Statistical Analysis Plan (SAP)

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 Version No./Date:	3.0 / 12SEP2023
ICON Study ID:	RTH19303-R19303
CRF Version No./Date:	2.0 / 06JUL2023
SAP Version No./Date:	1.0 / 01MAY2024

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On behalf of:
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1.0 Table of Contents

2.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under RAPT Protocol RPT193-03.

3.0 Scope

The Statistical Analysis Plan outlines the following:

- Study Objectives
- Study Design
- Study Estimands
- Applicable Study Definitions
- Statistical Methods

4.0 Introduction

The study protocol RPT193-03 is 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. This statistical analysis plan (SAP) contains a detailed description of the data presentations and statistical analyses that will be included in the clinical study report for the protocol.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol version 3.0 dated 12SEP2023 and CRF version 2.0 dated 06JUL2022. Any further changes to the protocol or CRF may necessitate updates to the SAP.

Versions of the SAP up to initial sponsor approval will be known as a draft SAP. Changes following approval of the first version SAP, known as the “stable SAP”, will be tracked in the SAP Change Log. The finalized version of the SAP will be issued for sponsor approval prior to the first planned analysis.

The analyses for the pharmacokinetic (PK) data will be described in a separate analysis plan. The analysis for pharmacodynamic (PD) and biomarkers will not be included in this SAP.

4.1 Changes from Protocol

RPT193-03 is terminated early; No formal analysis or modeling will be performed on primary and secondary endpoints. Only descriptive statistics will be presented. [redacted]

[redacted]

5.0 Study Objectives

Insert the study objectives as stated in the protocol. Poorly worded or ambiguous objectives should be followed by an explanation of the statistician's understanding of the objectives in the context of the study. If the corresponding section in the protocol is very lengthy and detailed, provide high level information only and add a reference to the protocol instead.

6.0 Study Design

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

Male or female adults aged 18 to 65 years will be included in this study. The study design is outlined in **Error! Reference source not found.**, and the visit schedule and planned assessments at each visit are detailed in Table 1: below:

SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Events

	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
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

				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
Fractional exhaled nitric oxide (FeNO)	X			X	X	X	X	X	X	X	X	X	X	X	X
Switch to standardized salmeterol-fluticasone inhaler		X													
Provisioning daily PEF meter/ electronic diary device to subject		X													
Collect daily PEF meter/electronic diary device from subject														X[f]	X
Asthma Control Questionnaire (ACQ-5)	X			X		X	X	X	X	X	X	X	X	X	X
Asthma Quality of Life Questionnaire (AQLQ)				X		X	X		X		X		X		X
Sino-Nasal Outcome Test Questionnaire (SNOT22) – only in those with a history of ongoing allergic rhinitis				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
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]											
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		X ---------- X[l]													

				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
(ICS, LABA) inhaler[m]															
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
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				

				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
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: ACQ-5 = Asthma Control Questionnaire-5; AE = adverse event; AQLQ = Asthma Quality of Life Questionnaire; 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 = pharmacodynamic; PEF = peak expiratory flow; PK = pharmacokinetic; RNA = ribonucleic acid; SABA = short-acting beta 2 agonist; SNOT-22 = Sino-Nasal Outcome Test Questionnaire; 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.
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 **Error! Reference source not found.** of Protocol for timing of the PEF assessments.

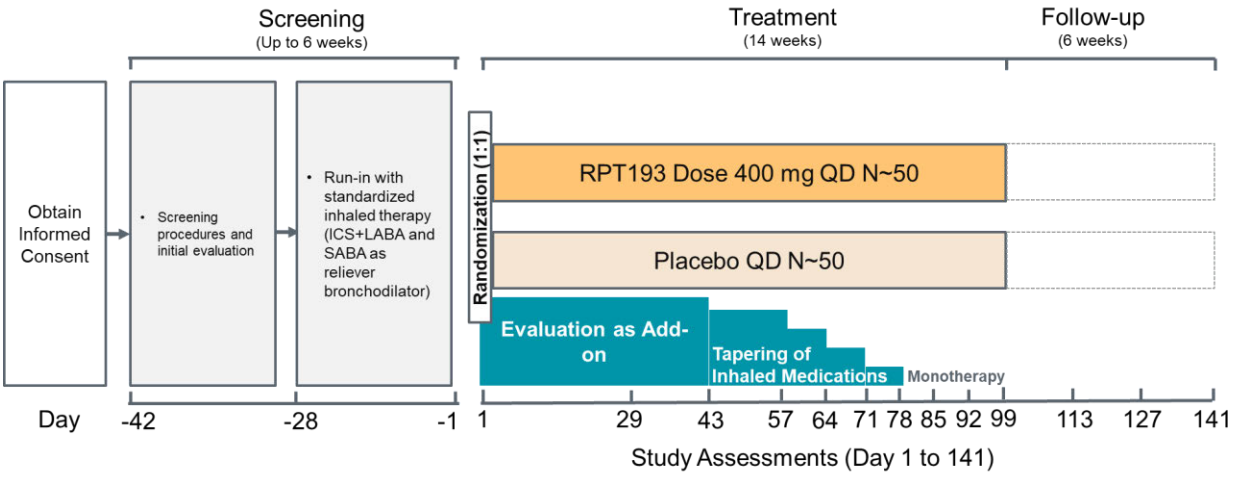
i. Blood samples will be collected from subjects who have consented to participate in the genetic analysis component of the study. Participation is optional. Please see Section **Error! Reference source not found.** of Protocol for further details.
j. The Investigator to provide clear and accurate instructions 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 **Error! Reference source not found.** of Protocol

After a 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). If a subject is considered eligible at the Baseline visit, subjects (n=100) will be randomized (1:1) on Day 1 (Week 1) to receive RPT193 or placebo as oral tablets daily from Day 1 (Week 1) to Day 98 (Week 14). Enrolled subjects will receive RPT193 or matching placebo for 14 weeks with management of background inhaled corticosteroids (ICS) and LABA during the following periods:

- Period 2) from 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 2-3 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 loss of asthma control (LOAC) event. Subjects will be monitored for loss of asthma control (LOAC) events using the internet-enabled e-Diary/peak expiratory flow (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.If a subject has a LOAC event, the subject will be immediately discontinued from investigational product (IP), returned to the pre-screening, background inhaled therapy , and remain in the study for safety follow-up and further clinical management if necessary.

6.1 Study Flow Chart



6.2 Sample Size Considerations

The primary efficacy analysis for this study will be the comparison between treatment groups of the proportion of subjects experiencing a LOAC event during the 14-week treatment period. The study will be considered positive if the primary efficacy test indicates a statistically significant treatment effect versus placebo at the predefined significance level.

Sample size calculations were performed based on the following considerations:

In the dupilumab Phase 2a study in which subjects had elevated peripheral blood eosinophil counts (≥ 300 cells/μL) as per inclusion criteria of this study, the observed LOAC rate in the placebo group was 44% (Wenzel 2013).

This POC study is designed to detect an approximately 55% reduction in LOAC rate versus placebo, ie, a placebo group rate of 46% and RPT193 group rate of 20%.

Based on the assumption above, a Fisher's exact test with a 10% 2-sided significance level will have 80.97% power to detect an absolute difference between a placebo LOAC rate of 46% and an RPT193 LOAC rate of 20% when the sample size in each group is 47. Considering a 10% dropout rate during the study, a sample size of 52 subjects per group is planned for this study.

Sample size calculations were performed using nQuery ver.9.1.0.0.

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.

6.3 Randomization and Blinding

Randomization will be performed via the interactive voice response system/interactive web response system (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.

6.4 Study Assessments Table (optional)

N/A – information present in the TFL Shells.

7.0 Study Estimands

7.1 Estimand Attributes

Objectives	Estimands
Primary	Primary estimand
• 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	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

corticosteroid plus long-acting beta 2 agonists (LABA) over 14 weeks	period relative to baseline on 2 consecutive days, • Increase by a factor of 4 or more in the most recent dose of inhaled corticosteroids (ICS; or if ICS has been fully withdrawn, ≥50% of the prescribed ICS dose at baseline) • Exacerbation of asthma requiring systemic corticosteroids • Exacerbation of asthma 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.	• Change in Asthma Control Questionnaire (ACQ)-5 score at Day 99 (Week 14) and at each interval visit after treatment with RPT193 compared to baseline • Change in peak expiratory volume (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 asthma quality-of-life.	• Change in Asthma Quality of Life Questionnaire (AQLQ) 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 ACQ-5 from Day 99 to 140 (Weeks 14 to 20). • Change in ACQ-5 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 28, 42, 56, 11 and 98 (Weeks 4, 6, 8, 11, and 14).

7.2 Analysis Population Sets

7.2.1 Enrolled Analysis Set

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.

7.2.2 Full Analysis Set

The Full Analysis Set (FAS) will include all randomized subjects and will be analyzed according to the treatment group allocated by randomization following the intention to Treat (ITT) approach, regardless of which treatment they actually received. 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.

7.2.3 Safety Analysis Set

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

7.2.4 Per-Protocol Analysis Set

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.

7.2.5 Pharmacokinetic (PK) Analysis Set

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. PKAS will also be documented in PK plan.

8.0 Conventions and Derivations

8.1 Baseline and Change from Baseline

Baseline is defined as the last recorded non-missing measurement prior to first study treatment (dose of IMP). If time is not collected but the assessment is performed on the same day as the first study treatment, it would be considered as baseline. If subject does not receive study treatment, baseline is the closest recorded assessment on or prior to the randomization date. Change from baseline at any post-baseline time point will be defined as:

$$Change\ from\ baseline = value\ at\ post\ baseline\ time\ point - value\ at\ baseline$$

8.2 Trial Day 1

Trial Day 1 is defined as the date of first dose of IP. For subjects whose treatment assignment is randomly assigned but not dosed, Trial Day 1 is defined as the date of randomization assignment. For dates prior to Trial Day 1, the Trial Day is calculated as:

$$Trial\ Day = (Date\ of\ Interest/Assessment - Date\ of\ Trial\ Day\ 1)$$

For dates on or post Trial day 1, the Trial Day is calculated as:

$$Trial\ Day = (Date\ of\ Interest/Assessment - Date\ of\ Trial\ Day\ 1) + 1$$

8.3 Loss of Asthma Control (LOAC) Event

A LOAC event is defined as subject meeting any of the following 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 inhaled corticosteroids (ICS; or if ICS has been fully withdrawn, ≥50% of the prescribed ICS dose at baseline)
- Exacerbation of asthma requiring systemic corticosteroids.
- Exacerbation of asthma-related adverse events (AEs) that requires a hospitalization or emergency room visit.

8.4 Visit Windowing

Subjects are expected to attend biweekly site visits from Baseline through the start of ICS Taper and Monotherapy. During the Taper period, subjects will be attending weekly site visits through Week 14.

Table 2: Visit Windowing

	Week	Target Day	Lower Limit	Upper Limit
Baseline		1		
IP as Adjunctive to ICS/LABA	Week 4	Day 29	Day 26	Day 32
	Week 6	Day 43	Day 40	Day 46
LABA withdrawal	Week 8	Day 57	Day 54	Day 60
ICS Taper and Monotherapy	Week 9	Day 64	Day 61	Day 67
	Week 10	Day 71	Day 68	Day 74
	Week 11	Day 78	Day 75	Day 81

	Week 12	Day 85	Day 82	Day 88
	Week 13	Day 92	Day 89	Day 95
	Week 14	Day 99	Day 96	Day 102
Safety Follow-up / Early Termination	Week 16	Day 113	Day 110	Day 116
Extended Follow-Up	Week 20	Day 141	Day 138	Day 144

For each of daily-collected efficacy endpoints post-baseline analysis values for designated analysis visit will be calculated based on periodical average.

Below is the table for summary of periodical average of daily efficacy assessment:

Table 3: Average of Daily Efficacy Assessment:

Time Point	Morning PEF, asthma symptom score	Evening PEF, asthma symptom score	Number of Reliever Bronchodilator use
Week 6 (Day 43)	37 - 43	36 - 42	Diary Day 36 - 42
Week 14 (Day 99)	93 - (Day of EOT)	92 - (Day before EOT)	Diary Day 92 - (Day before EOT)
Week 20 (Day 141)	135 - (Day of Extended FU)	134 - (Day before Extended FU)	Diary Day 134 - (Day before Extended FU)

Note: A Diary Day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. For example, Diary Day 92 includes the evening dairy on day 92 and the morning dairy on day 93.

8.5 Laboratory and Vital Signs

Unless otherwise noted, values for missing safety laboratory and vital sign values will not be imputed. However, a missing baseline result will be replaced with a screening result, if available. If safety laboratory values for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point. If no pre-treatment laboratory value is available, the baseline value will be assumed to be normal (i.e., no grade [Grade 0]) for the summary of graded laboratory abnormalities.

For analyses of laboratory data that are continuous in nature but are less than the lower limit of quantitation (LLOQ) or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (e.g., if the result of a continuous laboratory test is < 30, a value of 29 will be assigned; if the result of a continuous laboratory test is < 30.0, a value of 29.9 will be assigned). If the results of continuous lab test is <1, the imputed value should be 0.9; If the results of the lab test is <0.1, the imputed value should be 0.09. The actual reported values will be provided in by-subject listings.

8.6 Imputation of Missing Dates

In general, no imputation of missing dates will be done except for the imputation of (partially) missing start dates for AEs and prior and/or concomitant medications. If end dates for AEs and prior and/ir concomitant medications are missing, then the assumption is that they are ongoing/continuing treatment. Incomplete dates of medical history will not be imputed.

- If year is missing, the date uncertainty is too high to impute a rational date. Therefore, if year is missing, the imputed start date is set to missing and the event will be assumed as treatment-emergent or concomitant.
- If year is before the year of the treatment start date, then:
  - If month is missing, the imputed start date is set to the mid-year point (i.e., 01JULYYYY).
  - If month is not missing, the imputed start date is set to the mid-month point (i.e., 15MONYYYY).
- If year is equal to the year of the treatment start date, the month needs to be compared against the month of treatment start date to determine the imputation rule to apply. Therefore:
  - If month is missing, then imputed month and day is the same as start of treatment.
  - If month is lower than month of treatment start date and start day is missing, the imputed start date is set to the mid-month point (i.e. 15MONYYYY).
  - If month is equal to month of treatment start date and start day is missing, the start day will be set to the start day of treatment.
  - If month is greater than month of treatment start date and start day is missing, the imputed start date is set to the beginning of the month (i.e., 01MONYYYY)
- If year is greater than the year of the treatment start , then:
  - If month is missing, the imputed start date is set to start of the year (i.e., 01JANYYYY).
  - If month of start date is not missing but start day is missing, the imputed start date is set to the beginning of the month (i.e., 01MONYYYY).
- If after imputation of start and resolution date (see below) a start date is after the resolution date (for example if a missing day of a start date is set to 15 and the resolution date is before the 15th of the same month and year) then the start date will be set to the resolution date.

8.7 Prior and Concomitant Medications

Prior medications are defined as those with a start date prior to the first dose of IMP. Prior medications can be discontinued before first IMP dose or can be ongoing during treatment phase. Medications that start and end prior to the first IMP dose date will be considered as prior medications only.

Medications which start prior to the first dose of IMP and are ongoing at the time of first dose of study drug will be summarized as both prior and concomitant medications.

Concomitant medications are defined as those started with a start date on or after the first dose of IMP.

8.8 Reliever Medication

Subjects may administer albuterol/salbutamol or levalbuterol/levosalbutamol as reliever medication as needed during the study. Salbutamol/albuterol nebulizer and levosalbutamol/levalbuterol nebulizer use will be converted to number of puffs as shown on the following tables:

Table 4: Conversion of Salbutamol/Albuterol to Puffs:

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

*Conversion factor: salbutamol/albuterol nebulizer solution (2.5 mg) corresponds to 4 puffs

Table 5: Conversion of Levosalbutamol to Puffs

Levosalbutamol/Levalbuterol Nebulizer Solution Total Daily Dose (mg)	Number of Puffs*
0.63	2
1.25/1.26	4
1.89	6
2.5/2.52	8
3.15	10
3.75/3.78	12
5/5.04	16

*Conversion factor: levosalbutamol/levalbuterol nebulizer solution (1.25 mg) corresponds to 4 puffs

8.9 Time to LOAC Event

The subject's Time to LOAC Event is derived as:

$$\begin{aligned} &Time\ to\ LOAC\ Event \\ &\quad = Onset\ date\ of\ LOAC\ or\ Censor\ date \\ &\quad - Date\ of\ First\ Dose\ Administration\ Date + 1 \end{aligned}$$

An adjudication committee will be established to determine whether subjects who withdraw from study or discontinue treatment may have had an LOAC event prior to withdrawal or discontinuation. Subjects who do not have a recorded LOAC will be censored at the latest of the following dates: date of withdrawal, date of death or last visit date.

8.10 Asthma Control Questionnaire (ACQ-5)

The shortened version of the ACQ (ACQ-5) used in this trial will be a 5-item questionnaire scoring 5 symptoms on a 7-point scale (0=no problem, 6=problem as bad as it can be). The overall score from the ACQ-5 is the mean of the five responses. The questionnaire is provided in Appendix III of the Protocol.

8.11 Asthma Quality of Life Questionnaire (AQLQ)

The Asthma Quality of Life Questionnaire (AQLQ) is a 32-item questionnaire used to assess the physical, occupational, emotional, and social qualities of adults aged 17 to 70 years with asthma. The AQLQ includes 32 questions grouped into four domains: (1) symptoms, (2) activity limitations, (3) emotional function, and (4) environmental stimuli. Each question is scored on a seven-point scale, which ranges from 7 (no

impairment) to 1 (severe impairment). The overall score is calculated as the mean of all questions. The questionnaire is provided in Appendix II of the Protocol.

9.0 Interim Analyses

No formal interim Analysis is planned for this study.

10.0 Statistical Methods

All analyses will use SAS® version 9.4 or higher. Descriptive summaries will be tabulated by treatment group and overall. Categorical data will be presented using frequency counts and percentages, with the number of subjects in each category as the denominator for percentages. Percentages will be rounded to one decimal place except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts. Continuous data will be summarized using the number of non-missing observations (n), mean, standard deviation (SD), median, minimum, and maximum. Minimum and maximum will be rounded to the precision of the original value. Mean and median will be rounded to 1 decimal place greater than the precision of the original value. The SD will be rounded to 2 decimal places greater than the precision of the original value, up to a maximum of 3 decimal places.

10.1 Subject Disposition

Subject disposition will be summarized by treatment group and overall for:

- Number of subjects screened
- Number of subjects with screen failure, and primary reasons for screen failure
- Number of subjects randomized
- Number (and percentage) of randomized subjects who received at least one dose of study drug
- Number (and percentage) of subjects discontinued from study drug, and primary reason for discontinuation
- Number (and percentage) of subjects discontinued study, and primary reason for discontinuation

By-subject listings of disposition details will also be provided.

Additionally, the analysis populations for safety, per-protocol, and PK will be summarized in a table by number of subjects on the Full Analysis Set.

10.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group and overall using descriptive statistics based on the Full Analysis Set. The following demographic, and baseline characteristics will be summarized:

Demographic characteristics

- Sex (Male, Female),
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Island, White, Other, Unknown, Not Reported)
- Age (years)
- Age group 1 (<45, ≥45 years)
- Ethnicity (Hispanic or Latino, non-Hispanic or Latino, Unknown, Not Reported)

- Region (North America: USA; Europe: Poland, Bulgaria and Czech Republic)
- Body weight (kg)
- Body weight group (<60, ≥60 - <100, ≥100 kg)
- Body mass index (BMI, kg/m^2)
- BMI group (<25, ≥25 - <30, ≥30 kg/m^2)

Baseline disease characteristics

- Background ICS dose level at randomization (medium, high*)

  Medium: total daily dose of fluticasone = 500 or 460 mcg; high: total daily dose of fluticasone = 1000 or 920 mcg
- Age at asthma onset
- Time since first diagnosis of asthma (years) at randomization
- Cigarette Smoking history (Never, Former*), time since cessation of cigarette smoking (years) and smoking quantity in pack-years for former smokers

  * Current smokers are excluded from this study.
- Alcohol drinking frequency (Never, At least monthly, At least weekly and At least daily) and number of standard alcohol drinks on a typical day when drinking (1 or 2, >2)
- Number of asthma exacerbation resulting in Emergency Department (ED) visit within 1 year before screening visit (qualitative variable: 1-3, >3)
- Number of asthma exacerbation resulting in Hospitalizations within 1 year before screening visit (qualitative variable: 1-3, >3)
- Time since last asthma exacerbation (months) at randomization
- Baseline blood eosinophil level (<0.15 x 10^9 /L; 0.15 - <0.3 x 10^9 /L; ≥0.3 x 10^9 /L)
- Baseline spirometry data including FEV1 (L), and percent predicted FEV1
- AM and PM peak expiratory flow (PEF, L/min)
- Asthma Control Questionnaire 5-question version (ACQ-5) score
- Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ[S]) global score
- Number of inhalations of salbutamol/albuterol and levosalbutamol/levabuterol per day
- Hypersensitivity to aspirin (Yes, No)
- Hypersensitivity to nonsteroidal anti-inflammatory drug (NSAID) (Yes, No)
- Baseline FeNO (< 25, ≥ 25 - < 50, ≥ 50 ppb)

By-subject listing of demographics and baseline characteristics will also be provided.

10.3 Medical History

Medical and surgical history events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.1 or above. Coded medical history will be summarized by system organ class (SOC) and preferred term (PT) by treatment group and overall based on the Full Analysis Set. A subject having more than one reported medical diagnosis within the same SOC or PT will be counted only once for that SOC or PT.

All medical history will be presented in a data listing.

10.4 Treatments

10.4.1 Extent of Study Drug Exposure

The following exposure parameters will be summarized by treatment group and overall using descriptive statistics in the Safety Analysis Set:

- Treatment duration (days), defined as the (date of last dose- date of first dose) +1
- The total number of tablets dispensed, defined as the number of bottles dispensed multiplied by 32.
- The total number of tablets returned according to drug accountability from EDC, defined as the number of tablets returned. If a bottle is not returned it will be assumed that no tablets were taken from that bottle
- Planned doses, defined as two tablets for duration of the study
- The total number of tablets taken, which is number of dispensed tablets minus total number of tablets returned.
- Treatment compliance during the treatment period, which will be derived using the following formula:

$$Treatment\ Compliance\ (\%) = 100 * (\frac{Total\ Number\ of\ Doses\ Administered}{Expected\ Number\ of\ Doses\ Administered})$$

The expected number of doses administered is based on the date of first study dose date and the date of last study medication dose. Subjects are expected to administer drug twice daily. Treatment Compliance will be summarized using frequency and percentage at each visit and overall treatment period for the following categories: <80% and ≥80%, <90% and ≥90%, and <120% and ≥120%.

Study drug administration data will also be listed by subject.

10.4.2 Background Therapy

Pre-screening ICS/LABA background therapy will be summarized by treatment group and overall based on the Full Analysis Set.

Compliance rate for the study-specific background therapy will be calculated for each subject. For each day, subject is considered as compliant if the actual dose taken is the same as or greater than the prescribed dose recorded on the eCRF. Compliance rate is defined as the number of days when the subject is compliant divided by the number of days subject stays in the adjunctive background therapy period and the background therapy withdrawal period.

10.4.3 Prior and Concomitant Medications

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.

Prior and concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and PT according to World Health Organization Drug Dictionary (WHO-DD). The number and percent of subjects taking prior and concomitant medications by treatment and overall using ATC class and PT will be summarized separately and then together based on the Safety Analysis Set. Any vaccinations will be

displayed together with the number and percentage of subjects with at least one prior or concomitant vaccination.

10.5 Important Protocol Deviations

Protocol deviations will be reviewed by RAPT and categorized into general deviation categories and classified as whether they are Important. The number and percentage of randomized subjects with any important protocol deviation and the number and percentage of subjects with any important protocol deviation by deviation category will be summarized overall and by treatment. All of the important protocol deviations will be summarized for the Full Analysis Set. A by-subject listing of all protocol deviations will be provided.

Per ICON/PRA processes, important protocol deviations data will be entered into the system of record (PSO). The study team and RAPT will conduct on-going reviews of the deviation data from PSO and the resulting set of randomized subjects throughout the study, adjusting the deviation criteria as seems appropriate. The randomized subjects set must be finalized at the post-freeze data review meeting (or earlier), prior to database lock.

10.6 Efficacy Analyses

10.6.1 Hypothesis Testing Strategy and Multiplicity

As there are only 2 treatment groups and one primary analysis test in this study, no multiplicity correction is necessary. No adjustments will be made in comparing the treatment groups based on the primary and secondary efficacy endpoints.

10.6.2 Primary Estimand

10.6.2.1 Imputation Methods

An adjudication committee will be established to determine whether subjects who withdraw from the study or discontinue treatment may have experienced an LOAC event prior to withdrawal or discontinuation. For subjects discontinued due to a reason other than LOAC, but for which LOAC could be suspected, the case will be medically reviewed, with appropriate queries sent to the respective site, for final determination of LOAC status to be recorded in the clinical database prior to database lock. As such, there should not be missing data for the primary LOAC endpoint. Subjects who were confirmed withdrawn from the study for other reasons will be considered as not experiencing LOAC.

10.6.2.2 Primary Analysis

The primary efficacy endpoint of this study is the proportion of subjects who experience LOAC (as defined in Section 8.3).

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% confidence interval (CI) for the difference. Because subjects who experience an LOAC are discontinued from trial IMP and returned to the background inhaled therapy, no consideration is made for intercurrent events. The primary analysis will be performed on the Full Analysis Set.

Number and percentage of subjects experiencing LOAC events will be summarized by treatment group and overall. The 90% and 95% CI's, Odds Ratios and 90% and 95% CI's for Odds Ratios and p-values will also be presented. A table summarizing the number of subjects experiencing an LOAC by each criterion will be presented by treatment arm and overall. Note that a subject may meet multiple criteria, in which case the earlier qualifying event will be used for analysis.

The SAS code to be used to conduct the analysis is presented below:

```
PROC GENMOD DATA=work;
CLASS usubjid trtp avisitn inhale region;
MODEL outcome = trtp inhale region / DIST=binary LINK=identity;
REPEATED subject=usubjid / type=unstr;
ESTIMATE 'Beta' trtp 1 -1 / EXP;
RUN;
```

Where

USUBJID: Subject ID
TRTP: Planned Treatment
AVISTN: Variable representing visit numbers
OUTCOME: LOAC indicator
INHALE: Pre-screening inhaled ICS + LABA (medium- or high-dose ICS)
REGION: Location of the study site (North America versus Europe)

10.6.2.3 Sensitivity Analyses

- *Sensitivity Analysis 1:* The same primary endpoint of incidence of LOAC will also be analyzed using a logistic regression model. The model will include terms for treatment, pre-screening inhaled ICS + LABA (medium- or high-dose ICS), and location of the study site (North America versus Europe). The odds ratio and corresponding 95% CI and two-sided p-value will be derived from this model.
- *Sensitivity Analysis 2:* The main analysis will be repeated for the per-protocol analysis set.

10.6.2.4 Supplementary Analyses

Additional analyses examining the consistency of the intervention effect by the following subgroups using the Full Analysis Set will be performed. A repeat of the analysis as per Section 10.6.2.2 in the following subgroups will be presented:

- Age group: (<45 vs ≥45 years; < median, ≥ median)
- Sex: (female vs male)
- Region: (North America vs Europe)
- Race (White vs. Non-White)
- Baseline weight (<60, ≥60 - <100, ≥100 kg)
- BMI (<25, ≥25 - <30, ≥30 kg/m^2)
- Background ICS + LABA at Screening: (medium- vs high- dose ICS)
- Baseline blood eosinophil level (<0.15 x 10^9 /L; 0.15 - <0.3 x 10^9 /L; ≥0.3 x 10^9 /L)
- Baseline FEV1 (< median, ≥ median)
- ACQ-5 (≤ 2, >2)
- Number of asthma exacerbation leading to ED Visits or Hospitalizations prior to the study (≤1,>1)
- Smoking history (Former, Never)
- Atopic medical condition (Yes, No)

(A patient is considered to have atopic medical condition if he/she has any of the following condition in his/her medical history: atopic dermatitis, allergic conjunctivitis or rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline total immunoglobulin E (IgE) ≥100 IU/mL.)

- Age at onset of asthma (<12, ≥12 - <18, ≥18 – 40, ≥40 years)
- Baseline predicted FEV1% (< median, ≥median)
- Baseline FeNO (< 25, ≥25- < 50, ≥50 ppb)

Within each subgroup, descriptive statistics including number of subjects and incidence of LOAC will be provided by treatment group. Odds ratio and the corresponding 95% CI for each pairwise comparison will be derived.

10.6.3 Secondary Estimands

The key secondary efficacy analysis of Time to LOAC Event (See Section 10.1.8) will use a stratified log-rank test to compare the hazard rates between the RPT193 and placebo group. A subject without experiencing the event of interest will be considered as censored at date of EOT/Week 14 or the last contact date, whichever occurs earlier. The Kaplan-Meier (K-M) method will be used to estimate and compare the distributions of time to LOAC between treatment groups. Within the LOAC table, the K-M 25th, 50th, an 75th percentile estimate and corresponding 95% CI for median survival will be estimated and displayed by treatment. The Kaplan-Meier figure will be generated; quartiles and point probabilities will be calculated.

Time to LOAC event will also be analyzed using a Cox regression model, which includes treatment, pre-screening inhaled ICS + LABA (medium- or high-dose ICS), and location of the study site (North America versus Europe) as covariates. The analysis will be performed on the Full Analysis Set.

10.6.3.1 Sensitivity analysis

An additional sensitivity analysis will be performed:

- *Sensitivity Analysis 1*: Time to LOAC Event where first missed visit will be imputed as subject experiencing LOAC Event.
- *Sensitivity Analysis 2*: The same analysis will be repeated for the per-protocol analysis set.

10.6.4 Secondary Analyses

Change from baseline in FEV1 at each visit up to Week 14 will be analyzed using a mixed effect model with repeated measures (MMRM) approach. The analysis model will include change from baseline values up to Week 14 as response variable, and treatment, gender, baseline height, pre-screening inhaled ICS + LABA (medium- or high-dose ICS), location of the study site (North America versus Europe), visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction as covariates.

To address any potential effects on FEV1 and obtain as precise a treatment effect estimate as possible, FEV1 values after a LOAC event or initiation of rescue medication will be excluded from primary assessment of the secondary endpoint of FEV1. Inclusion of change from baseline in FEV1 values in the model will follow the rules in Table 6. Data not included in the analysis according to these rules will be set to missing. No imputation will be made for other missing FEV1 measurements.

Table 6 – Data inclusion rules for analyses of secondary and other efficacy endpoints

If subject has	Use data up to
LOAC with rescue medication[a]	last value before start of LOAC
LOAC without rescue medication[b]	value collected at EOT
OCS use without LOAC	last value before start of OCS

neither LOAC or OCS	value collected at Week 14/EOT

a If subject meets at least one of the following three criteria:

- ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared to baseline) on 2 consecutive days
- Increase in ICS ≥4 times the last prescribed ICS dose (or ≥50% of the prescribed ICS dose at V2 if background therapy withdrawal completed)
- Requiring use of systemic (oral and/or parenteral) steroid treatment

b If subject meets none of the three criteria listed above and meets one or both of the following:

- A 30% or greater reduction from baseline in morning PEF on 2 consecutive days
- Requiring Hospitalization or emergency room visit

The MMRM analysis will be based on the restricted maximum likelihood method assuming an unstructured covariance to model the within-subject errors (type=UN). If the unstructured model fails to converge, other structures (Auto Regressive, TOEPLIX) might be explored in post-hoc analyses. A Kenward-Roger approximation will be used for the denominator degree of freedom.

Descriptive statistics including number of non-missing subjects, mean, median, standard error, and least squares (LS) means will be provided for each treatment group. Difference in LS means and the corresponding two-sided 95% CI and p-value will be provided for treatment comparison.

10.6.4.1 Sensitivity analysis

The following sensitivity analyses will be conducted to assess the robustness of the main model:

Analyses using the same MMRM model and estimation methods as specified above:

- *Sensitivity analysis 1*: Inclusion of all observed FEV1 measurements collected up to EOT for all subjects. Missing data will not be imputed.
- *Sensitivity analysis 2*: The same analysis will be repeated for the per-protocol analysis set.

Analyses with imputation for missing FEV1:

- Sensitivity analysis 3: Multiple imputation (MI)

  Missing continuous endpoints of FEV1 will be imputed using the multiple imputation (MI) with analysis of covariance (ANCOVA) model as the primary analysis for time-points at which no value is observed. MI will be performed under missing at random (MAR) assumption. The MI is a simulation-based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets.

  Imputation will be conducted sequentially as the imputation for each visit will incorporate information from prior visits. Specifically, the covariates included are treatment group, gender, baseline height, pre-screening inhaled ICS + LABA (medium- or high-dose ICS), location of the study site (North America versus Europe), baseline value, and change from baseline in FEV1 at all prior visits.

  100 imputations will be performed to generate 100 imputed datasets. For each imputation, the change from baseline in FEV1 at Week 14 will be analyzed by an ANCOVA model with treatment, gender, height, baseline value, pre-screening inhaled ICS + LABA (medium- or high-dose ICS), location of the study site (North America versus Europe) as covariates.

  These completed datasets are then analyzed using valid analysis methods and results combined (averaged) to present one MI result using Rubin's rule.

- Sensitivity analysis 4: Control-based Pattern Mixture Model Multiple Imputation (PMM-IM)

Data collected after the LOAC event or initiation of rescue medication or treatment discontinuation in the RPT-193 arm will be assumed missing not at random (MNAR) and resemble missing data from subjects from the placebo arm who do not discontinue treatment permanently/receive rescue medication. Imputation of missing data will be done using a control-based Pattern Mixture Model Multiple Imputation (PMM-IM) where missing data in the study drug (RPT-193) arm as well as the placebo arm will be imputed from observed data in the placebo arm.

The implementation is similar to that MI approach under MAR above (sensitivity analysis 3), except when fitting the imputation model, only data from the placebo group will be used and treatment will not be included as a covariate.

10.6.4.2 Subgroup analysis

Subgroup analyses of change from baseline in FEV1 will be conducted in the same subgroups as defined for the supplementary analysis for primary endpoint (Section 12.6.3). Within each subgroup, descriptive statistics including number of non-missing subjects, mean, median, standard error, and LS means will be provided for each treatment group. Difference in LS means and the corresponding two-sided 95% CI will also be provided for treatment comparison.

Treatment-by-subgroup interaction at Week 14 and its p-value will be derived from a MMRM model. The model will include change from baseline in FEV1 values up to Week 14 following the rules in Table 6. Treatment, gender, baseline height, pre-screening inhaled ICS + LABA (medium- or high-dose ICS), location of the study site (North America versus Europe), visit, treatment by-visit interaction, baseline value, baseline-by-visit interaction, subgroup (if different from the aforementioned covariates), subgroup-by-treatment interaction and subgroup-by-treatment-by-visit interaction will be the covariates.

Other secondary efficacy endpoints (below) will be analyzed using the MMRM approach described above. Inclusion of data will follow the rules listed in Table 6. The covariates will be treatment, pre-screening inhaled ICS + LABA (medium- or high-dose ICS), location of the study site (North America versus Europe), visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction. Gender and baseline height will also be included in the model for spirometry endpoints (PEF, FeNO). No imputation will be performed on missing values.

Descriptive statistics including number of subjects, mean, median, standard error, and LS means will be provided for each treatment group. Difference in LS means and the corresponding 95% CI and p-value will be provided for treatment comparison.

- Change in ACQ-5 at Week 14 compared to Baseline
- Change in PEF at Week 14 compared to Baseline
- Change in Reliever Bronchodilator Use at Week 14 compared to Baseline
- Change in FeNO at Week 14 compared to Baseline
- Change in AQLQ at Week 14 compared to Baseline

A responder analysis will also be performed for ACQ-5 and AQLQ(S) endpoints, where responder status is determined based only on data included according to the rules in Table 6. The responder analysis of ACQ-5 and AQLQ(S) will be further categorized as below and summarized:

1) Subjects with change from baseline in ACQ-5 ≤ -0.5 will be considered as subjects with the minimal clinically important differences (MCID). For each post-baseline visits:

   - Percent of subjects meeting the MCID of a decrease in ACQ-5 score of at least 0.5 (change from baseline in ACQ-5 ≤ -0.5)

   - Percent of subject who do not meet the MCID of a decrease in ACQ-5 of at least 0.5 (change from baseline in ACQ-5 > -0.5 or missing)

2) Subjects with change from baseline in AQLQ(S) global score ≥ 0.5 will be considered as subjects with the minimal clinically important differences (MCID). For each post-baseline visits:

   - Percent of subjects meeting the MCID of an increase in AQLQ(S) global score of at least 0.5 (change from baseline in AQLQ(S) global score ≥ 0.5)

   - Percent of subject who do not meet the MCID of an increase in AQLQ(S) global score of at least 0.5 (change from baseline in AQLQ(S) global score < 0.5 or missing)

A logistic regression model will be used to compare the percentage of responders with MCID at Weeks 6, 8, 10, 12, and 14 for ACQ-5 and AQLQ(S) overall scores. At each time point, the model will include treatment, baseline score, pre-screening inhaled ICS + LABA (medium- or high-dose ICS), and location of the study site (North America versus Europe). Odds ratio, the corresponding 95% CI and p-value will be derived for each treatment comparison. Descriptive statistics including number and percentage of responders will also be provided.

By-subject listings of each secondary efficacy endpoint will also be provided.

10.6.5 Exploratory Analyses

The below Exploratory Analyses will be summarized descriptively by treatment group and overall.

- Change in FEV1 from Day 99 to 141 (Weeks 14 to 20).
- Change in FEV1 from Day 43 to 99 (Weeks 6 to 14).
- Change in ACQ-5 from Day 99 to 141 (Weeks 14 to 20).
- Change in ACQ-5 from Day 43 to 99 (Weeks 6 to 14).
- Proportion of subjects who continue without inhaler therapy between Day 99 to 141 (Weeks 14 to 20).
- Proportion of subjects with lower dose of ICS/LABA at Day 141 (Week 20) compared to baseline.

By-subject listings of each exploratory efficacy endpoint will also be provided.

10.7 Safety Analyses

Safety analyses will be performed using the Safety Analysis Set with the actual treatment received. The analysis of safety endpoints will include treatment-emergent adverse events (TEAE) which are defined in the protocol 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 (Period 2 to 5). Pre-treatment AEs are AEs that developed, worsened or became serious during the screening and run-in periods (Screening + Period 1). Post-treatment AEs are AEs that developed, worsened or became serious during the post-treatment period (6-weeks Follow-up).

Also included in safety analyses are clinical laboratory test results, vital signs, and electrocardiogram (ECG) results. All safety analyses will be summarized by treatment group and overall using descriptive statistics.

10.7.1 Adverse Events

TEAEs will be coded using the MedDRA Version 24.0 or above). Severity and causality of TEAE will be evaluated by the investigator. Severity of TEAE will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version X.X. Incomplete start and end date of the TEAE will be imputed as described in Section 10.1.6.

Subjects with multiple incidents of events for a given PT and SOC will be counted only once. Similarly, if subject experiences multiple incidents of events for a given PT and SOC, the worst severity will be used in the summaries presenting severity, and the worst causality to study drug will be used in the summaries presenting causality, respectively.

Any missing severity will be queried for completion. If the severity is still missing in the final data and the outcome of AE is death, then it will be deemed as Grade 5, and if the life-threatening is marked, then it will be deemed as Grade 4. Otherwise, the severity still missing in the final data will be deemed Grade 3.

Any missing causality will also be queried for completion, and any events that still have missing causality in the final data will be deemed as 'Related'.

The imputed severity and relationship will be used in table summary, but the original value will be maintained as missing in the by-subject listing.

TEAE summaries will be sorted in terms of decreasing frequency by SOC, and PT within SOC, in the overall group, and then alphabetically for SOC, and PT within SOC if there are any ties in frequency.

TEAE summary tables will be provided by system organ class (SOC) and preferred term (PT) for subjects with

- any TEAE
- TEAE by maximum severity
- any TEAE occurring more than 5% of subjects (in all groups)
- any severe TEAE
- any treatment-related TEAE
- any TEAE with outcome of death
- any serious TEAE (SAE)
- any treatment-related serious TEAE (SAE)
- any TEAE leading to the discontinuation of trial treatment
- any TEAE leading to discontinuation from the trial
- any TEAE leading to interruption of trial treatment

An overall summary of TEAEs will be provided and will include summaries of the above TEAE categories and by treatment group and overall.

By-subject listings of corresponding AEs summary will also be provided.

10.7.2 Adverse Event of Clinical Interest (AECI)

The TEAEs of clinical interest are defined as:

- Malignancy
- Major adverse cardiac events (MACE)
- Tuberculosis (TB)
- Inflammatory bowel disease (IBD)
- Depression and suicidal ideation and behavior
- Serious or opportunistic infection
- Hypersensitivity reactions

Overall summary of AECIs will be provided and by treatment group. The TEAEs of clinical interests will be summarized using frequencies and percentages by SOC and PT.

By-subject listings will also be provided for all AECIs.

10.7.3 Laboratory Data

Central laboratory results will be reported and summarized using International System (SI) of units. The parameters within each panel are outlined in section 5.3.2 Table 3 of the trial protocol, and lab panels for hematology, serum chemistry, and urinalysis will be included.

Continuous test results for each parameter and changes from baseline will be summarized at each visit by treatment and overall using descriptive statistics. Categorical test results for each parameter will be summarized at each visit by treatment and overall using frequencies and percentages.

For labs that are retested at unscheduled visits, the following will be performed. Baseline is defined as the last recorded non-missing measurement prior to first study treatment, so if an unscheduled retest of lab data is performed closer to the Baseline target date (Day 1), then the retests taken during the unscheduled visit will be considered baseline results. For post-baseline visits, if the labs taken during scheduled visits are not available and results for unscheduled visits are available and unscheduled visit is within visit window, then lab results at unscheduled visit will be presented. If both scheduled visit and unscheduled visit results are available and within window then unscheduled visit results will be presented. If both scheduled visit and unscheduled visits are available but unscheduled visit is not within visit window then only scheduled visit will be considered for analysis.

Shift tables (i.e., low, normal, high at baseline versus low, normal, high at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from baseline to follow-up result at each scheduled follow-up visit. Shift tables showing the shift in laboratory values from baseline toxicity grade (0-4) to worst post-baseline toxicity grade will also be presented by lab panel and parameter. Lab results from unscheduled visits will be included in the shift tables. The counts and percentage of participants with each of the 9 possible “shift” outcomes will be calculated by treatment group.

Lab abnormalities are recorded as an AE or SAE if they meet the definition of an AE or SAE, per protocol.

By-subject listings of laboratory parameters will also be provided.

10.7.4 Vital Signs

Vital signs assessments include weight, BMI, heart rate, respiration, systolic and diastolic blood pressure. Measurements at each scheduled visit and changes from baseline will be summarized at each visit by treatment group and overall using descriptive statistics. All subjects’ vital signs data will be provided in a listing. Vital signs from unscheduled visits will not be included in the summary tables and will be included in the listing.

Vital signs that are associated with signs and/or symptoms are recorded as an AE or SAE if they meet the definition of an AE or SAE, per protocol.

10.7.5 ECGs

For all continuous ECG parameters, results at each scheduled visit and changes from baseline will be summarized by treatment group and overall using descriptive statistics. ECG results from unscheduled visits will not be included in the summary tables. Results collected in triplicate will have the mean of the measurements summarized.

All subject ECG data captured will be provided in a listing by treatment group, subject, and time point. ECG interpretation as determined by the investigator will be listed by treatment arm and will include ECG categorized as Normal, Abnormal not clinically significant, and Abnormal clinically significant. ECG data from unscheduled visits will be included in the listing.

ECG results that are associated with signs and/or symptoms are recorded as an AE or SAE if they meet the definition of an AE or SAE, per protocol.

10.7.6 Physical Examinations

The highest elevation of liver analyte parameters of interest at any post baseline visit will be summarized by treatment group. Incidence rates per 100 patient exposure year will be summarized by treatment groups at specific elevation levels above the Upper Limit of Normal (ULN). Risk Difference and 95 % CI's will also be summarized and presented between the treatment groups at each specific level of ULN.

A DILI scatterplot comparing highest level of any post baseline visit of total Bilirubin vs highest level of any post baseline visit of total ALT or AST (whichever is higher) will be presented and summarized in a summary table. Data for liver analyte parameters of interest will also be provided in a datalisting. Subjects excluded from the DILI scatterplot will also be listed out with reason for exclusion.

10.7.7 Liver Function

The complete physical examination will be conducted at Screening. Physical examinations will consist of 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.

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

Abnormal findings will be summarized by counts and percentages at each assessment timepoint by treatment group and overall. All data will be provided in a data listing. Abnormal physical examination findings will also be presented in a by-subject listing.

10.8 Pharmacokinetic (PK) Endpoints

Blood samples will be collected at timepoints noted in the schedule of assessments. The concentration of RPT193 will be determined using a validated assay by designated third party vendors.

PK Endpoints and details of PK analysis will be provided in a separate PK SAP.

11.0 References

See section 16 of the trial protocol.

12.0 Glossary of Abbreviations

Glossary of Abbreviations:	
ACQ	Asthma Control Questionnaire
AE	Adverse event
AQLQ	Asthma Quality of Life Questionnaire
ATC	Anatomic Therapeutic Classification
BMI	Body Mass Index
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of Variance
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
FAS	Full Analysis Set
FeNO	Fractional exhaled Nitric Oxide
FEV1	Forced Expiratory Volume at 1 second
ICS	Inhaled Corticosteroids
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
LABA	Long Acting Beta 2 Agonist
LOAC	Loss of Asthma Control
PD	Pharmacodynamic
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
QoL	Quality of Life
SAP	Statistical Analysis Plan
SABA	Short Acting Beta 2 Agonist
SAE	Serious Adverse Event
SD	Standard Deviation
SI	International System
SOC	System Organ Class

TEAE	Treatment Emergent Adverse Event

13.0 Approvals

[redacted]

14.0 Document History

Version Date	Modified / Reviewed By	Brief Summary of Changes
0.1	[redacted]	
0.2		
0.3		
1.0		

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Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
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ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

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