP administration.
15. Subject is willing to participate and is capable of giving informed consent.
    Note: Consent must be obtained prior to any study-related procedures.

Exclusion Criteria

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. History of smoking per age group as follows (see also Exclusion Criterion #3):
   a. < 30 years old: Smoked for ≥ 5 pack-years.*
   b. 30 to 39 years old (inclusive): Smoked for ≥ 10 pack-years.
   c. ≥ 40 years old: Smoked for ≥ 15 pack-years.

   *One pack-year of cigarettes is defined as 1 pack of cigarettes a day for 1 year and is equivalent to:
   - 1 cigar or pipe per day for 1 year.
   - 1 hookah or shisha smoking session per day for 1 year.
   - 0.5 mL e-liquid per day for 1 year or 1 cartridge/tank/pod per day for 1 year of vaped e-cigarettes.
   - 1 use of smoked marijuana per day for 1 year.
3. Active use of any inhalant >1 time weekly in the past year including:
   a. Active smoking of conventional tobacco, marijuana (in any inhaled form) or other drugs, or vaping of e-cigarettes or e-devices.
   b. Other forms of tobacco including: 1 cigarette, 1 hookah or shisha session, 1 cigar, or 1 pipe.

   Note: Subjects must agree to refrain from using any inhalant as noted above more than 1 time weekly from the time they provide written informed consent until they complete all safety follow-up visits (ie, Day 141 / Week 20).
4. Subject has any serious and/or uncontrolled medical condition (including cognitive impairment, alcohol/drug abuse, or signs/symptoms suspicious for a serious disease) or laboratory abnormality that would place subject's safety at risk or interfere with study participation, as judged by the Investigator.
5. Conditions that may mimic asthma (eg, vocal cord dysfunction, hyperventilation, panic attacks, cardiac asthma, uncontrolled gastroesophageal reflux disease).
6. Subject has a history of severe COVID-19 that required intensive care unit (ICU) admission or assisted ventilation (including both invasive and non-invasive) in the 6 weeks before screening and did not return to their previous (pre-COVID-19 infection) respiratory status.
7. Subject has any of the following serious and/or uncontrolled medical conditions:
   a. Chronic obstructive pulmonary disease (COPD).
   b. Idiopathic pulmonary fibrosis (IPF).
   c. Subjects with uncontrolled diabetes (eg, hemoglobin A1c [HbA1c] ≥ 9%).

d. Stage III or IV cardiac failure according to the New York Heart Association classification.
e. Acute myocardial infarction, clinically significant arrythmia, or indications of serious underlying heart disease)/vital signs abnormality that, in the opinion of the Investigator would be indicative of an underlying medical condition, puts the subject at undue risk, and/or interfere with interpretation of study results.
f. Severe renal conditions (eg, subjects on dialysis).
g. Active autoimmune disease (eg, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease).
h. Subject has a history of a clinically significant systemic infection or serious respiratory infection requiring parenteral antibiotic treatment within 4 weeks prior to the Baseline (Day 1) visit, or oral therapy within 2 weeks prior to the Baseline (Day 1) visit.
i. Subject has a diagnosis of, is suspected of having, or is at high risk for an endoparasitic infection unless clinical and laboratory assessment have ruled out active endoparasitosis prior to the Baseline (Day 1) visit.
j. Subjects with moderate-to-severe hepatic impairment (ie, Child-Pugh score ≥ 7).
k. Subject has a history of a life-threatening asthma exacerbation in the last 5 years including but not limited to requirements for intubation and ventilation.

8. Subject has had a major surgery in the past 8 weeks prior to Screening or has a major, elective surgery planned during the study.
9. Any of the following specific laboratory findings:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN).
   b. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 (Modification of Diet in Renal Disease (MDRD) equation) unless considered normal for age.
   c. Platelet count < 75,000 cells/mm^3.
   d. Hemoglobin < 10 g/dL.
   e. Absolute lymphocyte count < 800 cells per mm^3.
   f. Absolute neutrophil count < 1500 cells per mm^3.

   Note: Subjects who have abnormal laboratory values listed in this criterion may have repeat assessment of abnormalities once during the Screening and/or Run-In periods.
10. Subject has a history of drug and/or alcohol abuse in the last 12 months prior to Screening.
11. Subject has any evidence of an ongoing exacerbation of asthma at the Baseline (Day 1) visit.
12. Requires systemic oral corticosteroids for the treatment of asthma at the Screening visit.
13. Systemic corticosteroid use (oral or intravenous) in the 4 weeks prior to Screening.
    Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
14. Hospitalization for a severe asthma exacerbation in the 4 weeks prior to Screening.
15. Subject has any state of immunodeficiency due to primary or secondary immunodeficiency syndromes, organ transplant (except corneal transplant), previous opportunistic infections, or any other state of immunodeficiency, as judged by the Investigator.
16. Subject has received RPT193 in the past.
17. Subject who is still participating in a clinical trial or who has participated in a clinical trial within 1 month prior to the Screening visit.
18. Subject has received an investigational oral, systemic agent within 8 weeks or 5 half-lives (whichever is longer) prior to the Baseline (Day 1) visit.
19. Subject has received any of the following marketed biological agents within the following timeframes prior to the Baseline (Day 1) visit:
    a. Omalizumab within 20 weeks.
    b. Mepolizumab within 16 weeks.
    c. Benralizumab within 16 weeks.
    d. Reslizumab within 16 weeks.

e. Dupilumab within 16 weeks.
f. Tezepelumab within 16 weeks.
g. Intravenous or subcutaneous immunoglobulin G (IgG) within 16 weeks.

20. Subject has received any investigational (intravenous or subcutaneous) biological agent within 16 weeks or 5 half-lives, whichever is longer prior to the Baseline (Day 1) visit.
21. Subject has used a cell-depleting agent, including but not limited to rituximab, within 6 months prior to the screening visit, or until lymphocyte counts return to normal, whichever is longer.

    Note: If a subject has received rituximab, the subject's lymphocyte count must be within the normal range at randomization even if rituximab was received more than 6 months prior to the Baseline (Day 1) visit.
22. Subject has had bronchial thermoplasty within the last 2 years prior to Screening.
23. Subject has received treatment with systemic immunosuppressive/immunomodulating drugs (eg, methotrexate, cyclosporine A, systemic Janus kinase (JAK) inhibitors, mycophenolic acid, or azathioprine) within 4 weeks prior to the Baseline (Day 1) visit.
24. Subject has begun an allergen-specific immunotherapy regimen or had a clinically relevant change to their immunotherapy within 4 weeks prior to the Baseline (Day 1) visit.
25. Subject has received a live or live attenuated vaccine within 4 weeks prior to the Baseline (Day 1) visit or plans to receive a live or live-attenuated vaccine during the study and up to 4 weeks after the last IP administration.
26. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to the Baseline (Day 1) visit.

    Note: Subjects with the below medical conditions can be considered, as judged by the Investigator if it was treated and completely resolved:

    - Cutaneous basal cell carcinoma.
    - Cutaneous squamous cell carcinoma in situ.
    - Cervical cancer in situ.
    - Melanoma in situ.
27. Subject has a known active bacterial, viral, fungal, helminth, or mycobacterial, or any other infection at the Baseline (Day 1) visit (non-complicated recurrent muco-cutaneous infections such as cold sores, tinea pedis, or disto-lateral mild to moderate onychomycosis are not considered exclusionary).

    Note: Subjects for whom infections have resolved and otherwise meet eligibility criteria may be re-screened once.
28. Subject has had a positive tuberculosis (TB) infection test at Screening. Subject will be evaluated for latent TB infection with a QuantiFERON-TB Gold test. Subjects who demonstrate evidence of latent TB infection with a positive QuantiFERON-TB Gold test, irrespective of bacille Calmette-Guérin vaccination status, will not be allowed to participate in the study, unless the subject has a documented history of chemoprophylaxis for latent TB infection or a documented history of treatment for active TB infection along with review/approval from the Sponsor.
29. Subject has a positive screen for hepatitis B surface antigen (HbsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies. For HBsAg or HCV antibody positive screening, subjects may be enrolled if reflex testing (eg, HBV-DNA or HCV RNA) is negative and indicative that there is no active infection.
30. e-Diary completion compliance < 80%, or more than 2 consecutive days missing data during the run-in period. Less than 80% translates to less than 12 out of 14 days and this calculation can be used to assess eligibility of subject's e-Diary completion compliance during the run-in period.

    Note: If e-Diary compliance is < 80 %, or a subject has more than 2 consecutive days of missing data during the first 2 weeks of the run-in, retraining must be organized, and compliance assessed in the following 2 weeks. If during this second period compliance is ≥ 80% and there are no missing data for 2 or more consecutive days, the subject may be considered eligible related to this criterion.
31. Subject is an employee or is known to be a relative of an employee of the study center or RAPT.

Investigational Product:

Name: RPT193

Dose: 400 mg once daily for 14 weeks (98 consecutive days)

Mode of administration: Oral tablets

Control Product:

Name: Placebo

Dose: Once daily for 14 weeks (98 consecutive days)

Mode of administration: Oral tablets

Non-Investigational Medicinal Product:

Name: Fluticasone/Salmeterol, Fluticasone

Statistical Methods:

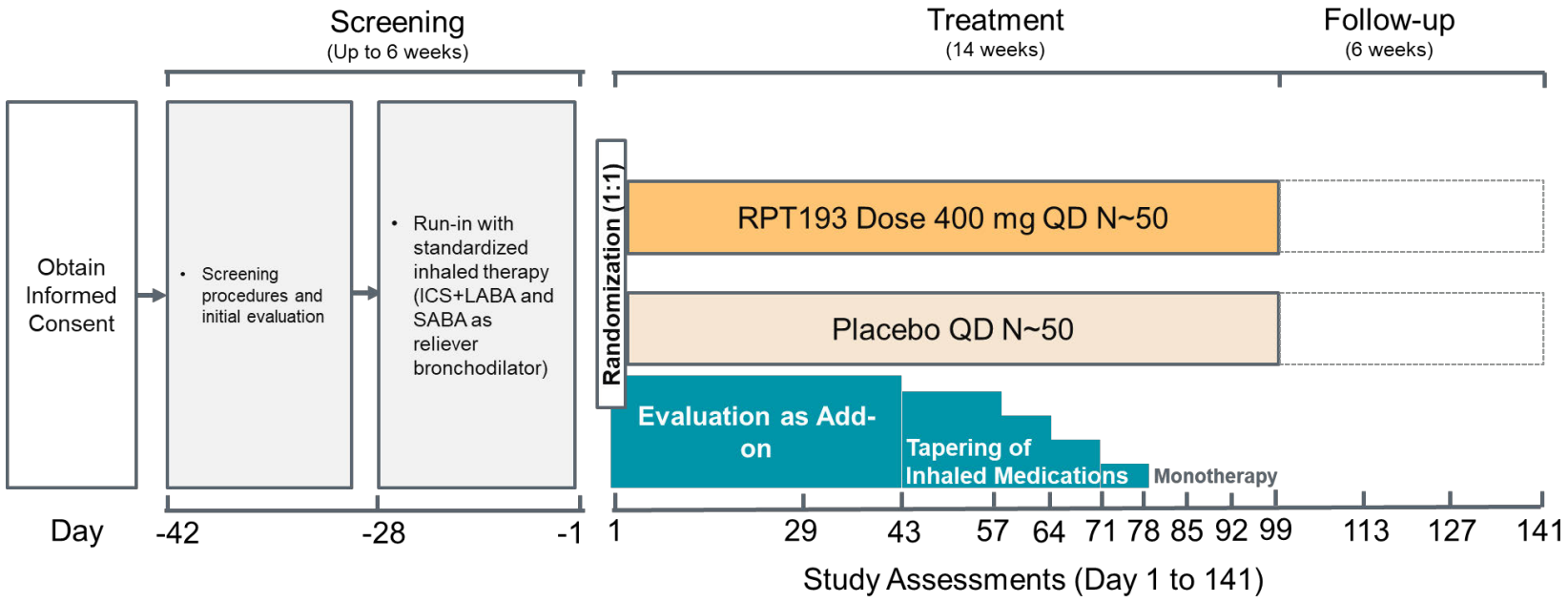
The primary analysis will compare rates of LOAC between treatment groups using a generalized linear model with binomial distribution and identity link with fixed effects for treatment, pre-screening inhaled ICS + LABA (medium- or high-dose ICS), and location of the study site (North America versus Europe). The absolute difference in the rate of LOAC between placebo and RPT193 will be estimated and presented with the 90% CI for the difference. LOAC rates, 90% and 95% confidence intervals (CIs) for LOAC rates, estimated treatment effects (ie, the odds ratio of RPT193 versus placebo), and 90% and 95% CIs of the odds ratio will be provided. The key secondary efficacy analysis of time to LOAC will use a log-rank test to compare the hazard rates between the RPT193 and placebo groups. The Kaplan-Meier method will be used to estimate and compare the distributions of time to LOAC between treatment groups. A mixed-model repeated-measures model with treatment group, visit, and treatment and visit interaction as fixed effects and subject as a random effect will be used for analyzing the following endpoints, expressed as change from baseline at each visit up to Week 14: FEV1, PEF, FeNO, [redacted] The remaining efficacy endpoints will be analyzed using descriptive statistics.

Treatment-emergent adverse events (TEAEs) will be presented by system organ class (SOC) and preferred term in frequency tables. Key subject information for subjects with an AE with an outcome of death, subjects with serious adverse events (SAEs), and subjects with AEs leading to discontinuation of IP will be listed. Laboratory data values and changes from baseline will be presented descriptively. Vital signs and electrocardiogram (ECG) parameters will be presented descriptively.

Protocol Version and Date: Amendment 2, 12Sep2023

STUDY SCHEMATIC

Figure 1: Study Schematic



Abbreviations: ICS = inhaled corticosteroids; LABA = long-acting beta 2 agonist; SABA = short-acting beta 2 agonist.

SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Events

				Treatment (Day 1 to Day 98)											
	Screening	Run-in (R1)	Run-in (R2)[k]	IP as Add-on to ICS/LABA		LABA withdrawal	ICS Taper and Monotherapy						EOT	Safety FU/ET	Extended FU
	Day -42 to -28	Day -28	Day -14	Day 1	Day 29	Day 43	Day 57	Day 64	Day 71	Day 78	Day 85	Day 92	Day 99	Day 113	Day 141
				Baseline	Week 4	Week 6	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week 14/ EOT	Week 16	Week 20
	Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
Procedure	--	±3 days	--	--	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Informed consent	X														
Eligibility criteria	X			X											
Medical history	X														
Demography	X														
Physical examination[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height, weight, and BMI[b]	X														X
TB screening	X														
Pregnancy test[c] (females only)	X			X	X		X				X			X	X
Clinical laboratory tests (hematology, chemistry)[d,e] including FSH at screening	X			X	X	X			X		X		X	X	X
Urinalysis	X			X		X							X	X	
12-lead ECG	X			X Pre-dose									X	X	
Complete randomization in IXRS system				X											
Spirometry test	X			X	X	X	X	X	X	X	X	X	X	X	X
Fractional exhaled nitric oxide (FeNO)	X			X	X	X	X	X	X	X	X	X	X	X	X
Switch to standardized		X													

Procedure	Screening	Run-in (R1)	Run-in (R2)[k]	Treatment (Day 1 to Day 98)									EOT	Safety FU/ET	Extended FU
				IP as Add-on to ICS/LABA		LABA withdrawal	ICS Taper and Monotherapy								
	Day -42 to -28	Day -28	Day -14	Day 1	Day 29	Day 43	Day 57	Day 64	Day 71	Day 78	Day 85	Day 92	Day 99	Day 113	Day 141
				Baseline	Week 4	Week 6	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week 14/ EOT	Week 16	Week 20
	Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
	--	±3 days	--	--	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
salmeterol-fluticasone inhaler															
Provisioning daily PEF meter/ electronic diary device to subject		X													
Collect daily PEF meter/electronic diary device from subject														X[f]	X
[redacted]															
[redacted]															
[redacted]				X		X							X	X	X
Study IP Administration – Study IP dosing at study center (after baseline assessments)[g]				X	X	X	X	X	X	X	X	X			
Study IP administration – study IP dosing daily at home[g]				X ---------- X[l]											

Procedure	Screening	Run-in (R1)	Run-in (R2)[k]	Treatment (Day 1 to Day 98)									EOT	Safety FU/ET	Extended FU
				IP as Add-on to ICS/LABA		LABA withdrawal	ICS Taper and Monotherapy								
	Day -42 to -28	Day -28	Day -14	Day 1	Day 29	Day 43	Day 57	Day 64	Day 71	Day 78	Day 85	Day 92	Day 99	Day 113	Day 141
				Baseline	Week 4	Week 6	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week 14/ EOT	Week 16	Week 20
	Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
	--	±3 days	--	--	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Dosing Diary – Daily subject diary for IP dosing at home				X ---------- X[l]											
Daily subject diary for background (ICS, LABA) inhaler(s) use		X ---------- X[l]													
Daily subject diary for reliever bronchodilator (SABA) use		X ---------- X[l]													
Daily diary PEF – daily AM and PM PEF[h]		X ---------- X[l]													
As needed reliever bronchodilator (SABA) use		X ---------- X[l]													
As applicable study-provided (ICS, LABA) inhaler[m]		X ---------- X[l]													
PK collection – blood sampling				X Pre-dose	X Pre-dose	X Pre-dose			X Pre-dose				X	X	
RNA collection – whole blood RNA sample				X		X					X		X		X
Serum cytokines/ chemokines and biomarker levels				X	X	X	X		X		X		X	X	X
Serum antigen-specific IgE				X		X							X		
PD sampling – blood				X		X					X		X		X

				Treatment (Day 1 to Day 98)											
	Screening	Run-in (R1)	Run-in (R2)[k]	IP as Add-on to ICS/LABA		LABA withdrawal	ICS Taper and Monotherapy						EOT	Safety FU/ET	Extended FU
	Day -42 to -28	Day -28	Day -14	Day 1	Day 29	Day 43	Day 57	Day 64	Day 71	Day 78	Day 85	Day 92	Day 99	Day 113	Day 141
				Baseline	Week 4	Week 6	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week 14/ EOT	Week 16	Week 20
	Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
Procedure	--	±3 days	--	--	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Pharmacogenomics[i]				X											
Nasopharyngeal brush test – nasal sampling for biomarker analysis				X		X				X			X		X
Nasal epithelial lining fluid (NELF) – nasal sampling for biomarker analysis				X	X	X	X			X	X		X	X	X
IP Accountability-Dispensed – Study IP distribution				X	X	X	X		X		X				
IP Accountability-Returned – Study IP collection/ review					X	X	X	X	X	X	X	X	X	X[f]	
NIMP (ICS, LABA, SABA) Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X
Inhaler Standardization[j]		X	X												
Management of inhalers[j]						X	X	X	X	X	X	X	X		
Prior and concomitant medication		Ongoing from screening													
Adverse events reporting		Ongoing from the time of signing the ICF (non-treatment and treatment-emergent adverse events)													

Abbreviations: [redacted] AE = adverse event; [redacted] BMI = body mass index; ECG = electrocardiogram; EOT = end of treatment; ET = early termination; FeNO = fractional exhaled nitric oxide; FEV1 = forced expiratory volume at 1 second; FSH = follicle-stimulating hormone; FU = follow up; ICS = inhaled corticosteroids; IP = investigational product; LABA = long-acting beta 2 agonist;

LOAC = loss of asthma control; PD = harmacod namic; PEF = eak expiratory flow; PK = pharmacokinetic; RNA = ribonucleic acid; SABA = short-acting beta 2 agonist; [redacted] TB = tuberculosis.

a. Full physical examination at Screening; targeted physical examination at all other visits.
b. Height and weight will be collected, and BMI calculated at Screening. Only weight will be collected at follow-up.
c. Serum pregnancy test at screening, and urine pregnancy test at other visits.
d. FSH at screening visit only for females of non-childbearing potential; fasting labs at Baseline (Day 1), Day 99 (Week 14), Day 113 (Week 16).
e. Laboratory tests may be repeated during Run-In if tests are missing or considered disqualifying for any subject at Screening. Subjects may enter run-in while repeat laboratory tests are being verified to ensure the screening window does not expand beyond 42 days.
f. Applies at ET only.
g. IP should be taken with approximately 240 mL (8 ounces) of water. Subjects may discuss the pros and cons of taking the IP with food with the Investigator of their site.
h. Please refer to Section 5.2.1.1 for timing of the PEF assessments.
i. Blood samples will be collected from subjects who have consented to participate in the genetic analysis component of the study. Participation is optional. Please see Section 5.7 for further details.
j. The Investigator to provide clear and accurate instructions to the subject on the dosage of inhaled corticosteroid and LABA in a step wise tapering manner. In case the taper of corticosteroid and/or LABA is not done at a particular visit, the reason will be documented.
k. If after 2 weeks of R1 the e-Diary compliance is < 80 %, or if there are more than 2 consecutive days of missing data during the first 2 weeks of run-in, a retraining will be organized (R2).
l. Denotes daily administration.
m. If subject has a LOAC event subject will return to their individual, pre-screening inhaled therapy per Section 5.2.1.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
[redacted]	[redacted]
ADR	adverse drug reaction
AE	adverse event
AECI	adverse event of clinical interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
[redacted]	[redacted]
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
BSA	body surface area
CCL	C-C motif chemokine ligand
CCR	C-C motif chemokine receptor
CI	confidence interval
C_{max}	maximum concentration
COPD	chronic obstructive pulmonary disease
CRO	clinical research organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
EAS	Enrolled Analysis Set
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ER	emergency room
ET	early termination
FAS	Full Analysis Set
FEF25%-75%	forced mid-expiratory flow
FeNO	fractional exhaled nitric oxide
FEV1	forced expiratory volume in 1 second
FIH	first in human
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	gamma-glutamyl transferase

Abbreviation	Definition
GINA	Global Initiative for Asthma
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1c
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether à go go gene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IC_{50}	50% inhibitory concentration
IC_{90}	90% inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids
ICU	intensive care unit
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
INR	international normalized ratio
IP	investigational product
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ITT	intention to treat
IXRS	interactive voice response system/interactive web response system
JAK	Janus kinase
K-M	Kaplan-Meier
LABA	long-acting beta 2 agonist
LAMA	long-acting muscarinic agonist
LOAC	loss of asthma control
LTRA	leukotriene receptor antagonist
MACE	major adverse cardiac event
MDI	metered dose inhaler
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
NCI	National Cancer Institute
NIH	National Institutes of Health
PD	pharmacodynamic(s)

Abbreviation	Definition
PDAS	Pharmacodynamic Analysis Set
PEF	peak expiratory flow
PI	Principal Investigator
PK	pharmacokinetic(s)
PKAS	Pharmacokinetic Analysis Set
PO	oral
POC	proof of concept
PPAS	Per-Protocol Analysis Set
PT	prothrombin time
QTL	quality tolerance limit
RO	receptor occupancy
RSI	reference safety information
SABA	short-acting beta 2 agonist
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SCORAD	Scoring of Atopic Dermatitis
SD	standard deviation
SE	standard error
[redacted]	[redacted]
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TMF	Trial Master File
ULN	upper limit of normal
vIGA	validated Investigator Global Assessment

1 INTRODUCTION AND RATIONALE

1.1 Background

Th2 cells express high levels of C-C motif chemokine receptor 4 (CCR4) and are clinically important drivers of allergic diseases which include atopic dermatitis, food allergy, asthma, and allergic conjunctivitis/rhinosinusitis as well as additional diseases such as chronic urticaria and eosinophilic esophagitis (Vestergaard 2003). Th2 cells trigger immune responses when a pathogen comes into contact with the skin or mucosal lining of the nose or lungs. It is believed that innate immune cells and antibodies that recognize the pathogen initiate a release of inflammatory cytokines, leading to the recruitment of other immune system components, including Th2 cells. Th2 cells secrete proinflammatory cytokines, such as interleukin (IL)-4, IL-5, and IL-13 (Koyasu 2011). Collectively, these cytokines and resultant biology have been coined "type 2 cytokines". While this type 2 cytokine response may be highly effective against foreign pathogens, particularly parasites, sometimes the body overreacts to benign substances in this way, resulting in a significant influx of Th2 cells, leading to a number of conditions (Bosnjak 2011; Kubo 2017).

At a cellular and molecular level, the Th2 response is initiated and sustained when Th2 cells are recruited to the site of inflammation by binding of C-C motif chemokine ligand (CCL)17 and CCL22 to CCR4 (Viney 2014). Subjects suffering from atopic dermatitis, asthma, and other allergic disorders have significantly elevated levels of both CCL17 and CCL22 (Hartl 2009; Kataoka 2014), suggesting that inhibiting the ability of these chemokines to bind to CCR4 may prevent migration of Th2 cells into these inflamed sites.

RPT193 is an orally (PO) bioavailable, highly selective small molecule CCR4 antagonist that blocks the recruitment of inflammatory immune cells, known as Th2 cells, which are clinically implicated in allergic inflammatory disorders (Vestergaard 2003). RPT193 is a first-in-class CCR4 antagonist being developed for allergic inflammatory diseases. Preclinical pharmacology and toxicology results suggested (i) efficacy similar to clinically validated mechanisms in allergic inflammatory disease models, (ii) once daily PO dosing may be sufficient, and (iii) a safety profile compatible with chronic dosing in humans.

RPT193 has demonstrated efficacy in multiple preclinical mouse models of atopic dermatitis and asthma. The observed efficacy was comparable to that of a commercially available anti-mouse IL-13 antibody, which represents the class of biologics such as dupilumab, lebrikizumab, and others targeting Th2-derived cytokines such as IL-4, IL-5, and IL-13. The results observed in these models demonstrate the clinical potential to treat a number of Th2-driven disorders in humans.

As a monotherapy in subjects with moderate-to-severe atopic dermatitis, RPT193 demonstrated evidence of clinical effect with improvements over placebo in Eczema Area and Severity Index (EASI), Scoring of Atopic Dermatitis (SCORAD), extent of body surface area (BSA) affected by atopic dermatitis, validated Investigator Global Assessment (vIGA) and patient-reported outcomes (eg, daily peak pruritus numerical rating scale as well as sleep and pruritus assessments within the SCORAD instrument) after 28 days of dosing. Further improvements in EASI, SCORAD, BSA, and vIGA were observed at Day 43, 2 weeks after the cessation of dosing. Overall, the results of the Phase 1 trial in subjects with moderate-to-severe atopic

dermatitis suggest that CCR4 inhibition has the potential to become a novel therapeutic option for subjects with atopic dermatitis. These data also support a larger Phase 2 study to further understand the potential of RPT193 as a safe and effective treatment for atopic dermatitis as well as other diseases of allergic inflammation, such as asthma.

For further details, refer to the Investigator's Brochure (IB).

1.2 Nonclinical Studies

Nonclinical studies were conducted to characterize the pharmacology, pharmacokinetics (PK), and toxicology of RPT193. The nonclinical studies support the following conclusions:

- Oral administration of RPT193 resulted in efficacy in multiple preclinical mouse models of atopic dermatitis and a model of allergic asthma, as demonstrated by the reduction of ear thickness, cellular infiltrate and Th2 effector cytokines such as IL-5 and IL-13. Reduction of inflammation by RPT193 in these preclinical models was similar to that observed with an anti-IL-13 antibody.

- The 50% inhibitory concentration (IC_{50}) of RPT193 for human ether-à- o- o gene (hERG) in a Good Laboratory Practice (GLP) manual patch clamp assay was [redacted]. Accordingly, the proarrhythmic risk in humans is considered low since unbound plasma concentrations in humans are predicted to be approximately 30-fold lower.

[redacted]

1.3 Clinical Studies

A completed first-in-human (FIH) randomized, double-blind, placebo-controlled, trial (RPT193-01) was conducted to characterize the PK and safety of single or multiple once daily doses (5 mg to 400 mg) of RPT193 in healthy subjects for up to 7 days and multiple doses in subjects with moderate-to-severe atopic dermatitis who received daily RPT193 at 400 mg for up to 28 days. A total of 77 subjects received RPT193 in study RPT193-01. Results from this study (also described in the RPT193 IB) support the following conclusion: RPT193 demonstrated increases in exposure following increasing single and multiple doses and up to approximately 2-fold accumulation following multiple doses, and no clear evidence for an effect of food, with a mean plasma half-life of approximately 24 hours.

In RPT193-01, RPT193 was found to be well-tolerated at all tested doses following single-dose (Part A) and multiple-dose (Part B) administration in healthy subjects and following multiple dose administration in subjects with atopic dermatitis (Part C). Overall:

- All treatment-emergent adverse events (TEAEs) were mild or moderate in severity; no severe TEAEs were reported in the study.

- The majority of TEAEs were considered not related to the study treatment and were resolved at the end of the study.

- The most common TEAE reported after single or multiple ascending doses in healthy subjects was headache, while the most common TEAE reported in subjects with atopic dermatitis was nausea.

- The proportion of subjects reporting TEAEs was similar under fasted and fed conditions in a crossover group who received RPT193 in a blinded fashion in a fasted and then fed state.

- In the 28-day portion of the Phase 1 study wherein subjects with atopic dermatitis received RPT193 400 mg once daily for 28 days, no hematologic TEAEs were reported and 1 cardiovascular TEAE was reported (mild/Grade 1 electrocardiogram [ECG] QT prolongation that was borderline [triplicate average ECG of 457 ms] and asymptomatic but considered by the Investigator as potentially treatment related). The adverse event (AE) resolved within 24 hours of observation.

- No serious adverse events (SAEs), or TEAEs leading to study discontinuation were reported in this study. There was 1 TEAE leading to discontinuation of receipt of study drug reported in the 28-day study (generalized rash of moderate severity, considered treatment-related by the Investigator).

- There were minimal changes from baseline in laboratory parameters, vital signs, and ECGs, and the majority of abnormal values were not clinically significant.

- The FIH trial included a portion wherein RPT193 was explored as monotherapy in subjects with moderate-to-severe atopic dermatitis. RPT193 was generally safe and well tolerated, and improvement in key atopic dermatitis disease severity parameters (EASI, SCORAD, vIGA, extent of BSA affected by atopic dermatitis) was observed compared to placebo on Day 29. These measures of atopic dermatitis severity continued to improve 2 weeks after treatment cessation, suggesting potentially unique kinetics associated with targeting Th2 cell migration and function with an oral CCR4 antagonist. In addition, evidence of symptomatic improvement on pruritus and sleep at Day 29 and Day 43 was observed.

1.4 Study Rationale

RPT193-03 will investigate the efficacy and safety of RPT193 in subjects with moderate-to-severe T2-high asthma. T2-high asthma is considered an "endotype" of asthma in which specific cytokines associated with type 2 immunity, such as IL-5, IL-4, and IL-13 are considered primary drivers of disease (Woodruff 2009). The study will assess a single dose level of RPT193 (400 mg) taken orally once daily for 14 weeks.

1.5 Dose Justification

[redacted]

1.6 Benefit/Risk Assessment

[redacted]

Based on the proposed mechanism of action of RPT193 (inhibition of CCR4-mediated recruitment of certain immune cells, Th2, into sites of inflammation), immune-mediated toxicity is not predicted to occur. Consistent with this hypothesis, no clear clinical or histopathologic signs of cytokine release, autoimmunity, or inflammation were observed in nonclinical studies, healthy volunteers, or participants with atopic dermatitis. As a precaution, this study excludes participants who have immunodeficiency or are taking immunosuppressive/immunomodulating drugs while the safety profile of RPT193 continues to be assessed.

Overall, the nonclinical and clinical safety profile and early indications of clinical effect in subjects with moderate-to-severe atopic dermatitis support the ongoing larger Phase 2 study to further understand the potential of RPT193 as a safe and effective treatment for atopic dermatitis as well as this proof-of-concept (POC) study in subjects with T2-high moderate-to-severe asthma.

To date, there have been no unexpected, SAEs related to RPT193, therefore any SAE considered to be related to RPT193 would be considered "unexpected" for purposes of safety reporting. More detailed information about the known and expected benefits, risks, and reasonably expected AEs of RPT193-03 can be found in the IB.

Considering the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with RPT193-03 are justified by the anticipated benefits that may be afforded to subjects with moderate-to-severe T2-high asthma.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of 400 mg RPT193 compared with placebo on loss of asthma control (LOAC) in adults with T2-high partially controlled asthma on inhaled corticosteroid (ICS) plus long-acting beta 2 agonists (LABA) over 14 weeks	Proportion of subjects who satisfy any of the following LOAC criteria: • ≥ 30% reduction in morning peak expiratory flow (PEF) from baseline on 2 consecutive days • ≥ 6 additional reliever inhalations of short-acting beta 2 agonist (SABA) in a 24-hour period relative to baseline on 2 consecutive days • Increase by a factor of 4 or more in the most recent dose of ICS (or if ICS has been fully withdrawn, ≥ 50% of the prescribed ICS dose at baseline) • Exacerbation requiring systemic corticosteroids. • Exacerbation of asthma-related AEs that requires a hospitalization or emergency room visit
Secondary	
• To evaluate the safety and tolerability of RPT193 administered orally	• Frequency of treatment-emergent adverse events
• To evaluate the effect of RPT193 on time to a LOAC event(s)	• Time to a LOAC event
• To evaluate the effect of RPT193 on lung function in subjects with asthma	• Change in forced expiratory volume in 1 second (FEV1) at Day 99 (Week 14) and at each interval visit after treatment with RPT193 compared to baseline
• To evaluate the effect of RPT193 on asthma control	• [redacted] at Day 99 (Week 14) and at each interval visit after treatment with RPT193 compared to baseline • Change in PEF at Day 99 (Week 14) and at each interval visit after treatment with RPT193 compared to baseline • Change in reliever bronchodilator use at Day 99 (Week 14) and at each interval visit after treatment with RPT193 compared to baseline • Change in fractional exhaled nitric oxide (FeNO) at Day 99 (Week 14) and at each interval visit after treatment with RPT193 compared to baseline
• To evaluate the effect of RPT193 on [redacted]	• [redacted] at Day 99 (Week 14) and at each interval visit after treatment with RPT193 compared to baseline
Exploratory	
• To evaluate the extent of sustained effect of RPT193 on lung function after 14 weeks of treatment	• Change in FEV1 from Day 99 to 140 (Weeks 14 to 20) • Change in FEV1 from Day 43 to 98 (Weeks 6 to 14)
• To evaluate the extent of sustained effect of RPT193 on asthma control after 14 weeks of treatment	• Change in [redacted] from Day 99 to 140 (Weeks 14 to 20) • Change in [redacted] from Day 43 to 98 (Weeks 6 to 14) • Proportion of subjects who are able to continue without inhaler therapy between Day 99 to 140 (Weeks 14 to 20) • Proportion of subjects with lower dose of ICS/LABA at Day 141 (Week 20) compared to baseline

• To evaluate the PK of RPT193 following administration of 400 mg of RPT193 administered orally once daily for 14 weeks to subjects with asthma	• PK parameters at Days 29, 43, 71, 99, and 113 (Weeks 4, 6, 10, 14, and 16)
• To evaluate the effect of RPT193 treatment on serum analytes, transcription in peripheral blood and peripheral immune populations and biomarkers associated with asthma	• Change in serum cytokines, chemokines, and other soluble analytes • Change in transcription in peripheral blood • Change in peripheral immune populations
• To evaluate the effects of RPT193 on nasal biomarkers	• Changes in the nasal transcriptome and nasal proteome

3 STUDY PLAN

3.1 Overall Study Design and Plan

This is a Phase 2, randomized, multicenter, double-blind, POC study with RPT193 in subjects with moderate-to-severe T2-high asthma who are partially controlled on medium or high doses of ICS and long-acting beta agonists (LABA). Approximately 100 subjects will be enrolled 1:1 into 1 of 2 arms (RPT193 versus matched placebo).

Male or female adults aged 18 to 75 years will be included in this study. The study design is outlined in Figure 1, and the visit schedule and planned assessments at each visit are detailed inTable 1.

The Investigator will obtain signed informed consent from the subject before any study procedures are performed. For further details regarding the informed consent process, see Section 10.3.

After an initial screening period of up to 14 days, subjects will enter a run-in period of 28 days to standardize background inhaled ICS and LABA (Period 1). The standardized background ICS/LABA regimen must be commensurate to the subject's ICS/LABA dose at the Screening visit as described in Appendix V – Section 17.5. If a subject is considered eligible at the Baseline (Day 1) visit, each subject (n~100) will be randomized (1:1) to receive RPT193 or placebo as oral tablets daily from Baseline (Day 1) to Day 98. Enrolled subjects will receive RPT193 or matching placebo for 14 weeks with management of background ICS and LABA during the following Periods:

- Period 2) from Baseline (Day 1) through Day 42, subjects will receive RPT193 as adjunctive therapy to background ICS and LABA,
- Period 3) from Day 43 (Week 6) to Day 56, subjects will have LABA withdrawn and remain on medium- or high-dose ICS,
- Period 4) starting at Day 57 (Week 8), subjects will undergo a 2- to 3-week taper of ICS, and
- Period 5) starting at Day 78 (Week 11) (or Day 71 [Week 10] for those on medium-dose ICS and LABA at baseline), subjects will have a 3- (or 4-) week period of monotherapy.

Throughout the treatment period, subjects will be followed for evidence of a LOAC event. If a subject has a LOAC event, the subject will be immediately discontinued from investigational product (IP), returned to their individual, pre-screening inhaled therapy, and remain in the study for safety follow-up and further clinical management if necessary.

Subjects will be administered RPT193 or a matching placebo during the treatment period. Both RPT193 and the matching placebo will be given orally. See Section 6.4 for further details on the method of assigning subjects to the treatment groups. See Section 6.6 for further details on the dose and administration of RPT193 and the matching placebo.

The study is randomized and double-blinded with regard to RPT193 and placebo in order to prevent bias in treatment allocation and in the assessment of treatment effect. The Investigator, site personnel, the Sponsor representatives involved in monitoring and conducting the study, and the subjects will be blinded to the IP administered. See Section 6.3 for details on access to the treatment codes in the event of emergency unblinding.

A safety monitoring plan includes real-time monitoring of subjects, using the daily e-Diary as well as the internet-enabled PEF meter, for evidence indicative of LOAC so that subjects may be quickly evaluated, discontinued from IP, and managed clinically. Per protocol, though such subjects will stop IP, they will continue in the trial for clinical follow-up. In addition, a Data Monitoring Committee (DMC) comprised of, at a minimum, 2 independent pulmonary physicians and 1 biostatistician will evaluate unblinded data at regular timepoints that will be outlined in the DMC charter; in addition, the charter will require ad hoc meetings as appropriate for potential emerging safety problems, or when important new information external to the trial arises.

3.2 Discussion of Study Design

As clinical development of systemic therapeutics in adults with moderate-to-severe asthma has moved toward requiring demonstration of an investigational therapeutic's capacity to decrease subjects' risk for severe exacerbations after 26 to 52 weeks of add-on therapy, designing efficient and informative POC studies has become more challenging. POC studies assessing lung function and FEV1 as a primary endpoint after add-on therapy with a novel therapeutic have been employed for many years. However, recent studies with novel, systemic agents suggest that improving FEV1 may not strongly correlate with a therapeutic's magnitude of effect on exacerbations (Zhudenkov 2021; Fielding 2019). Thus, alternative POC study designs may yield more information related to the potential of a novel therapy in asthma.

More recently, placebo-controlled withdrawal designs consisting of a period of add-on therapy followed by a period of prescribed tapering of background, inhaled therapies with assessment of a "loss of asthma control" as a primary endpoint have emerged as an efficient and informative means to assess a therapeutic's potential to limit asthma exacerbations (Wechsler 2021; Wenzel 2013). Thus far, at least 6 studies, from 2011 and continuing through the present, have utilized this design as POC for a variety of investigational therapies evaluated in Phase 2 studies, including dupilumab (NCT01312961, US only), AZD1419 (NCT02898662, EudraCT 2016-000977-19, GSK3772847 (NCT03207243; EudraCT 2017-001072-34), itepekimab (NCT03387852; EudraCT 2017-003289-29), TEV-48574 (NCT04545385; EudraCT 2020-001927-15), and rilzabrutinib (NCT05104892; EudraCT 2021-002490-26). Dupilumab has now been approved for patients with moderate-to-severe eosinophilic asthma as well as patients with asthma requiring chronic oral corticosteroids. Similarly, this study will investigate whether RPT193 is capable of preventing LOAC in subjects with partially controlled, moderate--to--severe T2 asthma. The current study will be a Phase 2, randomized, double-blind, POC study with RPT193 in subjects with moderate-to-severe asthma who are partially controlled on medium or high doses of ICS and LABA. Subjects who fulfill all the inclusion criteria and meet none of the exclusion criteria will be accepted into the study. After a screening/run-in period of no more than 42 days, subjects (n~100) will be randomized (1:1) on Baseline (Day 1) to receive RPT193 or placebo as oral tablet(s) daily from Baseline (Day 1) to Day 98.

3.3 End of Study

A subject is considered to have completed the study if s/he has completed all study visits.

The end of the study is defined as the date of the last visit or last procedure of the last subject in the study.

3.4 Study Committees

A DMC will review unblinded safety and efficacy data and has a primary responsibility of providing the Sponsor with recommendations regarding the conduct of the study. The DMC is comprised of individuals with expertise in asthma from a medical and biostatistical perspective. The DMC members are external to the Sponsor and the conduct of the study. The DMC procedures and data to be reviewed are described in the DMC charter. The DMC will evaluate unblinded data at regular timepoints that are outlined in the DMC charter; in addition, the charter requires ad hoc meetings as appropriate for potential emerging safety problems, or when important new information external to the trial arises.

3.5 Safety Monitoring Plan

Real-time monitoring of subjects for evidence indicative of LOAC is being implemented in this study so that subjects may be quickly evaluated and managed accordingly. Further details are found in the Safety Monitoring Plan and include the use of real-time alerts for evidence of LOAC and/or missing data. In addition, subjects are required to return to the study site weekly during the period of withdrawal of ICS therapy.

Per protocol, subjects who demonstrate evidence of LOAC will be returned to their individual, pre-screening inhaled therapy and managed for escalation of therapy as appropriate and determined by the Principal Investigator (PI) at the site. While subjects will be discontinued from study IP, subjects will continue in the trial for clinical follow-up (see Section 5.2.1).

4 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. The [redacted] Medical Monitor shall review the eligibility data of subjects during the screening period. The Investigator should confirm at the time of randomization that all of the inclusion criteria and none of the exclusion criteria are met.

4.1 Inclusion Criteria

The following inclusion criteria must be met for a subject to be eligible for inclusion in the study:

1. Male or female (biologic sex) adult aged 18 to 75 years, inclusive, at the time of consent.

2. Physician diagnosis of asthma for ≥ 6 months based on Global Initiative for Asthma (GINA) guidelines (GINA 2022).

3. Body mass index (BMI) ≥ 18 kg/m^2.

4. Pre-bronchodilator FEV1 of > 40% and < 80% at the Screening visit and > 40% and < 85% at the Baseline (Day 1) visit. The screening spirometry can be repeated once during the screening period at the discretion of the Investigator if it is nearly outside of eligibility criteria and in the Investigator's judgment there may be a scope of the potential for spirometry values aligned with eligibility based on subject's historic data.

5. Subjects with evidence of reversible airway obstruction, as defined by either of the following:

    a. ≥ 12% and 200 mL increase in FEV1 after administration of up to 4 inhalations (up to 400 µg) of albuterol during Screening, or documented history of a reversibility test that met these criteria within 12 months prior to Screening.

    b. Absolute relative change in FEV1 ≥ 12% and 200 mL over 2 measurements documented by repeat spirogram over the previous year and within 4 months after initiation of treatment with ICS with or without LABA (Wechsler 2019).

6. Subject has a history of at least 1 of either of the following in the past 12 months:

    a. Treatment with a systemic corticosteroid (either orally for ≥ 3 days or parenterally) OR

    b. Hospitalization or an emergency room visit for worsening asthma.

7. Medium- or high-dose equivalent ICS therapy (as defined by GINA 2022 guidelines) in combination with LABA at Screening with a stable dose in the 8 weeks prior to Screening and at the Baseline visit.

   Note: Subjects will receive standardized therapy equivalent to the dose of ICS the subject is taking at Screening.

8. [redacted] at Baseline.

9. Absolute eosinophil count ≥ 300/µL within the last 6 months prior to Screening OR FeNO ≥25 ppb at Screening.

10. Women of childbearing potential with a negative serum pregnancy test at Screening and negative urine pregnancy test at the Baseline (Day 1) visit.

11. For women of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method from at least 4 weeks prior to Baseline (Day 1) until at least 30 days after the last IP administration. Highly effective contraceptive methods include hormonal contraceptives (eg, combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s), tubal ligation or double barrier methods of contraception (eg, male condom with cervical cap, male condom with diaphragm, and male condom with contraceptive sponge) in conjunction with spermicide.

    Notes:

    a. A woman of nonchildbearing potential is defined as follows:

        i. Female subject who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).

        ii. Female subject who has had a cessation of menses for at least 12 months prior to the Screening visit without an alternative medical cause, and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).

    b. Subjects must have been on a stable regimen of hormonal contraceptives for at least 4 weeks prior to Baseline.

    c. The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Baseline (Day 1) and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

    d. For countries where double barrier methods are not accepted as highly effective contraception, then this option must not be considered.

12. Female subject agrees to not have egg retrieval during the study and for 30 days after the last IP administration.

13. For male subject involved in any sexual intercourse that could lead to pregnancy, subject must agree to use 1 of the highly effective contraceptive methods listed in Inclusion Criterion #11 from Baseline (Day 1) until at least 90 days after the last IP administration. If the female partner of a male subject uses any of the hormonal contraceptive methods listed above, this contraceptive method should be used by the female partner from at least 4 weeks before Baseline (Day 1) until at least 90 days after the last IP administration.

14. Male subject agrees not to donate sperm during the study and for 90 days after the last IP administration.

15. Subject is willing to participate and is capable of giving informed consent.

    Note: Consent must be obtained prior to any study-related procedures.

4.2 Exclusion Criteria

A subject who meets any of the following exclusion criteria will not be eligible for inclusion in the study:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.

2. History of smoking per age group as follows (see also Exclusion Criterion #3):

   a. < 30 years old: Smoked for ≥ 5 pack-years.*

   b. 30 to 39 years old (inclusive): Smoked for ≥ 10 pack-years.

   c. ≥ 40 years old: Smoked for ≥ 15 pack-years.

   *One pack-year of cigarettes is defined as 1 pack of cigarettes a day for 1 year and is equivalent to:

   - 1 cigar or pipe per day for 1 year.
   - 1 hookah or shisha smoking session per day for 1 year.
   - 0.5 mL e-liquid per day for 1 year or 1 cartridge/tank/pod per day for 1 year of vaped e-cigarettes.
   - 1 use of smoked marijuana per day for 1 year.

3. Active use of any inhalant >1 time weekly in the past year including:

   a. Active smoking of conventional tobacco, marijuana (in any inhaled form) or other drugs, or vaping of e-cigarettes or e-devices.

   b. Other forms of tobacco including: 1 cigarette, 1 hookah or shisha session, 1 cigar, or 1 pipe.

   Note: Subjects must agree to refrain from using any inhalant as noted above more than 1 time weekly from the time they provide written informed consent until they complete all safety follow-up visits (ie, Day 141 / Week 20).

4. Subject has any serious and/or uncontrolled medical condition (including cognitive impairment, alcohol/drug abuse, or signs/symptoms suspicious for a serious disease) or laboratory abnormality that would place subject's safety at risk or interfere with study participation, as judged by the Investigator.

5. Conditions that may mimic asthma (eg, vocal cord dysfunction, hyperventilation, panic attacks, cardiac asthma, uncontrolled gastroesophageal reflux disease).

6. Subject has a history of severe COVID-19 that required intensive care unit (ICU) admission or assisted ventilation (including both invasive and non-invasive) in the 6 weeks before screening and did not return to their previous (pre-COVID-19 infection) respiratory status.

7. Subject has any of the following serious and/or uncontrolled medical conditions:

    a. Chronic obstructive pulmonary disease (COPD).

    b. Idiopathic pulmonary fibrosis (IPF).

    c. Subjects with uncontrolled diabetes (eg, hemoglobin A1c [HbA1c] ≥ 9%).

    d. Stage III or IV cardiac failure according to the New York Heart Association classification.

    e. Acute myocardial infarction, clinically significant arrythmia, or indications of serious underlying heart disease)/vital signs abnormality that, in the opinion of the Investigator would be indicative of an underlying medical condition, puts the subject at undue risk, and/or interfere with interpretation of study results.

    f. Severe renal conditions (eg, subjects on dialysis).

    g. Active autoimmune disease (eg, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease).

    h. Subject has a history of a clinically significant systemic infection or serious respiratory infection requiring parenteral antibiotic treatment within 4 weeks prior to the Baseline (Day 1) visit, or oral therapy within 2 weeks prior to the Baseline (Day 1) visit.

    i. Subject has a diagnosis of, is suspected of having, or is at high risk for an endoparasitic infection unless clinical and laboratory assessment have ruled out active endoparasitosis prior to the Baseline (Day 1) visit.

    j. Subjects with moderate to severe hepatic impairment (ie, Child-Pugh score ≥ 7).

    k. Subject has a history of a life-threatening asthma exacerbation in the last 5 years including but not limited to requirements for intubation and ventilation.

8. Subject has had a major surgery in the past 8 weeks prior to Screening or has a major, elective surgery planned during the study.

9. Any of the following specific laboratory findings:

    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN).

    b. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 (Modification of Diet in Renal Disease [MDRD] equation) unless considered normal for age.

c. Platelet count < 75,000 cells/mm^3.

d. Hemoglobin < 10 g/dL.

e. Absolute lymphocyte count < 800 cells per mm^3.

f. Absolute neutrophil count < 1500 cells per mm^3.

Note: Subjects who have abnormal laboratory values listed in this criterion may have repeat assessment of abnormalities once during the Screening and/or Run-In periods.

10. Subject has a history of drug and/or alcohol abuse in the last 12 months prior to Screening.

11. Subject has any evidence of exacerbation of asthma at the Baseline (Day 1) visit.

12. Requires systemic oral corticosteroids for the treatment of asthma at the Screening visit.

13. Systemic corticosteroid use (oral or intravenous) in the 4 weeks prior to Screening.

Note: Intranasal corticosteroids and ICS are allowed. Eye and ear drops containing corticosteroids are also allowed.

14. Hospitalization for a severe asthma exacerbation in the 4 weeks prior to Screening.

15. Subject has any state of immunodeficiency due to primary or secondary immunodeficiency syndromes, organ transplant (except corneal transplant), previous opportunistic infections, or any other state of immunodeficiency, as judged by the Investigator.

16. Subject has received RPT193 in the past.

17. Subject who is still participating in a clinical trial or who has participated in a clinical trial within 1 month prior to the Screening visit.

18. Subject has received an investigational oral, systemic agent within 8 weeks or 5 half-lives (whichever is longer) prior to the Baseline (Day 1) visit.

19. Subject has received any of the following marketed biological agents within the following timeframes prior to the Baseline (Day 1) visit:

a. Omalizumab within 20 weeks.

b. Mepolizumab within 16 weeks.

c. Benralizumab within 16 weeks.

d. Reslizumab within 16 weeks.

e. Dupilumab within 16 weeks.

f. Tezepelumab within 16 weeks.

g. Intravenous or subcutaneous immunoglobulin G (IgG) within 16 weeks.

20. Subject has received any investigational (intravenous or subcutaneous) biological agent within 16 weeks or 5 half-lives, whichever is longer prior to the Baseline (Day 1) visit.

21. Subject has used a cell-depleting agent, including but not limited to rituximab, within 6 months prior to the screening visit, or until lymphocyte counts return to normal, whichever is longer.

    Note: If a subject has received rituximab, the subject's lymphocyte count must be within the normal range at randomization even if rituximab was received more than 6 months prior to the Baseline (Day 1) visit.

22. Subject had bronchial thermoplasty within the last 2 years prior to Screening.

23. Subject has received treatment with systemic immunosuppressive/immunomodulating drugs (eg, methotrexate, cyclosporine A, systemic Janus kinase (JAK) inhibitors, mycophenolic acid, or azathioprine) within 4 weeks prior to the Baseline (Day 1) visit.

24. Subject has begun an allergen-specific immunotherapy regimen or had a clinically relevant change to their immunotherapy within 4 weeks prior to the Baseline (Day 1) visit.

25. Subject has received a live or live attenuated vaccine within 4 weeks prior to the Baseline (Day 1) visit or plans to receive a live or live-attenuated vaccine during the study and up to 4 weeks after the last IP administration.

26. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to the Baseline (Day 1) visit.

    Note: Subjects with the below medical conditions can be considered, as judged by the Investigator if it was treated and completely resolved:

    - Cutaneous basal cell carcinoma.
    - Cutaneous squamous cell carcinoma in situ
    - Cervical cancer in situ.
    - Melanoma in situ.

27. Subject has a known active bacterial, viral, fungal, helminth, or mycobacterial, or any other infection at the Baseline (Day 1) visit (non-complicated recurrent muco-cutaneous infections such as cold sores, tinea pedis, or disto-lateral mild to moderate onychomycosis are not considered exclusionary).

    Note: Subjects for whom infections have resolved and otherwise meet eligibility criteria may be re-screened once.

28. Subject has had a positive tuberculosis (TB) infection test at Screening. Subject will be evaluated for latent TB infection with a QuantiFERON-TB Gold test. Subjects who demonstrate evidence of latent TB infection with a positive QuantiFERON-TB Gold test, irrespective of bacille Calmette-Guérin vaccination status, will not be allowed to participate in the study, unless the subject has a documented history of chemoprophylaxis for latent TB infection or a documented history of treatment for active TB infection along with review/approval from the Sponsor.

29. Subject has a positive screen for hepatitis B surface antigen (HbsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies. For HBsAg or HCV antibody positive screening, subjects may be enrolled if reflex testing (eg, HBV-DNA or HCV RNA) is negative and indicative that there is no active infection.

30. e-Diary completion compliance < 80%, or more than 2 consecutive days missing data during the run-in period. Less than 80% translates to less than 12 out of 14 days and this calculation can be used to assess eligibility of subject's e-Diary completion compliance during the run-in period.

    Note: If e-Diary compliance is < 80 %, or a subject has more than 2 consecutive days of missing data during the first 2 weeks of the run-in, retraining must be organized, and compliance assessed in the following 2 weeks. If during this second period compliance is ≥ 80% and there are no missing data for 2 or more consecutive days, the subject may be considered eligible related to this criterion.

31. Subject is an employee or is known to be a relative of an employee of the study center or [redacted]

4.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but who do not meet 1 or more criteria required for participation (see Exclusion Criteria in Section 4.2) and are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, eligibility criteria, and any AEs.

Individuals who are screen failures will be allowed to be rescreened once in the following situations:

- The reason for the screen failure was the occurrence of a respiratory infection that was treated and completely resolved. In this case, the rescreening can only be done after at least 6 weeks after the resolution of the medical condition. For screen failures due to other non-respiratory infections, including any active bacterial, viral, fungal, helminth, or mycobacterial infection, consultation with the study Medical Monitor is required prior to rescreening.

- The reason for the screen failure was an exacerbation happening during the screening/run-in period. In this case the exacerbation should have been treated, and a new medication level stable along with all other eligibility criteria met.

- The reason for the screen failure was due to eosinophil count, spirometry or an [redacted] (at the Screening visit). In these cases, the subject can be rescreened if the asthma control has changed and all other criteria are still met.

In case of rescreening, all screening procedures need to be repeated.

4.4 Discontinuation of Investigational Product and Subject Withdrawal from the Study

4.4.1 Discontinuation of Investigational Product

4.4.1.1 Temporary Interruption of Investigational Product

In the event of an AE or clinically significant laboratory abnormality, IP may be temporarily interrupted at the Investigator's discretion. A decision to temporarily interrupt dosing of IP and/or to reinstitute IP should be discussed with the [redacted] Medical Monitor and Sponsor. The Investigator may suspend dosing of IP at any time, even without consultation with the Medical [redacted] Monitor and Sponsor if the urgency of the situation requires immediate action and if it is determined to be in the subject's best interest. However, the [redacted] Medical Monitor and Sponsor should be contacted as soon as possible for all cases of IP interruption. Resumption of IP after temporary interruption should always be discussed with the [redacted] Medical Monitor and Sponsor. Resumption of IP may occur so long as the laboratory finding has returned to Baseline or has only mild out-of-range levels less than or equal to 2 weeks from onset of the laboratory abnormality.

The information pertaining to interruption of IP and the reasons for it must be recorded in the electronic Case Report Form (eCRF).

4.4.1.2 Criteria for Permanent Discontinuation of Investigational Product

Subjects should permanently discontinue the IP if any of the following occurs:

1. The subject withdraws consent to treatment.

2. The subject has a LOAC event (in this case, the subject's individual pre-screening inhaled medications should be resumed or increased while the subject is expected to continue in the study off IP).

3. The Investigator decides that the subject should discontinue IP for any of the following reasons, including but not limited to: difficulties in obtaining blood samples, violation of the protocol, Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Grade 3 or 4 AEs assessed as causally related to the IP, SAEs assessed as causally related to the IP, or for any other reason relating to the subject's safety or integrity of the study data.

   Note: If this decision is made because of a SAE assessed as causally related to the IP, the IP is to be discontinued for that subject immediately and appropriate measures are to be taken. The Investigator will notify the [redacted] Medical Monitor and Sponsor immediately.

   Note: If this decision is made because of a CTCAE v5.0 Grade 3 or 4 AE for any organ system assessed as causally related to the IP, the IP is to be discontinued for that subject immediately and, if applicable, the event should be followed for resolution.

4. The subject develops a severe laboratory abnormality (defined in Table 2).

5. The subject develops evidence of hepatocellular injury that may be caused by the IP consistent with Hy's Law. Such an AE should be reported as a SAE. For the Hy's law criteria and procedures for evaluating a potential Hy's law case, see Section 4.4.4.

6. If a subject exhibits clinical symptoms during the study that may indicate COVID-19 infection, the subject will be tested for active COVID-19 infection. If the subject tests positive and exhibits evidence of moderate or severe illness (based on National Institutes of Health (NIH) criteria as depicted in Appendix VI), s/he will be discontinued from IP and will attend an EOT visit. Remote assessment of safety via teleconference and/or videoconference, with videoconference being the preferred method, is recommended until the subject attends the early termination (ET) visit.

7. Onset of an opportunistic infection during the study.

8. The subject develops any other illness that would interfere with continued treatment in the study.

9. The subject, for any reason, requires treatment with another systemic therapeutic agent that has been demonstrated to be effective for treatment of the study indication (eg, oral corticosteroids, dupilumab, mepolizumab, reslizumab, benralizumab, or omalizumab). In this case, discontinuation from the study IP occurs immediately upon introduction of the new agent.

10. The subject requires treatment with any other prohibited medications as defined in this protocol.

11. The subject is noncompliant with study procedures or medication, in the opinion of the Investigator.

    Note: Compliance for the e-Diary is considered when > 80% of data are present as well as a lack of repeated instances of missing data for 2 or more days. For study IP, compliance would be considered if IP is taken > 80% of the time.

12. The subject is confirmed to be pregnant.

13. The Sponsor or regulatory agency requests withdrawal of the subject.

If IP is prematurely discontinued, subjects should be strongly encouraged to remain in the study and complete the End of Treatment and Safety Follow-up Visits (see Table 1). The information pertaining to discontinuation of IP and the reasons for it must be recorded in the eCRF. Subjects who discontinue IP prematurely will not be replaced.

4.4.2 Subject Withdrawal from the Study

Reasons for subject withdrawal from the study include the following:

1. The subject may decide to withdraw from the study for any reason, including withdrawal of consent.

2. The Investigator may request that the subject be withdrawn from the study if s/he feels it is in the best interest of the subject or if s/he is uncooperative or noncompliant.

3. The subject is lost to follow-up. In this case, a reasonable attempt to contact the subject and ascertain his or her status must be made, and these attempts must be documented (see Section 4.4.5).

4. The Sponsor or regulatory authorities, for any reason, stop the study. In this case, all subjects will be withdrawn from the study. The Investigator will immediately, on termination of the study by the Sponsor, in its entirety or at a clinical trial site, inform both the subjects and the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of the study termination, provide them with the reasons for the study termination, and advise them in writing of any potential risks to the health of subjects or other persons.

If a subject is withdrawn from the study, the [redacted] Medical Monitor and Sponsor will be informed immediately. If there is a medical reason for withdrawal, the subject will remain under the supervision of the Investigator until satisfactory health has returned. Subjects should be strongly encouraged to complete the Early Termination Visit.

The Investigator or one of his or her staff members should contact the subject to determine as accurately as possible the primary reason for the withdrawal from the study. The Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. A complete final evaluation at the time of withdrawal from the study should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded.

If the subject withdraws consent for disclosure of further information, the Sponsor may retain and continue to use any collected data before such a withdrawal of consent. If a subject withdraws from the study, s/he may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Subjects who prematurely withdraw from the study cannot subsequently rejoin the study.

For details on the termination of study sites or the study as a whole, see Section 14.

4.4.3 Laboratory Abnormalities Requiring Discontinuation of Study Intervention

Table 2: Severe Laboratory Abnormalities Requiring Permanent Discontinuation of IP

Laboratory Parameter	Abnormality
Absolute neutrophil count (ANC)	< 500 cells per mm^3
Absolute lymphocyte count (ALC)	< 200 cells per mm^3
Hemoglobin	< 6.5 mg/dL
Platelet count	< 50,000 per mm^3
Creatinine	> 3 × baseline value or > 3 × ULN
Alanine aminotransferase (ALT)	If abnormal baseline value, > 5 × baseline value for more than 2 weeks; If normal baseline value, > 5 × ULN for more than 2 weeks

Subjects should first have laboratory abnormalities verified by repeat measure, and if repeat measure confirms the new onset abnormality, such subjects should be discontinued from further IP dosing, and if applicable, followed for resolution(see Section 4.4.1).

4.4.4 Possible Case of Drug-Induced Liver Injury

Subjects who present with evidence of hepatocellular injury that may be caused by drug ingestion consistent with Hy's Law with all of the following criteria acutely should be re-evaluated:

- ALT or AST > 3 × ULN
- Total bilirubin > 2× ULN
- No signs of cholestasis (alkaline phosphatase [ALP] < 2 × ULN)
- No other assignable cause such as liver metastases, pre-existing hepatic disease, viral hepatitis, alcohol abuse, ischemia, etc.

Re-evaluation should include repeat of AST, ALT, total bilirubin, and alkaline phosphatase along with additional laboratory assessments including albumin, creatine kinase, direct bilirubin, gamma-glutamyl transferase (GGT), and prothrombin time (PT)/international normalized ratio (INR). Additional medical and/or laboratory investigation to investigate other potential causes (eg, alcohol use, infectious hepatitis) should also be considered and assessed as appropriate by the Investigator. Potential cases satisfying Hy's law should be reported as SAEs. If a subject satisfies Hy's law, IP should be discontinued for the subject (see Section 4.4.1).

4.4.5 Lost to Follow-up

Subjects will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow-up, the Investigator (or designee) must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file of the subject.

- Should the subject continue to be unreachable, s/he will be considered to have withdrawn from the study.

5 DESCRIPTION OF STUDY ASSESSMENTS

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF by the Investigator and study site personnel for all subjects throughout the study. Protocol -mandated procedures, tests, and encounters are excluded. Refer to Table 1 for the schedule of events.

Unless otherwise indicated, all laboratory samples will be processed and shipped to the central laboratory, as described in the central laboratory manual. The central laboratory will analyze the samples or send them to reference laboratory(ies) for analysis, as indicated in the manual. Refer to the central laboratory manual for the maximum total volume of blood to be collected per subject throughout the study.

Subjects who consent to study participation will have their biological samples used for study purposes only. All biological samples collected during the study will be identified by a unique subject ID number and will be stored at a location designated by the Sponsor for up to 15 years after study completion. Subjects who consent to optional genetic research (as described in Section 5.7) and/or future exploratory research may have their samples analyzed for additional research purposes.

5.1 Demographics and Other Screening Assessments

Safety assessments that are also part of the Screening assessments are described in Section 5.3.

5.1.1 Medical History

Two years of medical and surgical history, including any ongoing illnesses, will be recorded in the eCRF, with the start date and stop date (if applicable) of the illness/condition.

Any pre-study procedures and history that may affect eligibility (eg, cancer, use of permanent contraceptives such as tubectomy) will also be recorded in the eCRF as part of the medical history assessment.

5.1.2 Demography

Demographic data, including year of birth/age, sex, and race, will be recorded in the eCRF.

5.1.3 Tuberculosis Test

An interferon-gamma release assay/QuantiFERON TB Gold test for active/latent TB will be performed at screening. The test will be provided by [redacted] central laboratory. Local laboratory testing will also be permitted, if necessary.

Subjects with a negative test result will be eligible for the study.

In case of indeterminate results, the test may be repeated once. The subject can be included in the study if the repeat test is negative; however, if the repeat test is positive or indeterminate, the subject will be excluded from the study unless the subject satisfies the guidance found in Exclusion Criterion #28.

5.2 Efficacy Assessments

5.2.1 Loss of Asthma Control

LOAC will be measured as follows:

- ≥ 30% reduction in morning PEF from Baseline on 2 consecutive days,
- ≥ 6 additional reliever inhalations of SABA in a 24-hour period relative to baseline on 2 consecutive days,
- Increase by a factor of 4 or more in the most recent dose of ICS (or if ICS has been fully withdrawn, ≥ 50% of the prescribed ICS dose at baseline)
- Exacerbation requiring systemic corticosteroids.
- Exacerbation of asthma-related adverse events that requires a hospitalization or emergency room visit.

If a subject satisfies criteria for a LOAC event during any point after randomization, the subject will be discontinued from study IP and undergo an End of Treatment visit. Subjects will return to their individual pre-screening inhaled therapy once a LOAC event has occurred. Escalation of therapy may also be considered at PI discretion. While subjects will discontinue study IP upon a LOAC event, subjects will continue in the study with safety follow-up for further clinical monitoring and adjustment of therapy as needed per Investigator discretion.

5.2.1.1 Peak Expiratory Flow

The efficacy of 400 mg RPT193 on reducing LOAC events when administered orally once daily for 14 weeks to subjects with asthma will in part be measured by determining the number of subjects who have a ≥ 30% reduction in morning PEF from baseline on 2 consecutive days.

- Morning PEF should be performed within 15 minutes after arising (between 5 AM upon arising in the morning and 12 PM).
- Evening PEF should be performed between 5 PM And 11:59 PM.
- Three PEF efforts will be performed by the subject with all 3 values recorded on the device and the highest value used for evaluation.

During the Screening and run-in period, PEF data will be checked for compliance and correctness of performing the procedure in order to obtain consistent values. During Periods 2 through 5, PEF will be assessed for a drop in values and triggering subject contact if it falls below the threshold, which is ≥ 30% reduction from the Baseline value. The Baseline value will be considered as the mean AM measurement assessed for all available PEF measurements in the 7 days prior to the Day 1 visit. Per eligibility criteria, subjects must have at least 5 measurements during the 7 days prior to randomization.

5.2.1.2 e-Diary

5.2.1.2.1 Asthma Reliever Medication Use

Subjects will record if they have taken 6 or more distinct inhalations/puffs of SABA/quick-relief inhaler in the e-diary daily.

Note: SABA therapy used for exercise pretreatment or for reversibility testing should not be considered as being used for asthma relief and should not count toward the number of puffs to be recorded in the e-Diary. Study sites should monitor reliever medication use during the study visits at the time points indicated in Table 1.

5.2.1.2.2 Inhaled Corticosteroid Use

Subjects will record whether they have used ICS in the e-Diary daily and the number of puffs used daily. This is to be verified/confirmed by Investigator or study staff during site visits.

5.2.1.2.3 Systemic Corticosteroid Use

Subjects will record whether they have used systemic corticosteroid in the e-Diary daily and this is to be verified/confirmed by Investigator or study staff during site visits.

5.2.1.2.4 Emergency Room Visits Due to Asthma and Hospitalization Due to Asthma

Subjects will record whether they have had any emergency room (ER) visits and/or hospitalizations in the e-Diary daily and this is to be verified/confirmed by Investigator or study staff during site visits.

5.2.2 Fractional Exhaled Nitric Oxide

The change in FeNO at Day 99 (Week 14) and at each interval visit after treatment with RPT193 compared to baseline will be determined. Additionally, the change in FeNO from Day 99 to 140 (Weeks 14 to 20) will also be determined.

FeNO should be performed prior to spirometry and following a fast of at least 1 hour.

5.2.3 Spirometry

Pulmonary function testing will be performed using a spirometer. On-site spirometry will include full-flow volume loops (forced vital capacity [FVC], FEV1, FEV1/FVC, forced mid-expiratory flow [FEF25%-75%], and PEF) and should be done according to American Thoracic Society/European Respiratory Society procedural guidelines (Graham 2019), verified, and overread centrally. Measurements will be done according to methods described separately in the Spirometry Manual. A central spirometry reading facility will be used to provide standardized training on spirometry, qualification of the spirometry technician, and quality control of the spirometry throughout the study.

Spirometry should be performed after the FeNO with no SABA in the 6 hours prior and no LABA in the 12 hours prior to assessment. In order to limit the impact of diurnal variations in spirometry, all spirometry assessments should be conducted at approximately the same time as the baseline visit.

5.2.4 [redacted]

[redacted] of adults aged 17 to 70 years with asthma. Subjects will complete the [redacted] at the time oints noted in Table 1. All assessments will be ca tured electronicall . [redacted]

Changes in [redacted] at Day 99 (Week 14) and at each interval visit after treatment with RPT193 compared to baseline will be determined. [redacted]

5.2.5 [redacted]

[redacted] will be assessed at visits s ecified in Table 1. The [redacted] used in this trial will be [redacted] All assessments will be captured electronically. [redacted]

Changes in [redacted] at Day 99 (Week 14) and at each interval visit after treatment with RPT193 compared to baseline will be measured.

5.2.6 [redacted]

Sub ects with a histor of on oin aller ic rhinitis will com lete [redacted] All assessments will be captured electronicall . [redacted] This instrument will onl be assessed in sub ects reportin on oin chronic rhinitis and/or sinusitis at screening. [redacted]

5.3 Safety Assessments

5.3.1 Adverse Events

AEs will be followed, recorded, and reported in line with the procedures described in Section 8. The period of reporting of AEs is defined as the period from the time of signing of the informed consent form (ICF) to the end of follow-up (Day 141 / Week 20).

5.3.1.1 Treatment-Emergent Adverse Events

All AEs occurring from the time of randomization to the end of follow-up (Day 141 / Week 20) will be considered treatment-emergent and recorded both on the source documentation and the eCRF.

5.3.2 Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory. Blood and urine samples will be collected at the times indicated in Table 1. Subjects will be required to be fasting at Baseline (Day 1), Day 99 (Week 14), and Day 113 (Week 16). For fasting labs, a subject should refrain from eating or drinking (except for water) for a period of at least 8 hours prior to the laboratory draw. On dosing day(s) sampling for the analysis of clinical laboratory parameters will be performed before the administration of IP.

The parameters to be evaluated are shown in Table 3.

Table 3: Clinical Laboratory Evaluations

Clinical Chemistry Panel	**Hematology**	**Coagulation Panel**
Albumin Alkaline phosphatase Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Chloride Cholesterol HDL cholesterol LDL cholesterol Creatinine, enzymatic Direct bilirubin Total bilirubin Potassium Glucose Sodium Gamma-glutamyl transferase Triglycerides Urea Uric Acid Calcium Total protein Lactate dehydrogenase (LDH) Bicarbonate Magnesium Phosphorus	Red blood cells Hemoglobin Hematocrit MPV, MCV, MCH, MCHC Platelets White blood cells (WBC) WBC Differential (% and absolute) • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes **Urinalysis** Bilirubin Blood Glucose Ketones Nitrite pH Protein Microscopic examination[1] Urobilinogen Leukocytes Specific gravity	aPTT (sec) PT (sec) INR **Women Only Testing** Serum βhCG Urine hCG FSH (women of non-childbearing potential only) Estradiol (women of non-childbearing potential only) **Screening Tests** Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis B core antibody Hepatitis C antibody HIV-1/2 antibody & antigen QuantiFERON TB Gold TB Screen **Other Tests** Reticulocytes eGFR Hemoglobin A1C

Abbreviations: aPTT = activated partial prothrombin time; βhCG = β-subunit of human chorionic gonadotropin (pregnancy test); eGFR = estimated glomerular filtration rate; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MPV = mean platelet volume; PT = prothrombin time.
1. Will be performed on abnormal findings unless otherwise specified.

Refer to the Laboratory Manual for details regarding the collection, processing, and shipping of the blood and urine samples.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal

laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during the subject's participation in the study or within 42 days after the last dose of IP should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, then the etiology should be identified, and the Sponsor notified.

5.3.3 Loss of Asthma Control

Refer to Section 5.2.1 for further guidance related to LOAC events.

5.3.4 12-lead Electrocardiogram

Twelve-lead ECGs will be obtained as outlined in Table 1 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

The ECG tracing should include the date and time of the assessment and the signature of the person who made the interpretation; the tracing will be archived at the study site. Triplicate ECG should be performed prior to spirometry or FeNO measurements to prevent potential effects of beta agonist use on ECG measurements.

5.3.5 Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes' rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.

5.3.6 Physical Examination

Subjects will undergo complete physical examination as indicated in the schedule of assessments.

The complete physical examination will include assessments of the standard physical examination items, including general appearance, skin, eyes, ears, nose, throat, head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, neurological, and other body systems, if applicable, for describing the status of the subject's health.

Body weight and height will also be measured and recorded. The subject should be dressed in light clothing, without shoes. Subject height and weight will be recorded at Screening and weight will be recorded on Day 141 (Week 20).

After the initial, complete physical examination, a target physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses. Any new abnormalities or worsening of existing abnormalities should be reported as AEs, as appropriate (see Section 8.1.1).

5.4 Pharmacokinetics

Blood samples will be collected for measurement of blood concentrations of RPT193 immediately prior to dosing at the visits specified in Table 1.

Instructions for the collection and handling of PK samples will be provided in the Laboratory Manual. The actual date and time of collection of each sample will be recorded.

The exact date and time of the sample collection must be recorded in the eCRF. Actual sampling times will be used in the calculation of PK parameters. In the event that the actual time is not recorded, the scheduled sampling time will be used.

A complete list of PK parameters will be provided in a Statistical Analysis Plan (SAP).

5.5 Pharmacodynamics

Blood samples will be collected for pharmacodynamic analysis of RPT193 at the visits and time points specified in Table 1. [redacted]

5.6 Biomarkers

Blood samples will be collected for analysis of the biomarkers indicated in Sections 5.6.1 and 5.6.2.

Samples will be tested to evaluate the effect of 400 mg RPT193 administered orally once daily for 14 weeks to subjects with moderate-to-severe asthma on serum cytokines, chemokines, transcriptional changes, and other biomarkers associated with asthma.

Refer to the central laboratory manual for details regarding the processing and shipment of samples to the central laboratory.

5.6.1 Blood-Based Biomarker Levels

[redacted]

- [redacted]

[redacted]

[redacted]

5.6.2 Nasal Sampling for Biomarker Analysis

Changes in nasal biomarkers will be assessed at the time points indicated in Table 1.

5.7 Pharmacogenetics

A blood sample for DNA isolation will be collected from subjects who have consented to participate in the genetic analysis component of the study. Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the subject. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Details on processes for collection and shipment and destruction of these samples can be found in the central laboratory manual.

6 TREATMENTS

6.1 Investigational Product(s)

6.1.1 Description of Investigational Product

	Investigational Product	
Product name	RPT193	Placebo
Dosage form	Tablet	Tablet
Route of administration	Oral	Oral
Source of procurement of active substance	[redacted]	Not applicable
Manufacturer	[redacted]	[redacted]

The active medication and placebo will be provided by RAPT Therapeutics, Inc., USA.

6.2 Investigational Product Administered

RPT193-03 will consist of daily administration of 400 mg of RPT193 or placebo for 14 weeks (98 consecutive days). The IP will be administered orally at approximately the same time of the day. On study days where PK samples are to be collected, the subject will administer the IP at the study center, following the PK sample collection. The date and time of IP administration will be collected daily via an e-Diary provided to the subject whether IP is taken on- or off-site. The subject will be instructed to take the IP at approximately the same time of the day when taken off-site. The subject will complete an e-Diary to document the time of each dose taken when off-site. Also, in the event of an AE of the gastrointestinal system organ class, the subject may be asked to indicate the timing of taking the IP in relation to food intake.

6.2.1 Handling and Storage

Refer to the Pharmacy Manual for full details regarding the handling and dispensing of RPT193 and matched placebo.

[redacted]

The Investigator (or designee) is responsible for the safe and proper storage of IP at the site. RPT193 and placebo will be stored under controlled conditions according to the storage requirements described on the label(s). The Investigator (or designee) will instruct the subjects to store the IP in accordance with the instructions on the label(s).

6.2.2 Packaging, Labelling, and Shipment

RPT193 will be packaged and labelled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines.

RPT193 and placebo will be provided in a blinded manner with medication kits specific to each subject number. The placebo packaging will match that of RPT193 to ensure blinding.

RPT193 and placebo will be shipped and stored under controlled conditions according to the storage requirements.

Refer to the pharmacy manual for full details for packaging, labelling, and shipment of the IP.

6.3 Blinding

The study is double-blinded; therefore, the Investigators, study personnel, and the study subjects will remain blinded to treatment allocation.

Randomization data will be kept strictly confidential, accessible only to authorized staff and the DMC until the time of unblinding. Authorized staff may include the randomization statistician, who will store the master randomization list in a secure system, an unblinded statistician, and unblinded programmers. All authorized unblinded staff must be documented.

RPT193 and placebo will be coded and labelled in a manner that protects blinding. The coding system will permit rapid identification of the IP (in case of medical emergencies).

The Investigator is responsible for study-related medical decisions and may break the blind, if knowledge of the IP is essential for the clinical management of the subject. The Investigator should make every effort to contact the Sponsor's Medical Monitor prior to breaking the blind and must contact the Sponsor within 1 working day after the blind is broken, without revealing to the Sponsor (or clinical research organization [CRO]) the results of the code break, except to the designated global subject safety representative. Subjects whose treatment assignments are unblinded will not receive any further IP.

Emergency unblinding will be organized through interactive voice response system/interactive web response system (IXRS) system. The Investigator must record the date of unblinding and the reason. All breaks of the blind must be adequately documented.

If an SAE is reported, the designated global subject safety representative may unblind the treatment assignment for the individual subject through IXRS in order to meet regulatory reporting requirements.

6.4 Method of Assigning Treatment

Each subject will have a unique subject number obtained from a centralized IXRS. This will be assigned at the Screening visit. The Investigator will keep a record (the subject screening log) of subjects who entered Screening.

The unique subject identifier number will contain the site number (YYYY) and the subject number (SSSS) and will be assigned at the Screening visit (eg, 0401-5001).

Randomization will be performed via the IXRS at the Baseline (Day 1) visit prior to dosing. On Baseline (Day 1), eligible subjects will be assigned to RPT193 or placebo in a 1:1 ratio. Each subject will receive a unique subject number when he/she is assigned treatment. Subjects will be allocated to treatment according to the randomization code.

Prior to Baseline (Day 1), eligibility will be monitored by Study Personnel with permission required prior to randomizing any subject.

On Baseline (Day 1), subjects will be assigned a unique subject number by the IXRS. The subject number will encode the subject's assignment to either RPT193 or placebo, according to the randomization code generated prior to the study. Once a subject number has been assigned, it cannot be reassigned to a different subject.

Subjects will be stratified by pre-screening inhaled ICS + LABA (medium- or high-dose ICS) as well as by location of the Study Site (North America versus Europe).

If a subject withdraws from the study, his/her unique identification number(s) cannot be re-used for another subject.

6.5 Reliever Bronchodilator

A metered-dose inhaler (MDI) reliever with a SABA (eg, salbutamol, albuterol, levosalbutamol, or levoalbuterol) bronchodilator will be supplied by the site to all subjects in this study. Subjects may administer the SABA reliever bronchodilator as needed for asthma symptoms. Subjects will record if they have taken 6 or more distinct inhalations/puffs of SABA/quick-relief inhaler in the e-Diary daily.

SABA therapy used for exercise pretreatment or for reversibility testing should not be considered as being used for asthma relief and should not count toward the number of puffs to be recorded in the e-Diary. Study sites should monitor reliever medication use during the study visits at the time points indicated in Table 1.

If a subject were to receive a nebulized form of the SABA reliever, the following table converts nebulized salbutamol/albuterol to equivalent MDI puffs for use as part of the LOAC definition.

Salbutamol/Albuterol Nebulizer Solution - Total Daily Dose (mg)	**Number of Puffs**
2.5 mg	4
5 mg	8
7.5 mg	12
10	16

6.6 Dose and Administration

RPT193-03 will investigate the efficacy and safety of RPT193 in subjects with T2-high moderate-to-severe asthma. The study will assess 1 dose level of RPT193 (400 mg) (or matching placebo) taken orally once daily for 14 weeks (98 days).

6.6.1 Dose Modification

No IP dose modifications will be permitted during the study.

6.6.2 Meals and Dietary Restrictions

A prior formulation of RPT193 has been demonstrated to have similar PK and tolerability properties whether taken in a fasted or fed state. Coupled with preclinical data supportive of similar PK properties with the tablet formulation used in this study, no restrictions related to food and ingestion of IP have been put in place. IP should be taken with approximately 240 mL (8 ounces) of water. Subjects may discuss the pros and cons of taking the IP with food with the Investigator of their site.

6.6.3 Intervention After the End of the Study

Subjects will resume their pre-screening asthma therapy under the following circumstances:

- After completing the study
- Developing a LOAC event
- Discontinuation of study IP for other reasons
- Following early withdrawal from study participation
- At the Week 14 visit if the subject's [redacted] OR the subject's FEV1 is ≤ 80%
- In subjects who did not re-initiate pre-screening asthma therapy at the Day 99 (Week 14) visit and show any evidence of clinical or symptomatic evidence of worsening asthma status with PI discretion of whether the pre-screening asthma therapy can be adjusted

6.7 Description, Management and Withdrawal of Non-Investigational Medicinal Product

The following inhalers are needed at each of the Periods of the study:

Period	DPI Inhaler Needed (Individual Subjects will Use the Inhaler Commensurate with Screening ICS/LABA Requirements)
1) and 2) Run-in and Adjunctive Therapy Periods	Fluticasone/salmeterol 250/50 mcg per puff for those initially taking medium-dose ICS+LABA or 500/50 mcg per puff for those initially taking high-dose ICS+LABA
3), 4), and 5) Background Therapy Withdrawal Period	Fluticasone 250 mcg per puff Fluticasone 100 mcg per puff Fluticasone 50 mcg per puff

6.7.1 Withdrawal of Background Inhaled Therapies

Run-in and Adjunctive Therapy Periods: From the initiation of the Run-in period (Week -4) up to Day 42 (Week 6), clinically comparable doses of the study-specific ICS/LABA combination therapy with fluticasone/salmeterol, as approved per region. There is no withdrawal of background therapy during this period.

Background Therapy Withdrawal Period: Salmeterol will be withdrawn at Day 43 (Week 6) post-randomization. Subjects will be switched from their twice daily fluticasone/salmeterol combination therapy to a clinically comparable ICS dose of fluticasone twice daily monotherapy, as approved for region.

The ICS component (fluticasone) will then be subsequently withdrawn by a step-wise dose reduction starting at Day 57 (Week 8) based on inhaler therapy at the Screening Visit. The tables below summarize the management of background inhaled therapies for each subject class.

For subjects **initially taking medium-dose ICS + LABA**:

Period	Visit(s)	Inhaler to be Initiated (or Continued) at Visit
1) Run-in	Day -28 (Week – 4) through Day -1 (Week -1)	Fluticasone/Salmeterol 250/50 mcg 1 puff twice daily
2) Adjunctive Therapy	Baseline (Day 1) through Day 42 (Week 6)	
3), 4), and 5) Background Therapy Withdrawal	Day 43 (Week 6) through Day 56 (Week 8)	Fluticasone 1 puff 250 mcg twice daily
	Days 57-63 (Week 8-9)	Fluticasone 1 puff 100 mcg twice daily
	Days 64-70 (Week 9-10)	Fluticasone 1 puff 50 mcg twice daily
	Day 71 (Week 10) through Day 98 (Week 14)	Discontinue Fluticasone inhaler

For subjects **initially taking high-dose ICS + LABA:**

Period	Visit(s)	Inhaler to be Initiated (or Continued) at Visit
1) Run-in	Day -28 (Week -4) through Day -1 (Week -1)	Fluticasone/Salmeterol 500/50 mcg 1 puff twice daily
2) Adjunctive Therapy	Baseline (Day 1) through Day 42 (Week 6)	
3), 4), and 5) Background Therapy Withdrawal	Day 43 (Week 6) through Day 56 (Week 8)	Fluticasone 2 puffs 250 mcg twice daily
	Days 57-63 (Week 8-9)	Fluticasone 1 puff 250 mcg twice daily
	Days 64-70 (Week 9-10)	Fluticasone 1 puff 100 mcg twice daily
	Days 71-77 (Week 10-11)	Fluticasone 1 puff 50 mcg twice daily
	Day 78 (Week 11) through Day 98 (Week 14)	Discontinue Fluticasone inhaler

Subjects are to undergo each step in the withdrawal provided that subjects have not experienced a LOAC event. If a LOAC even occurs, subjects are to be withdrawn from study IP and managed as described in Section 5.2.1.

Sites are to source the ICS/LABA during the Run-in and Adjunctive Therapy Periods as well as the ICS inhalers during the Background Therapy Withdrawal Period. If sites are not able to source inhalers, they should work with their CRO study team to obtain. If a supply interruption occurs, the study site should contact CRO study personnel immediately.

6.7.2 Reliever Bronchodilator

Details on the description, use, and management of reliever bronchodilator are found in Section 6.5.

6.7.3 Identifying a Loss of Asthma Control Event

Subjects will be monitored for LOAC events using the internet-enabled e-Diary/PEF device which will allow real-time monitoring of subjects who meet the LOAC definition. In addition, subjects will be required to be seen at the study site and evaluated 2 weeks after the withdrawal of LABA and weekly during the ICS withdrawal and monotherapy periods. Site staff and Investigator will thoroughly evaluate whether the subject has met the criteria for LOAC based on review of e-Diary, PEF, medication usage, and medical history.

6.7.4 Managing a Loss of Asthma Control Event

If a subject satisfies criteria for a LOAC event during any point after randomization, the subject will be discontinued from study IP and undergo an End of Treatment visit. Subjects will return to the background inhaled therapy used at Screening once a LOAC event has occurred. Escalation of therapy may also be considered at Investigator discretion. While subjects will discontinue study IP upon a LOAC event, subjects will continue in the study with safety follow-up for further clinical monitoring and adjustment of therapy as needed per Investigator discretion.

6.8 Prior Medication and Procedures

Refer to the Inclusion and Exclusion criteria (Section 4) for a list of prior medications and procedures that may affect participation in this study.

6.9 Concomitant Medication and Procedures

All medication (including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken from 30 days before start of screening until the end of the follow-up period will be recorded in the appropriate section of the eCRF. The following details must be recorded in the eCRF:

- Medication name, ideally the generic name
- Reason for use
- Start and end date of administration
- The dose and frequency of administration

The Medical Monitor should be contacted if there are any questions regarding prior or concomitant medication or procedures.

Please note that for any biologic medications (eg, dupilumab, mepolizumab, benralizumab, reslizumab, or omalizumab), documentation of prior exposure and duration of treatment should be provided even if more than 30 days prior to the start of screening.

6.9.1 Prohibited Medications

From the start of the run-in period to the end of the treatment period, any ICS, LABA, or SABA beyond what is provided as part of the study is prohibited. This includes the following concomitant medications:

- Any ICS/LABA, ICS, or SABA inhaler (other than those supplied by the study site as part of the RPT193-03 study)
- Long-acting muscarinic agonist (LAMA)
- Leukotriene receptor antagonist (LTRA)
- Methylxanthines (such as theophylline, aminophyllines)
- Any biologic therapy received as a subcutaneous injection or intravenous infusion indicated for asthma or any other medical condition (excluding endocrinologic conditions including but not limited to hypothyroidism. Please consult the study Medical Monitor for any specific questions)
- Live vaccines
- Intra-articular steroids
- Cromones
- Bronchial thermoplasty

  Note: After the end of the treatment period, subjects will return to the ICS/LABA background therapy used at Screening. If safety concerns remain after re-initiation of prior background therapy, additional controller therapies, including those listed above may be prescribed after consultation with the study Medical Monitor.

A list of prohibited medications is provided in Table 4.

Table 4: List of Prohibited Medications

Medication Type and Additional Information
From the start of the run-in period to the end of the treatment period: • Any ICS/LABA, ICS, or SABA inhaler (other than those supplied by the study site as part of the RPT193-03 study) • Long-acting muscarinic agonist (LAMA) • Leukotriene receptor antagonist (LTRA) • Methylxanthines (such as theophylline, aminophyllines)
Systemic oral corticosteroids for the treatment of asthma at the Screening visit
Systemic corticosteroid use (oral or intravenous) in the 4 weeks prior to Screening
Investigational oral, systemic agent within 8 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit

Medication Type and Additional Information
From the start of the run-in period to the end of the treatment period: • Any ICS/LABA, ICS, or SABA inhaler (other than those supplied by the study site as part of the RPT193-03 study) • Long-acting muscarinic agonist (LAMA) • Leukotriene receptor antagonist (LTRA) • Methylxanthines (such as theophylline, aminophyllines)
Omalizumab within 20 weeks prior to the Baseline visit
Mepolizumab within 16 weeks prior to the Baseline visit
Benralizumab within 16 weeks prior to the Baseline visit
Reslizumab within 16 weeks prior to the Baseline visit
Dupilumab within 16 weeks prior to the Baseline visit
Tezepelumab within 16 weeks prior to the Baseline visit
IgG (subcutaneous or intravenous) within 16 weeks prior to the Baseline visit
Investigational biological agents within 16 weeks or 5 half-lives prior to the Baseline visit
Cell-depleting agents (eg, rituximab) within 6 months prior to the screening visit, or until lymphocyte counts return to normal, whichever is longer
Methotrexate, cyclosporine A, systemic JAK inhibitors, mycophenolic acid, or azathioprine within 4 weeks prior to the Baseline visit
Initiation of allergen-specific immunotherapy regimen or clinically significant change to allergen-specific immunotherapy regimen within 4 weeks prior to the Baseline visit
Live or live attenuated vaccine within 4 weeks prior to the Baseline visit or plans to receive a live or live-attenuated vaccine during the study and up to 4 weeks after the last IP administration

Abbreviations: ICS = inhaled corticosteroids; IgG = immunoglobulin G; LABA = long-acting beta 2 agonist; LAMA = long-acting muscarinic agonist; LTRA = leukotriene receptor antagonist; SABA= short-acting beta 2 agonist.

6.9.2 Permitted Medications

- Topical therapies for skin conditions
- Intranasal steroids
- Anti-histamines

6.10 Overdose

Neither the effects of overdose of RPT193 nor an antidote to overdose are known.

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

In the event of an overdose, subjects should receive appropriate supportive medical care and be followed until resolution/stabilization of any clinical issues.

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved RPT193) must be communicated to the Sponsor (or a specified designee) using the overdose eCRF page(s) within 24 hours of its occurrence.

Any overdose associated with clinical symptoms will be recorded as an AE or SAE, as appropriate. Details of any signs or symptoms and their management should be recorded, including details of any treatments administered for the overdose. All overdoses with clinical symptoms meeting the SAE criteria must be reported as described in Appendix I.

6.10.1 Treatment of Overdose

IP overdose is any accidental or intentional use of IP in an amount at least 2 times higher than the dose indicated per-protocol for a given subject. IP compliance (see Section 6.11) should be reviewed to detect potential instances of overdose (intentional or accidental).

The Sponsor must be immediately notified of any instances of overdose and a protocol deviation must be thoroughly documented and reported per local regulations. Any IP overdose during the study should be recorded on the source document and eCRF. The excess quantity and duration of the overdose should be recorded.

In the event of overdose, the subject should be closely monitored for any potential AEs. All AEs associated with an overdose should be entered on the Adverse Event eCRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor or designee within 24 hours of awareness of the event. Any AEs or SAEs associated with an overdose will be reported using the procedures detailed in Appendix I.

6.11 Compliance

The Investigator (or designee) will explain the correct use of the IP to each subject and will check that each subject is following the instructions properly. Compliance will be assessed at each visit by direct questioning and will be documented in the source documents and eCRF. Any deviation from the correct use of the IP will be recorded in the eCRF.

A record of the number of IP tablets dispensed to and taken by each subject will be maintained and reconciled with IP and compliance records. The IP start and stop dates, including dates for IP delays and/or dose reductions, will also be recorded in the eCRF.

At study visits, subjects will be administered IP by the Investigator or site personnel, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and in the eCRF. In addition, subjects will capture the date and time of dosing in a daily e-Diary when the IP is taken at the site or at home.

Treatment compliance will be assured by site reconciliation of all IP supplies and comparing the number of tablets taken with the number planned to be taken.

The Investigator (or designee) will explain the correct use of the Non-Investigational Medicinal Products (fluticasone, fluticasone/salmeterol, salmeterol) to each subject and will check that each subject is following the instructions properly. Compliance will be assessed at each visit by direct

questioning and if available, the mechanical counter present on the inhaler device, and will be documented in the source documents.

Subjects who are significantly noncompliant with IP or Non-Investigational Medicinal Product treatment (ie, missing > 20% of doses) will be counseled and could be discontinued from the study, at the discretion of the Investigator, following consultation with the Sponsor. A subject will also be considered significantly noncompliant if he or she intentionally or repeatedly takes more than the prescribed amount of IP in the same time frame, as judged by the Investigator.

6.12 Accountability

The IP must not be used for any purpose other than that defined in this protocol. All supplies of IP will be accounted for in accordance with Good Clinical Practice (GCP).

The Investigator, a member of the study staff, institution, or a hospital pharmacist (where applicable) must maintain accurate records of all IP supplies received during the study. These records should include the dates and amounts of IP that were received at the site, dispensed, and destroyed or returned to the Sponsor (or designee). The records should include dates, quantities, batch numbers, expiration dates (if applicable), and the unique code (kit) numbers assigned to the IP and study subjects. If errors or damage in the IP shipments occur, the Investigator should contact the Sponsor (or its designee) immediately. Copies of the IP accountability records will be provided by each Investigator for inclusion in the trial master file (TMF). The study monitor will periodically check the supplies of IP held by the Investigator, member of the study staff, or pharmacist to verify accountability of the IP used.

The Investigator (or designee) will administer the IP only to the identified subjects in this study, according to the procedures described in this study protocol. Details of IP administered to subjects will be recorded in the eCRF. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all IP received from the Sponsor (or designee).

After the end of the study, all unused IP and all medication containers should be destroyed at the study center or returned to the Sponsor (or designee) for destruction. In either instance, complete documentation will be returned to the Sponsor. The IP initial and resupply will be managed by the IXRS.

7 STUDY PROCEDURES

- Study procedures and their timing are summarized in Table 1.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor and Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue IP.
- Adherence to the study design requirements, including those specified in Table 1, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The maximum amount of blood collected from each subject over the duration of the study, not including any extra assessments that may be required, will be specified in the ICF. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Demographic information related to age and ethnicity will be collected at screening.
- **The clinical trial consists of 5 distinct periods during the treatment portion of the study:**
  - **Period 1) Screening (up to 2 weeks)/Run-in (4 weeks):** Subjects will be enrolled and assessed for initial eligibility. At Day -28, subjects will begin standardized background inhaled therapy commensurate with each subject's inhaled therapy at Screening (See Appendix V – Section 17.5). In addition to continued assessment of eligibility, subjects will be assessed for compliance with medication and e-Diary entries. Eligibility will be monitored by the study team with permission for randomization required beforehand.
  - **Period 2) Randomization and adjunctive therapy with study IP (Baseline [Day 1] to Day 42):** Subjects will self-administer study IP once daily in conjunction with medium- or high-dose ICS + LABA.
  - **Periods 3) and 4) Background Therapy Withdrawal (Day 43 to Day 71 or Day 78 [Week 6 to Week 10 or Week 11]):** Provided that a subject has not had a LOAC event, each subject will undergo withdrawal of background therapy starting at the Day 43 (Week 6) visit. At Day 43 (Week 6), LABA will be withdrawn for 2 weeks. Beginning at the Day 57 (Week 8) visit, ICS withdrawal will be initiated in a step-wise fashion. For subjects on medium-dose ICS + LABA at Screening, the withdrawal will be completed at the Week 10 visit. For subjects on high-dose ICS + LABA at Screening, the withdrawal will be completed at the Day 78 (Week 11) visit.

    If a subject satisfies criteria for a LOAC event during any point after randomization, the subject will be discontinued from study IP and undergo an End of Treatment visit.

Subjects will return to their individual, pre-screening inhaled therapy once a LOAC event has occurred. Escalation of therapy may also be considered at PI discretion. While subjects will discontinue study IP upon a LOAC event, subjects will continue in the study with safety follow-up for further clinical monitoring and adjustment of therapy as needed per Investigator discretion.

- **Period 5) Monotherapy (Day 71 or Day 78 to Day 99 [Week 10 or Week 11 to Week 14]):** Provided that a subject has not had a LOAC event, each subject will continue to take study IP once daily for 3 (or 4) weeks to the end of the treatment period at the Day 99 (Week 14) visit depending on the subject's initial ICS dose with those on high-dose ICS at Screening receiving 3 weeks of monotherapy, and those on medium-dose ICS at Screening receiving 4 weeks of monotherapy.
- **Follow-up (Day 99 [Week 14] to Day 141 [Week 20]):** At the end of the treatment period, subjects will be assessed for degree of control. For those considered well-controlled ([redacted] and FEV1 > 80% of predicted) and who have not had a LOAC event, subjects will enter into the 6-week follow-up period with re-initiation of ICS and LABA therapy conditional upon any clinical or symptomatic evidence of worsening of asthma status (as advised in GINA 2022 guidelines). At the end of the 6-week follow-up period, subjects will be re-evaluated in terms of asthma control and be prescribed accordingly as per GINA 2022 guidelines and per Investigator discretion.

  For those who have not had a LOAC event and are not considered well-controlled with an [redacted] and/or FEV1 < 80% predicted, subjects will re-initiate their individual, pre-screening inhaled therapy and enter the 6-week follow-up period. Subjects should continue to be re-evaluated in terms of asthma control during the follow-up period and be prescribed accordingly as per GINA 2022 guidelines and per Investigator discretion.

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Events

The definition of an AE can be found in Appendix I.

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IP or study procedures, or that caused the subject to discontinue the IP or withdraw from the study (see Section 4.4).

8.1.2 Serious Adverse Events

The definition of an SAE can be found in Appendix I.

8.1.3 Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is defined as an untoward and unintended response to an IP, which is not listed in the IB as an expected AE, and meets one of the following serious criteria: results in death, is life threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect; and is assessed as causally related to the IP.

8.2 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs will be collected from the signing of the ICF until Extended Follow-up/Visit 14 or 42 days after the last dose of IP if a subject withdraws from the study.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of the Investigator's awareness of the event, as indicated in Appendix I. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has withdrawn from the study, and he/she considers the event to be reasonably related to the IP or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix I.

8.3 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 4.4.5. Further information on follow-up procedures is given in Appendix I.

8.5 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of the IP under clinical investigation are met.

- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the IP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.

- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary. The approved IB reference safety information (RSI) will be used by Sponsor or Sponsor designee for determining the expectedness of a serious, related AE. If the event is not included in the RSI, the case will be considered a SUSAR and submitted as required to applicable the competent authorities (i.e. EMA, FDA).

- In the US and EU, SUSARs are to be reported to the regulatory authorities within 15 calendar days of initial notification to Sponsor or its designee. If the suspected adverse reaction is serious, unexpected, and is fatal or life threatening, the event will also be reported per required mode of communication to the regulatory authorities within 7 calendar days.

- In the EU, SUSARs will be reported to all participating Member States through the Eudravigilance database and local regulatory authorities if applicable.

- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.6 Adverse Events of Clinical Interest

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.7 Pregnancy

Details of all pregnancies in female subjects and female partners of male subjects, will be collected after the start of IP and until 42 days after the last administration of IP.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix I.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]), the Investigator will report according to the SAE reporting procedures described in Appendix I.

8.8 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities without clinical significance should not be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis abnormalities) that require medical or surgical intervention or lead to IP interruption discontinuation must be recorded as an AE or SAE, as applicable. In addition, laboratory or other abnormal assessments (eg, in ECGs, X-rays, or vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Appendix I. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

9 STATISTICS

9.1 General Procedures

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol. The SAP will be approved prior to any lock of the study database and unblinding of the study data.

All personnel involved with the analysis of the study will remain blinded until database lock and identification of protocol deviations. Analyses will be performed using SAS® (SAS Institute, Cary, NC, US) by the Sponsor or its representatives.

All data will be presented by treatment group. Descriptive statistics (number of observations, mean, standard deviation [SD], median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables.

Baseline is defined as the last non-missing measurement before or on the date of first administration of IP.

9.2 Analysis Populations

The Enrolled Analysis Set (EAS) will include all subjects who provide informed consent. This analysis set will be used to report disposition and screening failures.

The Full Analysis Set (FAS) will include all randomized subjects and will be analyzed according to randomized treatment following the intention to treat (ITT) approach, regardless of which treatment they actually received (RPT193 or placebo). This analysis set will be the primary set used for analyses/summaries of the primary efficacy endpoint, as well as for all secondary and other efficacy endpoints.

The Safety Analysis Set (SAS) will include all subjects who receive at least 1 dose of IP and will be analyzed according to actual treatment. This analysis set will be used for summaries of safety data.

The Per-Protocol Analysis Set (PPAS) will include all subjects in the FAS who do not have an important protocol deviation that could affect the primary endpoint. Important protocol deviations that could affect the primary endpoint will be defined and agreed upon before unblinding. This analysis set will be used for sensitivity analyses.

The PK Analysis Set (PKAS) will include all subjects who receive at least 1 dose of IP and enough bioanalytical assessments to calculate reliable estimates of the PK parameters.

The Pharmacodynamic (PD) Analysis Set (PDAS) will include all subjects in the Safety Set for whom the PD data are sufficient and interpretable.

9.3 Sample Size

[redacted]

This is a proof-of-concept study that will develop initial supportive data that RPT193 has the potential to promote clinically meaningful effects in subjects with moderate-to-severe asthma. The results of this study will be used to facilitate and support the design of a dose-ranging Phase 2b study. Thus, for the purposes of this study, a 10% significance level was considered adequate.

9.4 Statistical Methods

The FAS analysis set will be used for all efficacy analyses unless otherwise noted. Summaries will be presented by treatment group. The PPAS will be used as sensitivity analysis for the primary analysis.

9.4.1 Primary Endpoint

The primary efficacy endpoint of this study is the proportion of subjects who experience LOAC during the treatment period. For a definition of LOAC criteria, see Section 2.

The primary analysis will compare rates of LOAC between treatment groups using a generalized linear model with binomial distribution and identity link with fixed effects for treatment, pre-screening inhaled ICS + LABA (medium- or high-dose ICS), and location of the study site (North America versus Europe). The absolute difference in the rate of LOAC between placebo and RPT193 will be estimated and presented with the 90% CI for the difference. The primary analysis will be performed on the FAS analysis set. Subjects who withdraw from the study or discontinue IP due to lack of efficacy or due to an asthma-related AE will be analyzed as having experienced LOAC. Subjects who withdraw from the study for other reasons will be analyzed as not experiencing LOAC.

The same analysis as to be undertaken for the primary endpoint on the Full Analysis Set will be repeated for the per-protocol analysis set. An additional sensitivity analysis will be performed considering all missing data for LOAC criteria to be considered as meeting LOAC.

Additional sensitivity analyses may be detailed in the SAP.

As there are only 2 treatment groups and 1 primary analysis test in this study, no multiplicity correction is necessary. Secondary endpoints will be considered as hypothesis generating.

9.4.2 Secondary Endpoints

For a complete list of secondary endpoints, refer to Section 2.

All efficacy variables will be summarized by treatment group (RPT193 or placebo). For continuous variables, the summary statistics will include n, mean, SD, standard error (SE), median, minimum, and maximum. For categorical variables, subject counts and percentages will be provided.

[redacted]

- FEV1
- PEF
- FeNO
- [redacted]
- [redacted]

Additional covariates or factors may be added to the statistical models. These will be detailed in the SAP.

The remaining efficacy endpoints will be analyzed using descriptive statistics.

9.4.3 Exploratory Endpoints

Refer to Section 2.

Exploratory endpoints will be analyzed using descriptive statistics.

9.4.4 Safety Endpoints

The SAS will be used for the analysis of safety data (AEs, exposure to IP, clinical laboratory, vital signs, and ECGs).

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

TEAEs are defined as AEs with an onset date on or after the date of first administration of IP and before the date of last administration of IP. TEAEs will be presented by system organ class (SOC) and preferred term in frequency tables. Subjects with multiple AEs will be counted only once within each preferred term and SOC.

Key subject information for subjects with an AE with an outcome of death, subjects with SAEs, and subjects with AEs leading to discontinuation of IP will be listed.

Laboratory data (hematology, serum chemistry, and urinalysis) will be converted to Système International units for reporting and processing purposes. Absolute values and changes from baseline will be presented descriptively. For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, subject counts and percentages will be provided. Descriptive summaries of SAEs, AEs leading to treatment discontinuation, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will be provided as well.

Vital signs and ECG parameters will be presented descriptively.

9.4.5 Demographic and Baseline Characteristics

Demographic characteristics (including age, sex, ethnicity, and race) and baseline characteristics (including height, weight, BMI, and disease characteristics) will be presented descriptively.

9.4.6 Pharmacokinetic Endpoints

Individual and mean plasma concentrations at each sampling time point for RPT193 will be listed and summarized in a tabular format including means, geometric means, ranges, SDs, and coefficients of variation (CVs). Mean and/or median concentrations will be plotted versus time on semilogarithmic scales.

PK parameters will be calculated using noncompartmental analysis. Summary statistics of PK parameters including means, geometric means, medians, ranges, SDs, and CVs will be presented.

9.4.7 Pharmacodynamic Endpoints

All PD data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical format. Statistical analysis will be performed on PD parameters to compare the treatment groups.

9.4.8 Subgroup Analyses

To explore the uniformity of the detected overall treatment effect on the primary, and when applicable, key secondary efficacy endpoints, subgroup analyses may be performed. The following subgroup analyses are planned to be performed using a repeat of the analysis method used for the primary endpoint:

- Age group: based on the median age of the Full Analysis Set
- Sex: female vs. male
- Background ICS + LABA at Screening: Medium- or high-dose ICS
- Study Site: North America vs Europe

Full details of the subgroup analyses will be prespecified in the SAP.

9.4.9 Handling of Missing Values

Rules for imputation of missing data will be detailed in the SAP.

Subjects who withdraw from the study will be evaluated based on the data collected at each visit attended. Data collected during the withdrawal visit will be used as an end of study assessment for these subjects. If the withdrawal visit was performed > 1 day after the last dose was administered, then the previous visit will be used as the end of study assessment.

9.5 Interim Analysis

No interim analysis is planned.

10 ETHICS AND RESPONSIBILITIES

10.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the Note for Guidance on GCP International Council for Harmonisation (ICH) Harmonised Tripartite Guideline E6 (R1)/Integrated Addendum E6 (R2); US FDA CFR (Title 21 Parts 50, 56, 312); the general guidelines indicated in the Declaration of Helsinki; and all applicable regulatory requirements including, with respect to the conduct of the study in the EU, Regulation (EU) No. 536/2014 of the European Parliament and the Council of the European Union.

In accordance with the requirements of the Regulation No. 536/2014 of the European Parliament and the Council of the European Union, the Sponsor will obtain approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as applicable, for any amendments to the study that are deemed as "substantial" (i.e., changes which are likely to have a significant impact on the safety or physical or mental integrity of the study participants or on the scientific value of the study) prior to their implementation at European sites.

10.2 Institutional Review Board/Independent Ethics Committee

Before initiating a study, the Investigator/institution must have written and dated approval/favorable opinion from the IRBs/IECs for the study protocol/amendment(s), written ICF, any ICF updates, subject recruitment procedures (eg, advertisements), and any written information to be provided to subjects and a statement from the IRBs/IECs that these comply with GCP requirements (if applicable). A current copy of the IB should be included as part of the written application to the IRB/IEC.

The IRB/IEC approval(s) must identify the protocol version as well as the documents reviewed. Any amendments to the protocol will require IRB/IEC approval before the implementation of the changes made to the study, except for changes necessary to eliminate an immediate hazard to the study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

- Notifying the IRB/IEC of SAEs or other significant safety findings, including adverse drug reactions (ADRs) that are both serious and unexpected, as required by IRB/IEC procedures

- Providing oversight of the conduct of the study at the site and adherence to the requirements of 21 CFR, ICH guidelines, the applicable IRB/IEC, and all other applicable regulations including, for European sites, Regulation (EU) No. 536/2014.

- Promptly reporting deviations from, or changes to, the protocol to eliminate immediate hazards to the study subjects

10.3 Informed Consent

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the study, the Investigator should have the IRB/IEC's written approval/favorable opinion of the written ICF and any other written information to be provided to subjects.

- The Investigator or his/her representative will explain the purpose and nature of the study as well as possible adverse effects to the subject or his/her legally acceptable representative and answer all questions regarding the study.

- Subjects must be informed that their participation is voluntary, and consent can be withdrawn at any point.

- Subjects or their legally acceptable representatives will be required to sign a statement of informed consent that meets the requirements of US FDA CFR Title 21 Part 50, local regulations, ICH guidelines, the Health Insurance Portability and Accountability Act (HIPAA) in the US, Regulation (EU) No. 536/2014 in Europe, and the applicable IRB/IEC for the study site.

- Prior to a subject's participation in the study, the written ICF should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained.

- The original copy of the signed ICF will be retained at the study site.

- A copy of the ICF and any other written information must be provided to the subject or the subject's legally acceptable representative.

- If the ICF is revised, the revised ICF must have received the IRB/IEC's approval/favorable opinion in advance of its use. Subjects must be informed of the changes to the ICF and must re-consent to the most current version during their participation in the study. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

Subjects who are rescreened are required to sign a new ICF.

Provision of separate informed consent is mandatory for the genetic research. The subjects will be informed about its purpose and confidentiality of test results, and will be asked for their authorization to perform the test. If the subject does not consent to the blood sample for genetic testing, they may still participate in the study but will not have a sample taken for the genetic testing.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator (or authorized designee) will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

By signing the ICF, the witness attests that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

When a clinical study (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the study with the consent of the subject's legally acceptable representative (e.g., minors or subjects with severe dementia), the subject should be informed about the study to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

10.4 Data Protection

All subject data will be recorded, processed, stored, and handled in such a way that it can be accurately reported, interpreted, and verified, while preserving the confidentiality of the records and protecting the information and personal data of all subjects in accordance with applicable data protection laws including, for subjects located in the EU, the General Data Protection Regulation (GDPR) and applicable Member State laws. The subject personal data that will be collected in the study includes health information, date of birth, age, sex, race, and ethnicity.

Appropriate technical and organizational measures shall be implemented and maintained to protect information and personal data of subjects processed against unauthorized or unlawful access, disclosure, dissemination, alteration, destruction or accidental loss, including the following:

- Study subjects will be assigned a unique subject identification number. Any study records or datasets that are transferred by the investigative site will contain the subject identification number only; subject names and any information that would make the subject personally identifiable (e.g., phone number, address) will be redacted in all records and data before they are transferred by the investigative site.
- Information technology systems used to collect, process, and store study-related data will be secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access
- The Sponsor will implement data security controls which include, at a minimum, logical segregation of data, restricted (e.g. role-based) access and monitoring, password controls, and utilization of commercially available industry standard encryption technologies for subject personal data that is transmitted over public networks (i.e. the Internet) or when transmitted wirelessly or stored on portable or removable media (i.e. laptop computers, CD/DVD, USB drives, back-up tapes).

- The contract between the Sponsor, Investigators, and study sites will specify the responsibilities of the parties related to the handling of data security breaches and the respective communication and cooperation of the parties. The Investigators and the study sites will be required to notify the Sponsor without undue delay of becoming aware of any data security breaches in relation to subject personal data and detail in the notification the nature of the breach and other information to allow the Sponsor to assess the personal data breach in accordance with applicable data protection laws.
- The Investigators and study sites will be obligated to provide reasonable assistance to the Sponsor in ensuring the Sponsor's fulfilment of its obligations in respect of personal data breaches under applicable data protection laws, including reporting the personal data breach to study subjects and/or regulatory authorities if and as required by applicable data protection laws. The Sponsor will work with Investigators and study sites to investigate any data breach incidents involving subject personal data, take appropriate actions to remedy and mitigate such incidents and, as applicable, take measures to prevent similar data security breaches in the future.
- The Investigator or his/her designee must explain to each subject, before enrollment into the study, that, for evaluation of study results, the subject's confidential medical information obtained during the study and medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities. The Investigator (or designee) is responsible for obtaining written permission from subjects for the use and disclosure of their confidential medical information as described in the informed consent and/or data privacy authorization in accordance with country-specific regulations (such as the Health Insurance Portability and Accountability Act in the US and the GDPR in the EU) before they are allowed to participate in the study. If permission to use and disclose confidential medical information is withdrawn by a subject, the Investigator is responsible for documenting that no further personal data from the subject will be collected unless required by applicable law.

10.5 Financing and Insurance

10.5.1 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly.

10.5.2 Insurance, Indemnity, and Compensation

The Sponsor will maintain an appropriate clinical study insurance policy.

10.5.3 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

11 RECORDS MANAGEMENT

All clinical study information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. This principle applies to all records referenced in this protocol, irrespective of the type of media used.

An eCRF will be used to store and transmit subject information. The eCRF must be reviewed and electronically signed and dated by the Investigator. The Investigator is responsible for verifying that the data entries are accurate and correct by signing the eCRF.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorized site personnel (eg, Investigators and the study coordinator). The eCRF must be completed as soon as possible after any subject evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

During each study visit, a physician participating in the study will maintain progress notes in the subject's medical records to document all significant observations. At a minimum, these notes are to contain:

- The date of the visit and the corresponding day or visit in the study schedule
- General condition and status remarks by the subject, including any significant medical findings. The severity, frequency, duration, and resolution of any reported AE, and the Investigator's assessment as to whether or not the reported AE is related to IP
- Changes (including dosages) in concomitant medications/therapies (including medical foods) or procedures
- A general reference to the procedures completed
- The signature or initials of all physicians making an entry in the medical record (progress notes)

In addition, any contact with the subject via telephone or other means that provides significant clinical information is to also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents is to be promptly entered into the appropriate section of the eCRF.

Changes to information in the medical record (progress notes) and other source documents are to be initialed and dated on the day the change is made by the Investigator (or designee). If the reason for the change is not apparent, a brief explanation for the change is to be written adjacent to the change. Changes to the eCRF will be electronically tracked.

The [redacted] data management department will write a data management plan, which will be finalized prior to performing any data validation.

11.1 Source Documentation

Source documents contain the results of original observations and activities of a clinical investigation. They are the original records in which raw data are first recorded. Source documents include, but are not limited to, medical records (progress notes), ECG and computer printouts, screening logs, completed scales, quality of life questionnaires, and recorded data from automated instruments.

The Investigator/site personnel should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

All source documents from this study are to be maintained by the Investigator and made available for inspection by authorized persons. The Investigator will provide direct access to source documents/data for study-related monitoring, audits, IRB/IEC review, and regulatory inspections. The Sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for study-related monitoring, audit, IRB/IEC review, and regulatory inspection.

11.2 Electronic Case Report Form Completion and Data Management

An eCRF will be used to store and transmit subject information. The file structure and format for the eCRF will be provided by the Sponsor or its representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed and dated by the Investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorized site personnel (eg, Investigators and the study coordinator). The eCRF must be completed as soon as possible after any subject evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track the changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors. Changes to the eCRF will be electronically tracked.

Data will be entered/loaded into a validated electronic database using a clinical data management system. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

11.3 Study Files and Record Retention

All data derived from the study will remain the property of the Sponsor. The Sponsor assumes accountability for actions delegated to other individuals, e.g., the CRO.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents, including records of subjects, source documents, eCRFs, and the IP inventory, must be kept on file.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of RPT193. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the Investigator when these documents need no longer be retained.

The Investigator is not to dispose of any records relevant to this study without written permission from the Sponsor and is to provide the Sponsor the opportunity to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives, and regulatory authorities.

If an Investigator moves, withdraws from a study, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

12 AUDITING AND MONITORING

Sponsor-assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study, such as assessing subject enrollment, compliance with protocol procedures, completeness and accuracy of data entered into the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The Investigator must agree to Sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) to ensure compliance with applicable regulations, and the Investigator will assist with the Sponsor's monitoring activities.

Quality control will occur at each stage of data handling to ensure that all data are reliable and have been processed correctly. The Sponsor should ensure oversight of any study-related duties and functions carried out on its behalf, including study-related duties and functions that are subcontracted to another party by the Sponsor's contracted CRO(s).

The eCRFs should be completed in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Details describing the strategy, responsibilities, and requirements of the study monitoring are provided in the study monitoring plan.

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are being fulfilled. The Sponsor or its representative may conduct audits at the investigative sites including, but not limited to, IP supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. Government regulatory authorities may also inspect the Investigator during or after the study. The Investigator (or designee) should contact the Sponsor/CRO immediately if this occurs. All medical records (progress notes) must be available for audit. The Investigator must agree to participate with audits conducted at a convenient time in a reasonable manner.

12.1 Risk and Quality Tolerance Limits

Perceived risks and quality tolerance limits (QTLs) will be identified and documented before the start of the study.

The Sponsor will review risk control measures periodically to ascertain whether the implemented quality management activities remain effective and relevant. The quality management approach and any important deviations from the predefined QTLs (and remedial actions adopted) will be described in the Clinical Study Report (CSR).

12.2 Protocol Adherence and Deviations

The Investigator and site personnel should conduct the study in compliance with the protocol and should use continuous vigilance to identify and report protocol deviations.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol that may be on the part of the Investigator, site personnel, or the subject.

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study.

The Investigator should not implement any deviation from the protocol. In the event of an important protocol deviation, the Investigator will discuss the deviation with the Sponsor's Medical Monitor and will come to an agreement as to whether the subject should be withdrawn from the study due to the important protocol deviation.

13 STUDY REPORT AND PUBLICATIONS

This study will be registered on ClinicalTrials.gov in accordance with applicable laws or publication policy and may also be registered on other publicly accessible websites as necessary.

The Sponsor is responsible for preparing and providing the appropriate regulatory authorities with the CSR according to the applicable regulatory requirements. The Sponsor will ensure that the CSR meets the standards of the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).

The publication policy of the Sponsor is discussed in the Investigator's clinical research agreement.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

14 STUDY START AND TERMINATION

The study start date is the date on which the first subject provides informed consent.

The end of the study is defined as the last subject's last assessment.

Both the Sponsor and the Investigator reserve the right to terminate the study or the participation in the study at an Investigator's site at any time. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

If the study is prematurely terminated or suspended for any reason, the Sponsor/Investigator/site personnel should promptly inform the study subjects and should ensure appropriate therapy and follow-up for the subjects. Where required by the applicable regulatory requirements, the IRB/IEC should be informed promptly and be provided with a detailed written explanation of the termination or suspension.

If the Investigator terminates or suspends a study without prior agreement of the Sponsor, the Investigator should inform the site personnel. The Investigator/site personnel should promptly inform the Sponsor and the IRB/IEC. The Investigator/site personnel should also provide the Sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

15 CONFIDENTIALITY

All information generated in this study, including subject medical information and other personal data collected during this study, is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, IRB/IEC personnel, the Sponsor and its authorized representatives are allowed full access to the records. Applicable data protection laws will be complied with in full.

Study records containing subject medical information will be identified by the subject's identification number and not by the subject's full name, except for the subject informed consent form, which is archived at the study site only. The subject's name will not be used in any public report of the study. Where possible, subject identification information will be removed from study-specific data before it is shared with the Sponsor and any third parties. The code list that links the subject identification number to an identifiable subject will be stored separately from the study-specific data (e.g., by the study doctor and/or study team and not by the Sponsor).

Additional data protection measures are described in Section. 10.4.

All personal details will be treated as confidential by the Investigator, staff at [redacted], and [redacted].

16 REFERENCES

Bosnjak B, Stelzmueller B, Erb KJ, Epstein MM. Treatment of allergic asthma: modulation of Th2 cells and their responses. Respir Res. 2011;12:114.

Fielding S, Pijnenburg M, de Jongste JC, et al. Change in FEV_1 and Feno measurements as predictors of future asthma outcomes in children. Chest. 2019;155:331-41.

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention (2022 update). Accessed February 3, 2023. Available at: https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf.

Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. Am J Respir Crit Care Med. 2019;200:e70-88.

Hartl D, Lee CG, Da Silva CA, Chupp GL, Elias JA. Novel biomarkers in asthma: chemokines and chitinase-like proteins. Curr Opin Allergy Clin Immunol. 2009;9:60-6.

[redacted]

Kataoka Y. Thymus and activation-regulated chemokine as a clinical biomarker in atopic dermatitis. J Dermatol 2014;41:221-9.

Koyasu S, Moro K. Type 2 innate immune responses and the natural helper cell. Immunology. 2011;132:475-81.

Kubo, M. Innate and adaptive type 2 immunity in lung allergic inflammation. Immunol Rev. 2017;278:162-72.

National Institutes of Health (NIH). Clinical spectrum of SARS-CoV-2 infection. Updated September 26, 2022. Accessed February 7, 2023. Available at: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/

Vestergaard C, Deleuran M, Gesser B, Grønhøj Larsen C. Expression of the T-helper 2-specific chemokine receptor CCR4 on CCR10-positive lymphocytes in atopic dermatitis skin but not in psoriasis skin. Br J Dermatol. 2003;149:457-63.

Viney JM, Andrew D, Phillips R, et al. Distinct conformations of the chemokine receptor CCR4 with implications for its targeting in allergy. J Immunol. 2014;192:3419-27.

Wechsler ME, Szefler SJ, Ortega VE, et al. Step-up therapy in black children and adults with poorly controlled asthma. N Engl J Med. 2019;381:1227-39.

Wechsler ME, Ruddy MK, Pavord ID, et al. Efficacy and safety of itepekimab in patients with moderate-to-severe asthma. N Engl J Med. 2021;385:1656-68.

Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med. 2013;368:2455-66.

Woodruff PG, Modrek B, Choy DF, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. Am J Respir Crit Care Med. 2009;180:388-95. Erratum in: Am J Respir Crit Care Med. 2009;180:796.

Zhudenkov K, Palmér R, Jauhiainen A, et al. Longitudinal FEV_1 and exacerbation risk in COPD: quantifying the association using joint modelling. Int J Chron Obstruct Pulmon Dis. 2021;16:101-11.

17 APPENDICES

17.1 Appendix I - Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a subject administered an IP and which does not necessarily have a causal relationship with that IP. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease (new or exacerbated) temporally associated with the use of IP, whether or not considered related to the IP.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after IP administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either IP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • Because worsening of asthma is captured by efficacy assessments, it will not be recorded as an AE, unless more severe than expected for the subject's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of TEAE

TEAE Definition
• A TEAE is any condition that was not present prior to treatment with the IP but appeared following treatment, was present at IP initiation but worsened during treatment, or was present at IP initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the IP was initiated).

Definition of AECI

AECI Definition
• [redacted]

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d) Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other medically important serious event: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor and/or designee in lieu of completion of the applicable AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor and/or designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor and/or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of severity for each AE reported during the study. AEs should be assessed and graded for severity based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

Toxicities that are not specified in the NCI-CTCAE will be graded for severity as follows:

- Grade 1 (Mild): Asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated
- Grade 2 (Moderate): Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3 (Severe): Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4 (Life-threatening): Urgent intervention indicated required to remove or abrogate risk of death
- Grade 5: Death related to AE

Note: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (as characterized above) whereas seriousness as defined above, defines the requirements for reporting obligations from the Sponsor to applicable regulatory authorities.

Assessment of Causality

The Investigator will establish causality of the AE to the IP. The Investigator should take into account the history of the subject, most recent physical examination findings, and concomitant medications.

The following definitions will be used to determine causality of an AE:

- Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to IP administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the IP (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the IP, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Potentially Related: There is some evidence to suggest a causal relationship (eg, the event occurred within a reasonable time after administration of the IP). However, other factors may have contributed to the event (eg, the subject's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be Related: A clinical event, including an abnormal laboratory test result, whose temporal relationship to IP administration makes a causal relationship improbable (eg, the event did not occur within a reasonable time after

administration of the IP) and in which other drugs or chemicals or underlying disease provides plausible explanations (eg, the subject's clinical condition, other concomitant treatments).

- Not Related: The AE is completely independent of IP administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

  For regulatory reporting purposes, AEs assessed as "Unlikely Related" will map to "Not Related." Events assessed as "Definitely Related", "Probably Related", and "Potentially Related" will map to "Related."
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IP administration will be considered and investigated.
- The Investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

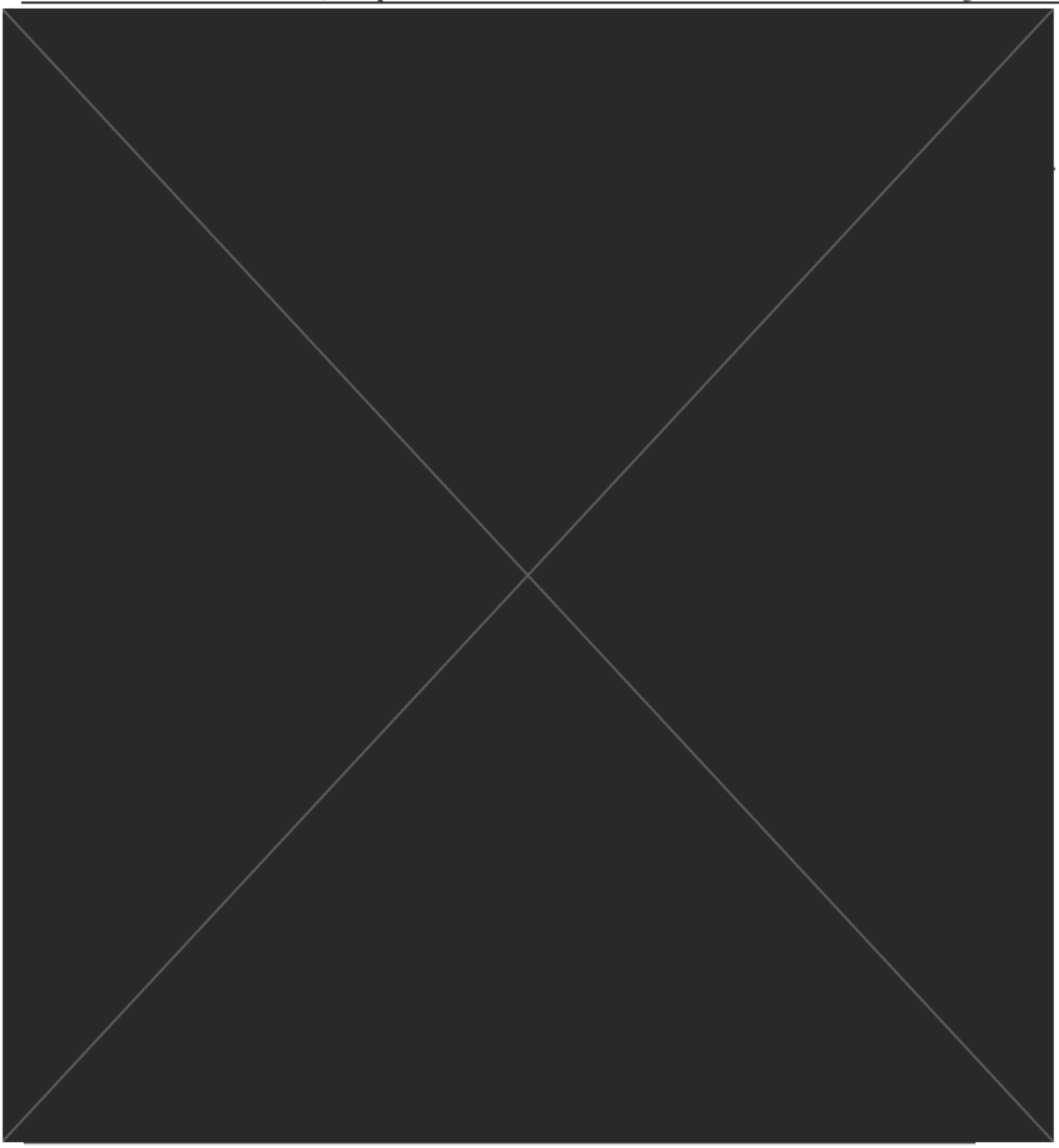
Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor and/or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor and/or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor and/or designee within 24 hours of receipt of the information.

Reporting of SAEs and AECIs

Safety Event Reporting via Paper Form & eCRF

- Email transmission of the paper Safety Event Report Form is the preferred method to transmit safety event information to [redacted] Safety with facsimile as a back-up method, if necessary.
- Safety events should be reported to [redacted] at:
  [redacted]
- The Investigator will also record all relevant SAE/AECI information in the EDC using the AE/SAE eCRF. Each event must be recorded separately.



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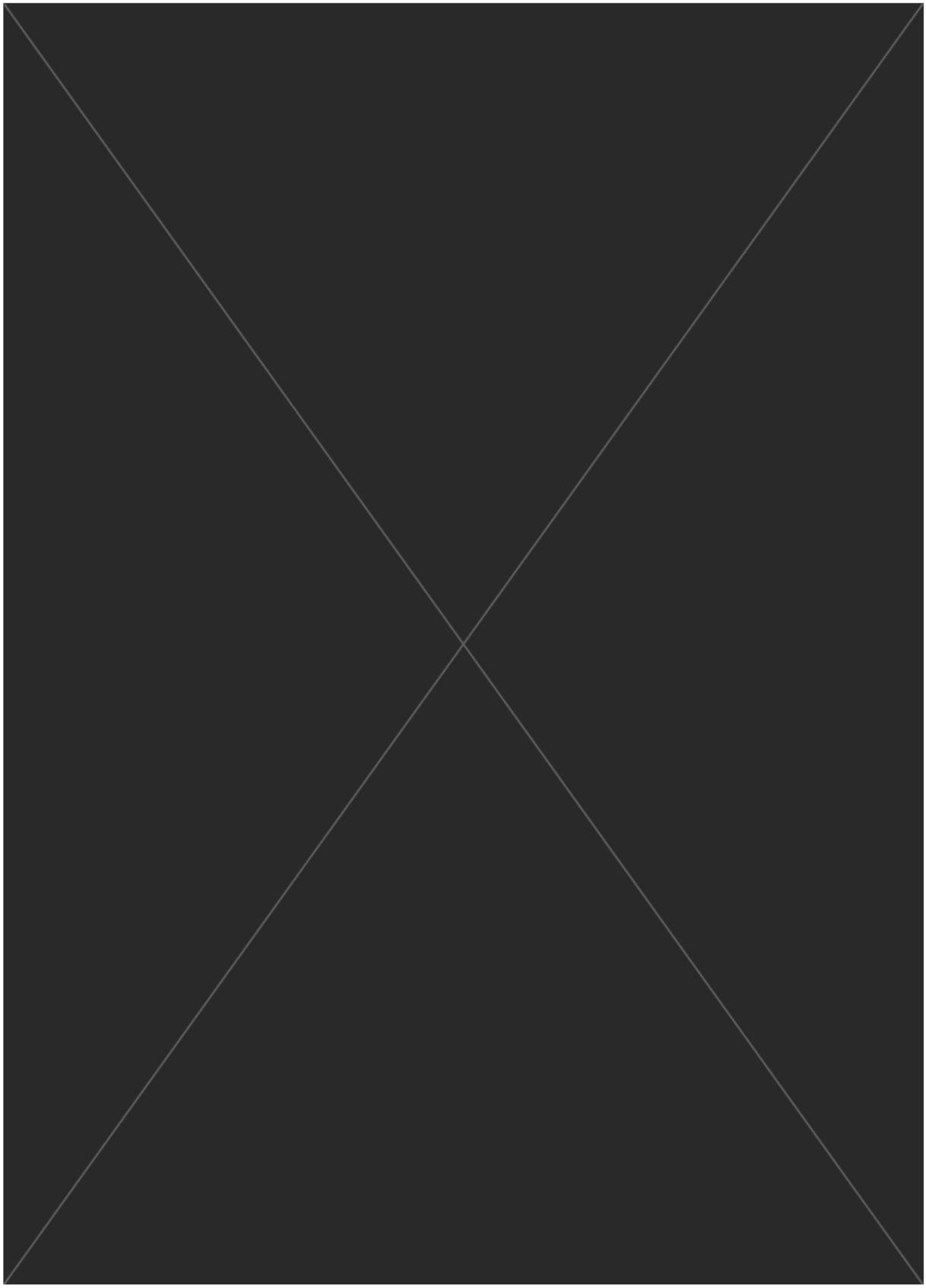

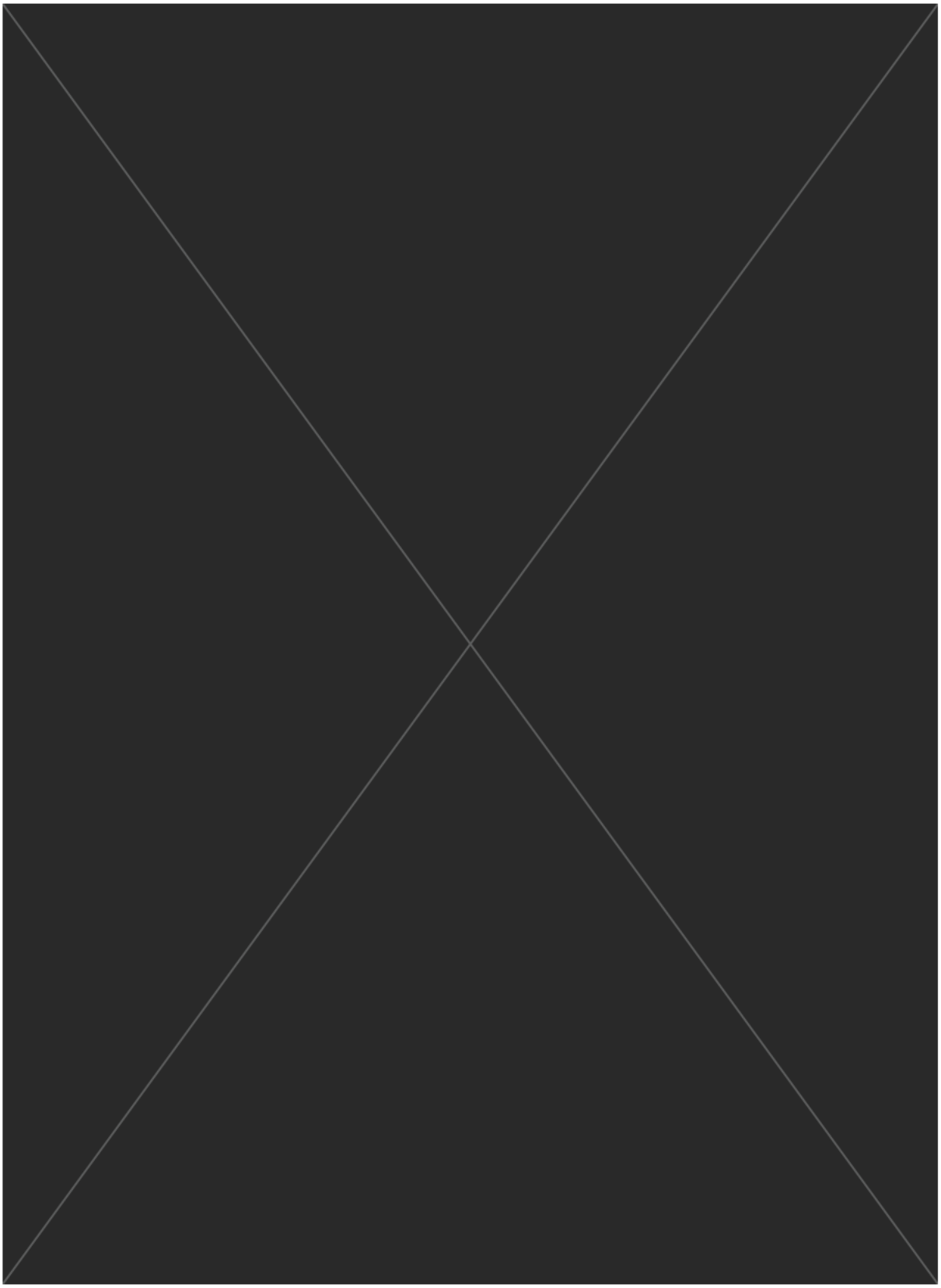

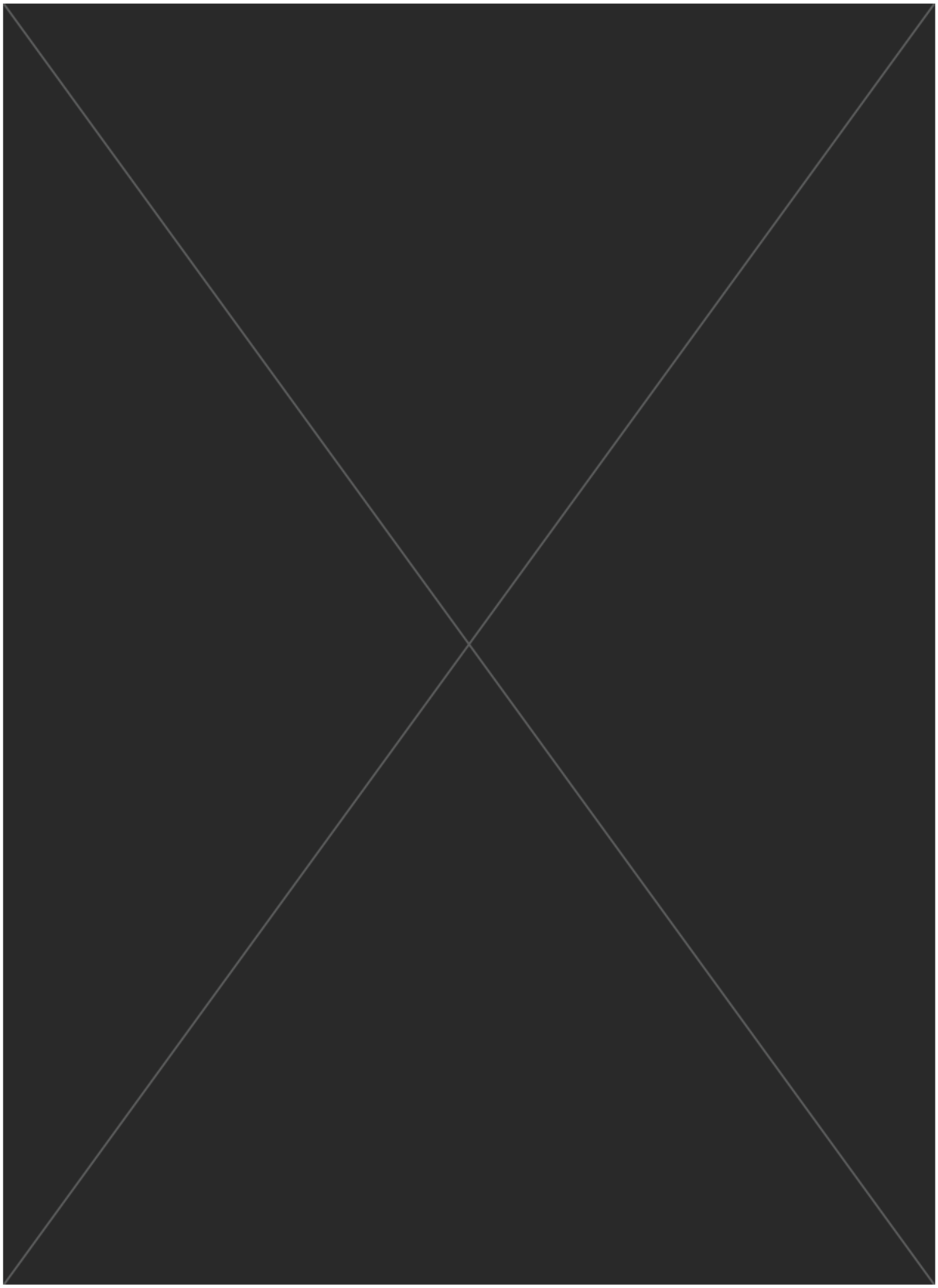

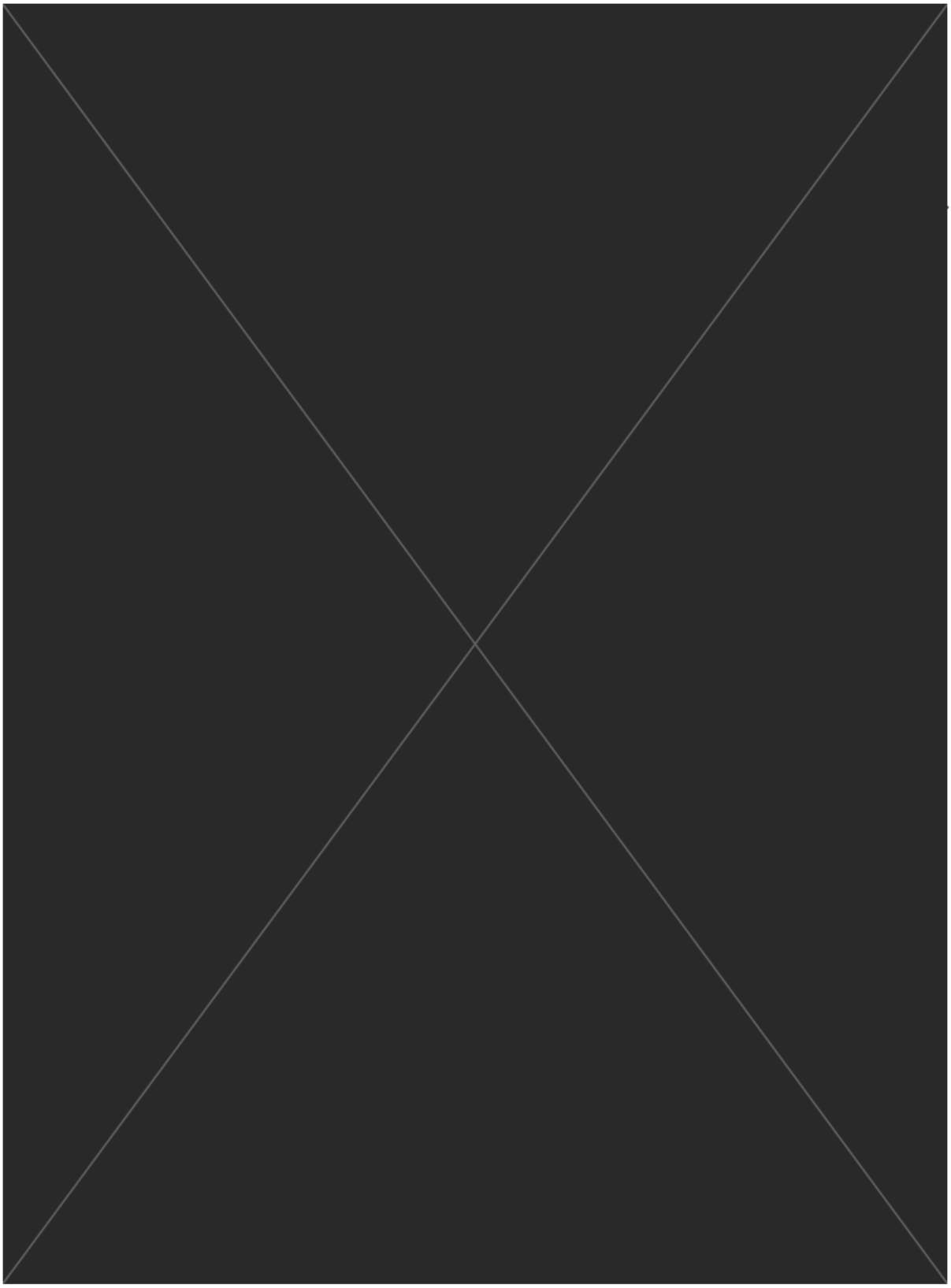

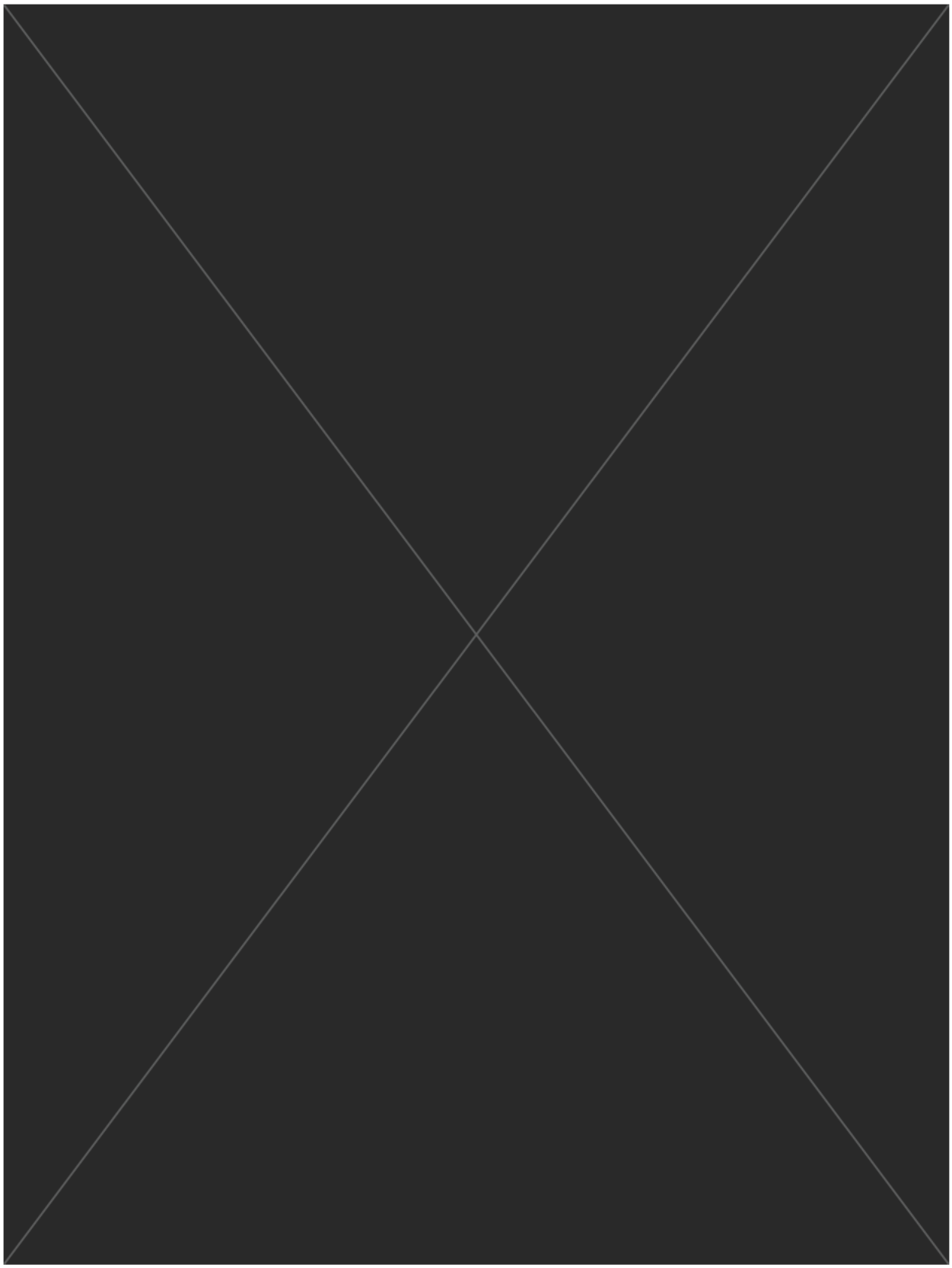

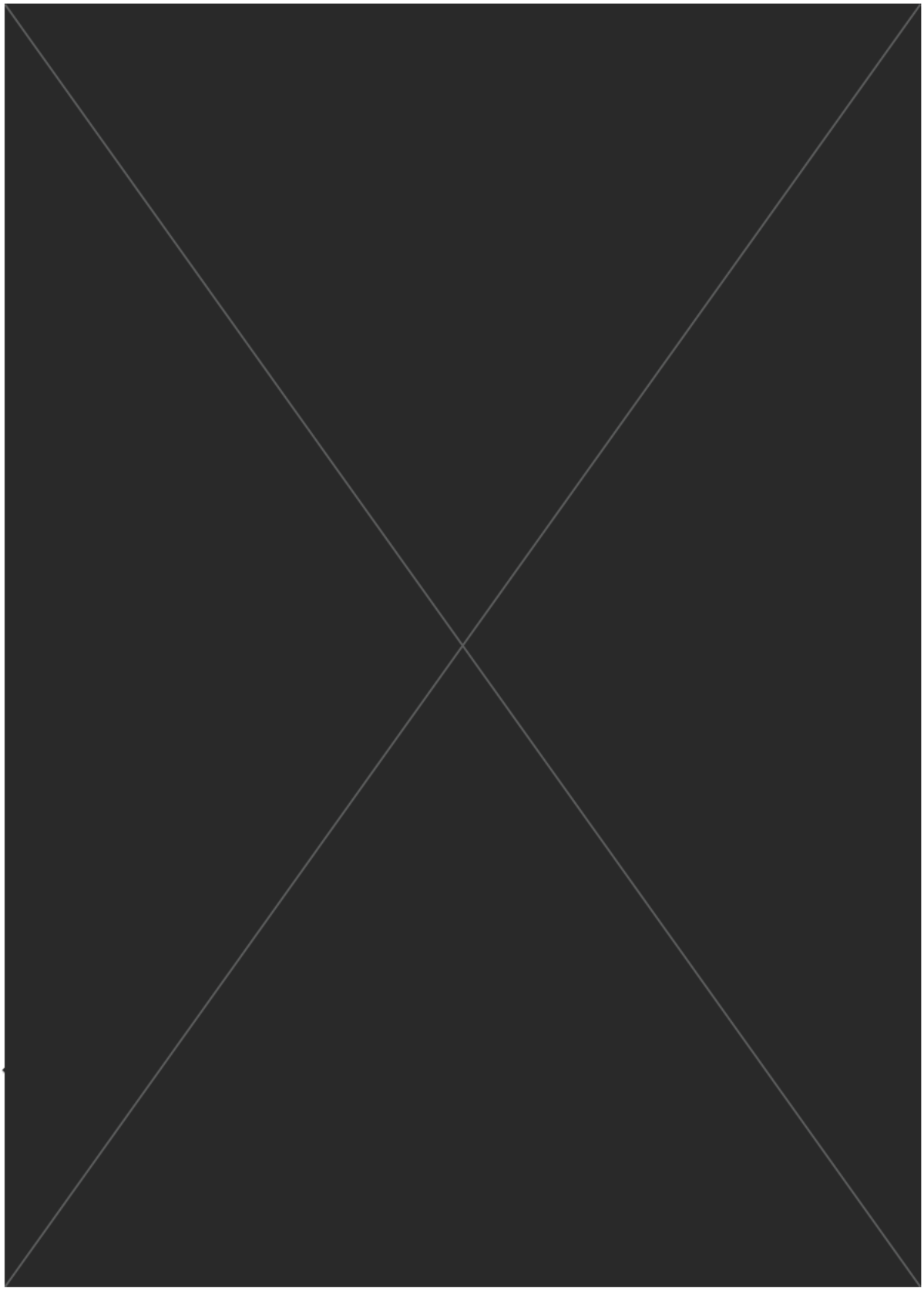

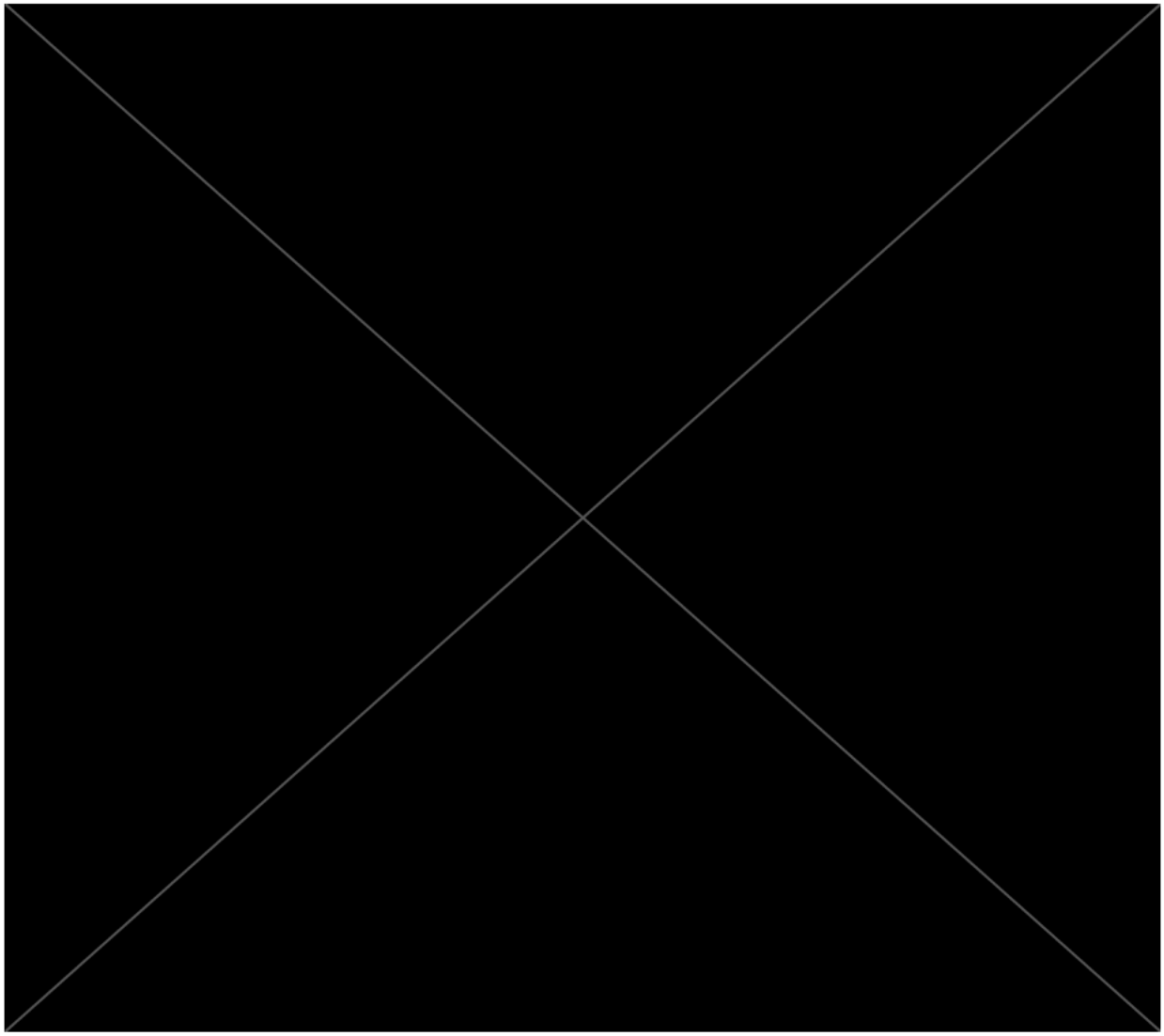

17.6 Appendix VI – COVID-19 Severity Criteria

Asymptomatic or Presymptomatic Infection

Asymptomatic SARS-CoV-2 infection can occur, although the percentage of patients who remain truly asymptomatic throughout the course of infection is variable and incompletely defined. It is unclear what percentage of individuals who present with asymptomatic infection progress to clinical disease. Some asymptomatic individuals have been reported to have objective radiographic findings consistent with COVID-19 pneumonia.

Mild Illness

Patients with mild illness may exhibit a variety of signs and symptoms (eg, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell). They do not have shortness of breath, dyspnea on exertion, or abnormal imaging. Most patients who are mildly ill can be managed in an ambulatory setting or at home through telemedicine or telephone visits. No imaging or specific laboratory evaluations are routinely indicated in otherwise healthy patients with mild COVID-19. Older patients and those with underlying comorbidities are at higher risk of disease progression; therefore, health care providers should monitor these patients closely until clinical recovery is achieved.

Moderate Illness

Moderate illness is defined as evidence of lower respiratory disease during clinical assessment or imaging, with $SpO_2 \geq 94\%$ on room air at sea level. Given that pulmonary disease can progress rapidly in patients with COVID-19, patients with moderate disease should be closely monitored. If bacterial pneumonia is suspected, administer empiric antibiotic treatment, re-evaluate the patient daily, and de-escalate or stop antibiotics if further testing indicates the patient does not have a bacterial infection.

Severe Illness

Patients with COVID-19 are considered to have severe illness if they have $SpO_2 < 94\%$ on room air at sea level, $PaO_2/FiO_2 < 300$ mm Hg, a respiratory rate > 30 breaths/min, or lung infiltrates > 50%. These patients may experience rapid clinical deterioration. Oxygen therapy should be administered immediately using a nasal cannula or a high-flow oxygen device. If bacterial pneumonia or sepsis is suspected, administer empiric antibiotics, re-evaluate the patient daily, and de-escalate or stop antibiotics if further testing indicates the patient does not have a bacterial infection.

Critical Illness

SARS-CoV-2 infection can cause acute respiratory distress syndrome, virus-induced distributive (septic) shock, cardiac shock, an exaggerated inflammatory response, thrombotic disease, and exacerbation of underlying comorbidities.

Successful clinical management of a patient with COVID-19, as with any patient in the intensive care unit (ICU), includes treating both the medical condition that initially resulted in ICU admission as well as other comorbidities and nosocomial complications.

Source: NIH 2022

17.7 Appendix VII – Protocol Amendment Summary of Changes

17.7.1 Amendment 2, 12Sep2023

Section	Description of Change	Brief Rationale
SAE and AECI Contact Information	Updated the section to include AECIs and current safety reporting contact information	Updated to clarify reporting of AECIs and include current contact information ([redacted])
Synopsis, 2. Study Objectives and Endpoints, 5.2.1. Loss of Asthma Control	Updated study endpoint from "Exacerbation of adverse events (AEs) that requires a hospitalization or emergency room visit" to "Exacerbation of ***asthma-related*** adverse events (AEs) that requires a hospitalization or emergency room visit	Correction of an error in the previous amendment
Synopsis, 4.2 Exclusion Criteria	Added exclusion criteria to exclude subjects with a history of life-threatening asthma exacerbation requiring intubation and ventilation.	Updated in response to comments from DMC
Synopsis, Section 9.4.1	The primary analysis was updated from logistic regression to a generalized linear model with binomial distribution and identity link with fixed effects for treatment, pre-screening inhaled ICS + LABA, and location of the study site.	Regulatory authority request; Updated in response to regulatory authority question regarding use of logistic regression
Table 1 Schedule of Assessments	Added clarity to footnote "e" to indicate subjects may enter run-in while repeat lab tests are being confirmed.	Updated for clarity on timing of screening window
1.6 Benefit/Risk Assessment	Added more detail regarding potential risks with RPT193 treatment with references to relevant sections in the IB.	Regulatory authority request; additional information on potential risk/benefit
3.2 Discussion of Study Design	Added NCT and EudraCT numbers for referenced studies of similar study design	Regulatory authority request; provide examples of similarly designed proof-of-concept studies
5 Description of Study Assessments	Added details on handling, storage, and future use of biological samples	Regulatory authority request; additional detail on collection, storage, and future use of samples
5.1.3 Tuberculosis Test	Added text indicating that local laboratory testing for tuberculosis is permitted	Update included from protocol clarification memo
6.3 Blinding	Revised text related to breaking the blind	Regulatory authority request; updated to emphasize Investigator responsibility for trial

Section	Description of Change	Brief Rationale
		related medical decisions
6.7 Description, Management and Withdrawal of Non-Investigational Medicinal Product	Added text to specify inhaler needed during Periods 1 and 2 is Fluticasone/salmeterol 250/50 mcg per puff for subject initially taking medium-dose ICS+LABA or 500/50 mcg per puff for those initially taking high-dose ICS+LABA	Update included from protocol clarification memo
6.7.1. Withdrawal of Background Inhaled Therapies	Revised dose of Fluticasone/Salmeterol inhaler for subjects initially taking high-dose ICS + LABA from 250/50 mcg 2 puffs twice daily to 500/50 mcg 1 puff twice daily during period 1 (Run-in) and Period 2 (Adjunctive Therapy)	Update included from protocol clarification memo
8.5 Regulatory Reporting Requirements for SAEs	Added text to confirm sponsor plan and adherence to regulations for reporting SAEs/SUSARs	Regulatory authority request; updated to confirm adherence sponsor reporting obligations
8.6 Adverse Events of Clinical Interest	Added text indicating that AECIs should be reported to the [redacted] Safety team on the Safety Event Report form.	Updated for clarity in safety reporting of AECIs
9.3 Sample Size	[redacted]	Regulatory authority request; clarify sample size determination
9.4.1 Primary Endpoints	[redacted]	Regulatory authority request; clarify planned statistical analyses
9.4.8 Subgroup Analyses	Added details on planned subgroup analyses	Regulatory authority request; clarify subgroup analyses plans
10.1 Regulatory and Ethical Considerations	Added text to confirm study conduct adherence to relevant regulations included in Regulation (EU) No. 536/2014	Regulatory authority request; confirm Sponsor's intent to conduct study in adherence to applicable regulations
10.2 Institutional Review Board/Independent Ethics Committee	Added reference to Regulation (EU) No. 536/2014	Regulatory authority request; confirm Sponsor's intent to conduct study in adherence to applicable regulations
10.3 Informed Consent	Added reference to Regulation (EU) No. 536/2014	Regulatory authority request; confirm Sponsor's intent to

Section	Description of Change	Brief Rationale
		conduct study in adherence to applicable regulations
10.4 Data Protection	New section added	Regulatory authority request; clarify data protection practices during the study
15 Confidentiality	Revised to describe the process for maintaining subject confidentiality when sharing study-specific data with Sponsor or third parties	Updated to include measures to maintain confidentiality
Appendix 1	Updated reporting of SAEs section to include [redacted] for safety reporting; added definition of AECI; guidance for reporting of AECIs	Updated to reflect current safety team contact information and add clarity for reporting AECIs