RAPT Therapeutics, Inc.
Protocol #: RPT193-02

A Phase 2 Study to Evaluate the Efficacy and Safety of RPT193 as Monotherapy in Adults with Moderate-to-Severe Atopic Dermatitis

Statistical Analysis Plan

Version 1.1

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Approved by:

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List of Abbreviations

Definition	Abbreviation
Analysis Of Covariance	ANCOVA
Anatomical-Therapeutic-Chemical	ATC
Asthma Control Questionnaire	ACQ-5
Atopic Dermatitis	AD
Atopic Dermatitis Sleep Scale	ADSS
Body Mass Index	BMI
Body Surface Area	BSA
Confidence Interval	CI
Dermatology Quality Of Life Index	DLQI
Eczema Area Severity Index	EASI
Electrocardiogram	ECG
Electronic Case Report Forms	eCRF
Electronic Diary	e-Diary
Full Analysis Set	FAS
Inflammatory Bowel Disease	IBD
Last Observation Carried Forward	LOCF
Least Square	LS
Markov Chain Monte Carlo	MCMC
Medical Dictionary For Regulatory Activities	MedDRA
Missing Not At Random	MNAR
Multiple Imputation	MI
Orally Once Daily	QD
Pain Numeric Rating Scale	Pain NRS
Patient Global Assessment	PtGA
Patient-Oriented Eczema Measure	POEM
Peak Pruritus Numerical Rating Scale	PP-NRS
Per-Protocol	PP
Pharmacodynamic	PD
Pharmacokinetic	PK
Preferred Term	PT
Scoring Atopic Dermatitis	SCORAD
[redacted]	
Statistical Analysis Plan	SAP
System Organ Class	SOC
Table, Listing And Figures	TLF
Treatment Failure	TF
Treatment-Emergent AEs	TEAE
Tuberculosis	TB
Validated Investigator Global Assessment	vIGA
Visual Analog Scale	VAS
World Health Organization Drug Dictionary	WHO-DD

I. Introduction

A. Background

RPT193-02 is designed to assess the efficacy and safety of multiple dose levels of RPT193 in subjects with moderate-to-severe atopic dermatitis (AD). This randomized, double-blind, placebo-controlled study will compare 3 dose levels of RPT193 to placebo with a treatment duration of 16 weeks. Investigational product will be administered as monotherapy for AD in adult subjects who have had an inadequate response to topical medications for AD (e.g., corticosteroids) or who are otherwise unable to take topical medications. Maximum clinical benefit in the 4-week Phase 1b (RPT193-01) trial was observed 2 weeks after cessation of treatment and suggested that RPT193 may have therapeutic effects beyond the dosing period. Thus, after completion of treatment at 16 weeks, subjects will continue to be followed for an additional 8 weeks to understand whether further improvement in clinical parameters and/or sustained responses are observed beyond the treatment period. The data generated during the current study will contribute to efficient and appropriate design of future clinical studies, including pivotal studies with RPT193 in subjects with AD.

The protocol for Study RPT193-02 describes the general approach to analysis of data from the study. This analysis plan describes additional details needed to complete such an analysis.

B. Statistical Analysis Plan Scope

This Statistical Analysis Plan (SAP) is based on Protocol RPT193-02 Amendment v2.0. (dated 07 July 2023) and electronic Case Reports Form (eCRF) casebook version 4.0.

This SAP will govern the analysis of data from this study. The plan may be modified until the time of treatment unblinding. Any deviations from the analysis plan, including any after the time of treatment unblinding, will be documented as such in the study report.

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 and will be described in a separate analysis plan.

C. Changes to Planned Analyses from Protocol

The following changes or additions to the planned analyses described in the protocol are noted:

- In Protocol Amendment v2.0, the randomization list is stratified based on region (North America vs. rest of world), baseline vIGA scores (vIGA of 3 vs. 4), and prior dupilumab or tralokinumab use (yes or no). It was later determined that no subjects will be recruited from rest of the world, and therefore stratifying by region in randomization will no longer be required. The existing randomization master list including region as a stratification factor will not be modified or replaced. Any strata related to rest of world region will be disregarded by the IWRS in assigning randomized treatment. All statistical analyses will be adjusted to align with this change by removing region as a stratification factor as applicable.

- Subgroup analysis by pretreatment CCL17/22 levels as required by the protocol is

[redacted] ([redacted]) not included in this SAP. This analysis will be covered by a separate analysis plan for PD data.

II. Protocol Objectives and Study Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of RPT193 administered orally once daily (QD) for 16 weeks to subjects with moderate-to-severe AD.	• % change in Eczema Area Severity Index (EASI) from baseline at Week 16.
• To evaluate the safety and tolerability of RPT193 administered orally QD for 16 weeks.	• Incidence of treatment-emergent adverse events.
Key Secondary	

• To evaluate the efficacy of RPT193 administered orally QD for 16 weeks to subjects with moderate-to-severe AD.	• % of subjects achieving a Validated Investigator Global Assessment (vIGA) score of 0 or 1 at Week 16. • % of subjects achieving EASI-75, defined as a 75% reduction in EASI from baseline to Week 16.
• To evaluate the efficacy of RPT193 administered orally QD for 16 weeks to subjects with moderate-to-severe AD on subject reported symptoms associated with AD. Itch peak pruritus numerical rating scale (PP-NRS).	• % change from baseline in PP-NRS from an itch daily e-Diary at Week 16.
Secondary	
• To evaluate the efficacy of RPT193 administered orally QD for 16 weeks to subjects with moderate-to-severe AD. • To evaluate the efficacy of RPT193 administered orally QD for 16 weeks to subjects with moderate-to-severe AD on subject reported symptoms associated with AD.	• % of subjects achieving EASI-50, defined as a 50% reduction in EASI from baseline to Week 16. • % of subjects achieving EASI-90, defined as a 90% reduction in EASI from baseline to Week 16. • % of subjects achieving at least 2-point reduction in vIGA score from baseline to Week 16. • % of subjects achieving EASI-75 from baseline to Week 2, 4, 8, and 12. • % of subjects achieving EASI-50 from baseline to Week 2, 4, 8, and 12. • % of subjects achieving EASI-90 from baseline to Week 2, 4, 8, and 12. • % of subjects achieving at least 2-point reduction in vIGA score from baseline to Week 2, 4, 8, and 12. • Time to achieving EASI-75 from baseline. • Time to achieving EASI-50 from baseline. • Time to achieving EASI-90 from baseline. • Change from baseline PP-NRS from an itch daily electronic Diary (e-Diary) at Week 16. • For subjects with baseline PP-NRS ≥4: o % of subjects achieving ≥4-point reduction in PP-NRS from baseline at Week 2, 4, 8, 12, and 16. o Time to achieving ≥4-point reduction in PP-NRS from baseline. • For subjects with baseline PP-NRS ≥3: o % of subjects achieving ≥3-point reduction in PP-NRS from baseline at Week 2, 4, 8, 12, and 16. o Time to achieving ≥3-point reduction in PP-NRS from baseline.
Exploratory (Clinical)	
• To evaluate the clinical efficacy of RPT193 administered orally QD for 16 weeks to subjects with moderate-to-severe AD.	• % change in SCORing Atopic Dermatitis (SCORAD) from baseline at Week 2, 4, 8, 12, and 16. • % change in Body Surface Area (BSA) of AD affected AD from baseline at Week 2, 4, 8, 12, and 16.

• To evaluate the efficacy of RPT193 administered orally QD for 16 weeks to subjects with moderate-to-severe AD on subject reported symptoms associated with AD.	• Change from baseline to Week 16 in: ○ Sleep quality (visual analog scale [VAS] from SCORAD) ○ Patient-oriented eczema measure (POEM) ○ Dermatology Quality of Life Index (DLQI) ○ Skin pain NRS ○ Patient global assessment (PtGA). ○ Atopic dermatitis sleep scale (ADSS) [redacted] ○ Asthma Control Questionnaire (ACQ-5) (in subjects with a history of asthma) • % of subjects achieving a PtGA score of 0 or 1 and a ≥2 point reduction from baseline at Week 2, 4, 8, 12, and 16.
• To evaluate the efficacy of RPT193 administered orally QD for 16 weeks to subjects with moderate-to-severe AD in subject subpopulations.	• % change in EASI in the following subgroups: ○ Prior treatment with dupilumab or tralokinumab (Yes or No) ○ Baseline EASI score of <21 or ≥21 ○ Baseline %BSA of AD affected skin <50% or ≥50% ○ Baseline vIGA score (3 or 4) ○ Age group ○ Race ○ Ethnicity ○ Pretreatment CCL17 levels ○ Pretreatment CCL22 levels.
• Explore durability of treatment effect in those who have demonstrated an objective response at Week 16.	• Proportion of subjects maintaining EASI-50 at Weeks 18, 20, 24 among those achieving an EASI-50 at Week 16 and not receiving rescue therapy from Week 8 to Week 16. • Proportion of subjects maintaining EASI-75 at Weeks 18, 20, 24 among those achieving an EASI-75 at Week 16 and not receiving rescue therapy from Week 8 to Week 16. • Proportion of subjects maintaining EASI-90 at Weeks 18, 20, 24 among those achieving an EASI-90 at Week 16 and not receiving rescue therapy from Week 8 to Week 16. • Proportion of subjects maintaining a vIGA score of 0 or 1 at Weeks 18, 20, 24 among those achieving a vIGA score 0 or 1 at Week 16 and not receiving rescue therapy from Week 8 to Week 16.

• Explore the durability of the treatment effect after cessation of treatment at Week 16.	• % change in EASI at Weeks 18, 20, and 24 compared to Week 16 among those not receiving rescue therapy from Week 8 to Week 16. • % change in SCORAD at Weeks 18, 20, and 24 compared to Week 16 among those not receiving rescue therapy from Week 8 to Week 16.
Exploratory (Pharmacokinetic)	
• To evaluate the PK of RPT193 following administration of multiple oral doses of RPT193 administered orally QD for 16 weeks to subjects with moderate-to-severe AD.	• PK parameters at Week 2, 4, 8, 12, 16, and 18.

A. Estimand

The main estimands associated with the primary and key secondary endpoints to support regulatory decisions are described in the following table:

Attribute	Description
Treatment	RPT 193-02 (50mg, 200mg, 400mg) and Placebo
Population	Adult subjects with moderate-to-severe AD as defined by the inclusion/exclusion criteria
Endpoint	**Primary Endpoint** • **%** change in Eczema Area Severity Index (EASI) from baseline at Week 16 **Key Secondary Endpoints** • % of subjects achieving a Validated Investigator Global Assessment (vIGA) score of 0 or 1 at Week 16 • % of subjects achieving EASI-75, defined as a 75% reduction in EASI from baseline to Week 16 • % change from baseline in PP-NRS from an itch daily e-Diary at Week 16.
Intercurrent Events	• **Early termination of study treatment:** Subjects who discontinue from the study treatment prior to Week 16 will be analyzed by the treatment policy strategy, i.e., all data collected after termination of study treatment but prior to rescue medication will be included in the analysis. Missing post discontinuation values will be imputed according to details provided below. • **Use of rescue medications**: Subjects who use rescue medication during the 16-week treatment period will be analyzed by the hypothetical strategy. All EASI/vIGA/PP-NRS scores collected after the start of rescue medication will be set to missing. The missing data after the use of rescue medication will be imputed to follow a similar profile as the placebo group.
Population-level Summary	**Primary Endpoint** • Difference in mean percent change from baseline in EASI score between each RPT193 dose and placebo at Week 16. **Key Secondary Endpoints** • Difference in percentage of subject achieving vIGA of 0 or 1 between each RPT193 dose and placebo at Week 16. • Difference in percentage of subject achieving EASI-75 between each RPT193 dose and placebo at Week 16. • Difference in mean percent change from baseline in PP-NRS

[redacted]	between each RPT193 dose and placebo at Week 16.

III. Study Design

A. Design Overview

RPT193-02 is a randomized, double-blind, dose-ranging study in adults with moderate-to-severe AD who have had an inadequate response to topical therapies or in whom topical therapies are contraindicated with a treatment duration of 16 weeks (112 days).

Approximately 268 subjects who meet eligibility criteria and consent to participate in the study are randomly assigned in a 1:1:1:1 ratio to one of four treatment groups:

- RPT193 50mg once daily
- RPT193 200mg once daily
- RPT193 400 mg once daily
- Placebo once daily

A subject is considered to have completed the study if he/she has completed all phases of the study including a 35-day maximum screening period (Week -5 to Day -1), a 16-week double-blind treatment period (Day 1 to Week 16) and an 8-week follow-up period (Week 16 to Week 24).

B. Study Population

1. Inclusion Criteria

Adult subjects with moderate-to-severe AD are eligible to be included in the study only if all 17 criteria were met according to the protocol.

2. Exclusion Criteria

Adult subjects with moderate-to-severe AD are excluded from the study if any of the 35 criteria were met according to the protocol.

C. Sample Size Predictions

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Based on the assumptions above and using a two-sample t-test, a sample size of 60 subjects per treatment group is needed to detect the treatment effect on the primary endpoint between RPT193 and placebo. Assuming a 10% drop out rate, a total sample size of 268 subjects (67 per treatment group) will be needed.

D. Treatment Randomization

In all parts of the study, randomization will occur prior to first dosing, at the Day 1 visit. Approximately 268 subjects will be randomized 1:1:1:1 to one of 4 groups (3 dose levels of RPT193 or placebo). In total and accounting for a dropout rate of 10%, approximately 60 subjects are anticipated to complete the study in each group.

A randomization list will be generated using validated software. The randomization list will be kept secured until the study blind is broken at the end of study.

The randomization list is stratified based on baseline vIGA scores (vIGA of 3 vs. 4) and prior dupilumab or tralokinumab use (yes or no). The list is uploaded into an Interactive Web Response System (IWRS) and the Investigator or designee will be able to acquire a randomization number for eligible subjects by connecting to the IWRS.

E. Assessment Schedule

Refer to Appendix 1 for the schedule of assessments.

IV. General Analytical Considerations

A. Data Sources

All information requested in this protocol will be recorded on the electronic Case Report Forms (eCRFs) or external source (or via other data collection methods, eg, electronic laboratory data transfer or patient questionnaire data).

B. Definitions

Baseline
Unless otherwise specified, Baseline is defined as the last non-missing assessment prior or equal to the date and time of the first administration of study treatment. In the case where the last non-missing assessment and the first administration of study drug coincide and time of measurement is not available, that measurement will be considered Baseline unless the assessment was scheduled to be post-dose in the protocol.

Change from baseline/Week 16
Change from baseline is defined as the post-baseline value minus the baseline value, unless specified otherwise. Percent change from baseline = (Change from Baseline/Baseline) x 100.

Change from Week 16 is defined as the post-baseline value minus the Week 16 value, unless specified otherwise. Percent change from Week 16 = (Change from Week 16 /Week 16) x 100.

Study Day 1
Study day 1 is defined as the date of randomization for untreated randomized subjects, or the date of first administration of study treatment for treated subjects.

Study Day
Study day is calculated relative to date of Day 1 as following:

- Study Day = (date of event –date of first dose) + 1 if the date of the event is on or after the randomization date or date of first dose.
- Study Day = (date of event – date of first dose) if the date of the event is prior to the randomization date or date of first dose.

C. Analysis Windows

Efficacy assessments that are collected at scheduled visits as defined in the protocol will be analyzed according to their windowed visits defined by actual study day. Unscheduled visits will not be used in the analysis if a scheduled visit is available and the scheduled visits fall into the their corresponding analysis windows. Unscheduled visit will be used in the analysis only if the scheduled visit is not available or none of the scheduled visits are fall into the corresponding analysis windows.

If more than one assessment occurs within a single visit window, then the analysis will take the one closest to the target day. If assessments are equidistance to the target day, then earliest assessment will be selected.

The following efficacy visit windows will apply to all efficacy data except for PP-NRS, Pain NRs or ADSS:

Visit	Week	Target Study Day	Efficacy Assessment Windows (Inclusive)
2	Baseline	1*	-35 to 1
3	Week 2	15	2 to 21
4	Week 4	29	22 to 42
5	Week 8	57	43 to 70
6	Week 12	85	71 to 98
7	Week 16	113	99 to 119
8	Week 18	127	120 to133
9	Week 20	141	134 to 154
10	Week 24	169	155 to 172

*Note: Day of last non-missing assessment prior or equal to the date and time of the first administration of study treatment

PP-NRS, Pain NRS and ADSS are collected daily throughout the study. These efficacy endpoints will be analyzed according to their windowed weekly assessments defined by actual study day.

For the continuous assessments of PP-NRS, Pain NRS, and ADSS item 2, if there are at least three non-missing results collected within the weekly analysis window, the average of these assessments will be used for the analysis. Otherwise, the assessment will be considered missing.

For the categorical ADSS item 1 and 3, if there are at least three results collected within the weekly analysis window, the worst assessment within the weekly analysis window will be used for analysis purposes. The worst assessment will be order from best to worst as 0 ("not at all") to 4 ("very difficult"). Otherwise, the assessment will be considered missing.

The following weekly efficacy visit window will be applied for PP-NRS, Pain NRS and ADSS:

Weekly Analysis Visit	Efficacy Assessment Windows (Inclusive)
Baseline	1*
Week 1	2 to 8
Week 2	9 to 15
Week 3	16 to 22
Week 4	23 to 29
Week 5	30 to 36
Week 6	37 to 43
Week 7	44 to 50
Week 8	51 to 57
Week 9	58 to 64
Week 10	65 to 71
Week 11	72 to 78
Week 12	79 to 85
Week 13	86 to 92
Week 14	93 to 99
Week 15	100 to 106
Week 16	107 to 113
Week 17	114 to 120
Week 18	121 to 127
Week 19	128 to 134
Week 20	135 to 141
Week 21	142 to 148
Week 22	149 to 155
Week 23	156 to 162
Week 24	163 to 169

*Note: Day of last non-missing assessment prior or equal to the date and time of the first administration of study treatment

D. Missing Data

1. Missing Dates

Unless stated otherwise as below, missing dates will not be replaced with imputed values. The sections below will address how missing dates will be handled for the analyses.

Missing or Partial Adverse Events, Medications and Procedure start or stop date:

For partial start dates:

- If the year is unknown, no imputation will be performed, and the event will be

assumed as treatment-emergent or concomitant.

- If the year is known and the month and day are unknown, then:
  - If the year matches the year of the first dose date, then impute the month and the day the same as first dose date.
  - If the year is not the same year of the first dose, then month and day will be imputed as 01 January.
- If the month and year are known and the day is unknown, then:
  - If the month and year match the month and year of the first dose date, then impute the day the same as first dose date.
  - If year and month are not the same as the first dose date, then the day will be imputed as "01".

For partial end-dates:

- If the year is missing, no imputation will be performed, and the event will be assumed as ongoing.
- If the year is present and both month and day are missing and the year is not the same as the last study date (including date of last visit or lost to follow-up date if early terminated), then the month and day will be imputed as the last day of the year, 31 December.
- If the year is present and both month and day are missing and the year is the same as the last study date (including date of last visit or lost to follow-up date if early terminated), then the month and day will be imputed as the last study date.
- If the year and month are present and only the day is missing, and the year and month is not the same as the last study day (including date of last visit or lost to follow-up date if early terminated) then the day will be imputed as the last day of the month.
- If the year and month are present and only the day is missing, and the year and month is the same as the last study day (including date of last visit or lost to follow-up date if early terminated) then the day will be imputed as the last day of the study.

If the imputed end date is before the corresponding start date, then the end date will be set to the start date.

If a subject died during the study and date of death is missing, then it will be set to the end of study date.

2. Missing EASI, vIGA and PP-NRS

Missing data will be imputed for the primary and secondary endpoints, which includes the composite EASI score, vIGA and PP-NRS for the 16-week treatment period. Assessment after the use of rescue will be set to missing prior to any imputation. No imputation is planned for the follow-up period. The following missing data techniques will be utilized:

Last Observation Carried Forward (LOCF): All missing data up to Week 16 will be imputed by the last observed value carried forward for any subsequent missing values. For patients with only baseline value, the baseline value will be carried forward to Week 16. This will be applied to the continuous endpoints of composite EASI score and PP-NRS.

Worst Observation Carried Forward (WOCF): All missing data up to Week 16 will be imputed by the worst observed value carried forward for any subsequent missing values. For patients with only baseline value, the baseline value will be carried forward to Week 16. This will be applied to the continuous endpoints of composite EASI score and PP-

NRS.

Treatment Failures (TF): All missing binary endpoint data up to Week 16 will be imputed as failure. This will be applied to key secondary binary endpoints of EASI-75, responder and vIGA score of 1 or 0, and other secondary endpoints of EASI-50, EASI-90, at least 2-point reduction in vIGA, at least 3-point/4-point reduction PP-NRS.

Observed Cases (OC): No missing data will be imputed. All observed data will be included. To reiterate, data after the rescue medication will be set to missing.

Multiple Imputation (MI) under MAR: Missing continuous endpoints of EASI, and PP-NRS 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.

For the EASI assessment, all missing scheduled visits as outlined in the protocol will be imputed. For the PP-NRS assessment, all missing weekly visits will be imputed.

The missing EASI, and PP-NRS values will be imputed 100 times to generate 100 complete data sets by using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS PROC MI procedure. The example code can be found in Appendix II.

100 imputed datasets will be generated following the 2 steps below:

1. The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure. The monotone missing pattern means that if a subject has missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the subject.

2. The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with adjustment for covariates including treatment groups, the randomization stratification factors of baseline vIGA score (3,4), and prior dupilumab or tralokinumab use (yes or no), and relevant baseline value.

These completed datasets are then analyzed using standard analysis methods and results combined (averaged) to present one MI result.

Control-based PMM-MI procedures for EASI, PP-NRS, and vIGA under MNAR

Similar to MI under MAR, but for EASI, PP-NRS, and vIGA, data collected after the intercurrent events of rescue medication or treatment discontinuation in the RPT193 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 at Week 16 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 intermittent missing data will be imputed separately for each treatment group using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS PROC MI procedure. 100 imputed datasets will be generated.

For each of the 100 datasets a monotone missing data pattern will be achieved. The monotone missing values will then be imputed from subjects in the placebo group using the SAS PROC MI procedure with MNAR statement. This assumes that the missing data will follow a similar profile as the placebo group.

After the completion of the imputation, the assessments collected after the discontinuation of study treatment yet before to the use of rescue medication will be restored. The example code can be found in Appendix II.

The categorical secondary endpoints will be derived from the imputed scores in each MI datasets.

E. Multiple Study Centers

The primary and key secondary efficacy analyses will not include study sites as a factor. The impact of site or geographical location will be done as a sensitivity analysis. In the event some sites have small enrollment numbers, smaller sites may be pooled for the analysis geographically. The determination of the pooled sites will be defined prior to the database lock.

F. Timing of Analyses

No formal interim analysis of efficacy is planned. The efficacy analysis including the primary and key secondary endpoints is scheduled to be conducted after the last subject has completed treatment [Week 16] (or discontinued, whichever is sooner). This analysis will be provided to a limited group of unblinded RAPT team members. No subject level data will be provided.

The data cut-off for the primary analysis of efficacy will occur when all randomized subjects have completed the Week 16 (Day 113) efficacy evaluations (or discontinued, whichever is sooner). The primary evaluation of safety and additional efficacy data will be performed when all randomized subjects have completed the end of study (EOS) (Week 24) safety evaluation (or discontinued, whichever is sooner) and the database is locked.

To avoid any potential bias due to subjects still enrolled in the study at the time of the primary efficacy analysis, an unblinded team member at IQVIA Biotech will provide the analysis to a designated unblinded sponsor role. All blinded team members will maintain the blind until the end of the study and the database is locked.

G. Multiple Comparisons

For the primary efficacy endpoint of percent change from baseline in EASI at Week 16, to preserve the Type I error at 0.05, a serial gatekeeping strategy will be employed to address the multiplicity of the pairwise comparison of each RPT193 dose group vs. placebo. The order of the testing will be performed from the RPT193 400mg, 200mg to 50mg. Dose comparisons for percent change from baseline in EASI at Week 16 will stop when non-significance (2- sided p-value ≥ 0.05) is observed.

Analyses of secondary and exploratory endpoints will be presented without adjustment for multiplicity.

H. Analysis Sets

Three analysis sets will be defined for use with various analyses. The following table illustrates the relationship between each set and the analyses for which the data from the set will be used.

Analysis Set	Baseline	Subject Disposition	Efficacy	log
Full Analysis	X	X	X	
Safety Analysis	X			X
Per Protocol	X		X	

1. Full Analysis Set

All subjects who have been randomized to a study treatment group. Full analysis set (FAS) will be the primary analysis set for all efficacy analyses. Subjects will be analyzed according to their randomized treatment.

2. Safety Analysis Set

All randomized subjects who receive at least 1 dose of study treatment. This analysis set will be used for all safety analyses. Subjects will be analyzed according to the actual treatment they received.

3. Per-protocol Set

All subjects in FAS with no major protocol deviation that would have an impact on the primary and key secondary efficacy assessments will be included in the per-protocol (PP) set. Major protocol deviations will be reviewed and determined prior to database lock and unblinding.

Subjects may be excluded from the PP for the following, but not limited, to violations:

- Did not meet inclusion/exclusion criteria
- Was not compliant with study treatment
- Received incorrect treatment

Subjects to be excluded from the PP analysis set will be determined based on a blinded data review meeting prior to database lock.

I. Subgroups

The following subgroups will be considered for primary and key secondary analyses for descriptive purposes:

- Prior treatment with dupilumab or tralokinumab (Yes or No)
- Prior treatment with JAK inhibitor (Yes or No)
- Baseline EASI score (<21 or ≥21)
- Baseline EASI score (<median or ≥median)
- Baseline %BSA of AD affected skin (<50% or ≥50%)

- Baseline %BSA of AD affected skin (<median or ≥median)
- Baseline vIGA score (3 or 4)
- Baseline peak pruritus NRS (<7, ≥7, <median or ≥median)
- Age group (<median or ≥median)
- Sex (Male or Female)
- Race (White or Others, Asian or Others)
- Atopic dermatitis disease duration (< median years, ≥median years). The duration for patients with ongoing AD will be from the start date to the randomization date.
- Atopic comorbidities (food allergy (immediate type), allergic rhinitis, or asthma) (Yes or No)
- Baseline weight group (<70 kg, ≥70-<100 kg, ≥100 kg)
- BMI (<15, ≥15-<25, ≥25-<30, ≥30)

If the number of subjects is too small within a subgroup, then the subgroup categories may be redefined before unblinding the study.

J. Data Display Characteristics

Data displays produced for this study will include three types - summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables will be produced as specified in the following sections. Figures will be produced when specified in sections to follow.

Data listings will simply list the data recorded on the eCRF or derived for each subject. In general, listings will be ordered by treatment, subject number, and time of assessment. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within subject (e.g., further ordering by lab test names in the lab listings).

Continuous data will be summarized with the number of non-missing values, mean, standard deviation, minimum, median, and maximum. Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Percentages of subjects with each of the possible values will be calculated from the number of subjects in the corresponding analysis population, unless stated otherwise. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables. The Standard Display of TLFs and Precision of Data Displayed are documented in the appendix of SAP TLF Shell.

V. Subject Accountability

A. Disposition

Subject disposition will be summarized as the number and percentage of subjects screened, failed screening (include reason for screen failure), randomized, randomized who received at least one dose of study treatment, completed treatment through Week 16, discontinued study treatment (include primary reason for discontinuation), completed follow through Week 24, and discontinued the study (include primary reason for discontinuation).

Subjects who were excluded from the PP set (include reason for exclusion) will be listed and separately summarized in the protocol deviation table.

Enrollment and disposition will be listed by treatment and subject. Screen failures with reason for screen failure and subjects not randomized will also be listed.

B. Subject Characteristics

Demographics and baseline disease characteristics will be summarized by treatment group based on the Safety Analysis Set.

- Subgroups as outlines in section I. Subgroups
- Age at time of consent (years)
- Childbearing potential of female subject (Yes, No including reasons)
- Baseline weight (kg)
- Baseline height (cm)
- Baseline BMI (kg/m^2)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- Fitzpatrick skin type (Type I, II, III, IV, V and VI)
- Subjects with prior history of dupilumab experience (Yes, No)
- Subjects with prior history of tralokinumab experience (Yes, No)
- Subjects with prior history of dupilumab or tralokinumab experience (Yes, No)
- Subjects with prior history of JAK inhibitor (Yes, No)
- Baseline Pruritus Numerical Rating Scale
- Baseline Skin Pain Numerical Rating Scale
- Baseline Patient Global Assessment (0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate, 4=Severe)
- Baseline Total Dermatology Quality of Life Index
- Baseline Total Patient-Oriented Eczema Measure
- Baseline Atopic Dermatitis Sleep Scale
  - Item 1: Difficulty Falling Asleep (0=Not at all, 1=A little bit, 2= Somewhat, 3=Quite a bit, 4=Very difficult)
  - Item 2: Number of Night-time awakenings
  - Item 3: Difficulty to get bask to sleep last night (0=Not at all, 1=A little bit, 2= Somewhat, 3=Quite a bit, 4=Very difficult)
- Baseline Total Asthma Control Questionnaire
- Baseline Total SINO-Nasal Outcome Test

- Baseline Eczema Activity and Severity Index
- Baseline Validated Investigator Global Assessment
- Baseline Body Surface Area BSA Affected
- Baseline Total SCORing Atopic Dermatitis
- Atopic dermatitis disease duration (years)
- Atopic comorbidities (food allergy, allergic rhinitis, or asthma) (Yes or No)

All demographics and baseline disease characteristics will be provided in subject listings.

C. Medical and Surgical History

Medical and surgical history events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.1. Coded medical history will be summarized by system organ class (SOC) and preferred term (PT) by treatment group and overall based on the safety 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.

D. Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Any deviation from the protocol will be classified as either minor or major.

All major protocol deviations will be summarized in a summary table by treatment group and overall based on the FAS. All protocol deviations (major and minor) will be provided in a data listing.

VI. Efficacy Analyses

Efficacy analyses will use data from the FAS set. The PP set may be used for sensitivity analysis.

A. Efficacy Assessments

1. Eczema Area Severity Index (EASI)

The EASI is a clinician assessment that is collected at Screening/ Visit 1, Baseline/ Visit 2, Visit 3/ Week 2, Visit 4/ Week 4, Visit 5/ Week 8, Visit 6/ Week 12, Visit 7/ Week 16, Visit 8/ Week 18, Week 9/ Week 20 and Visit 10/ Week 24 using the e-Diary.

The EASI is a composite score ranging from 0 to 72 that takes into account the degree of erythema, induration/infiltration (papules), excoriation, and lichenification (each scored as =None, 1=Mild, 2=Moderate 3=Sever) for each of 4 body regions (head and neck, trunk, upper extremities and lower extremities), with adjustment for the percentage of BSA (assessed by the palmar method) involved for each body region (0= 0%, 1=1-9%, 2=10-29%, 3=30-29%, 4= 50-69%, 5=70-89%, 6=90-100%) and for the proportion of the body region to the whole body (.1 for head and neck, .3 for trunk, .2 for upper extremities and .4 for lower extremities)

The domain score will be calculated in the ADaM dataset when all assessments are completed. The following is the calculation for each body region:

Head and Neck

((Erythema + induration/infiltration (papules) + excoriation + lichenification) X Involvement score X 0.1)

Trunk

((Erythema + induration/infiltration (papules) + excoriation + lichenification) X Involvement score X 0.3)

Upper Extremities

((Erythema + induration/infiltration (papules) + excoriation + lichenification) X Involvement score X 0.2)

Lower Extremities

((Erythema + induration/infiltration (papules) + excoriation + lichenification) X Involvement score X 0.4)

The composite score will be the summation of the four domains when all assessments are collected, and will be used for analysis.

The composite score and the individual assessments will be presented in a data listing.

2. Validated Investigator Global Assessment (vIGA)

The vIGA is a clinician assessment that is collected at Screening/ Visit 1, Baseline/Visit 2, Visit 3/ Week 2, Visit 4/ Week 4, Visit 5/ Week 8, Visit 6/ Week 12, Visit 7/ Week 16, Visit 8/ Week 18, Week 9/ Week 20 and Visit 10/ Week 24 using the e-Diary.

The vIGA is a global assessment of the current state of the disease. It is a 5-point morphological assessment range (0-Clear, 1-Almost Clear, 2-Mild, 3-Moderate, 4-Severe) of overall disease severity.

The vIGA results will be presented in a data listing.

3. Peak Pruritus Numerical Rating Scale (PP-NRS)

The PP-NRS will be recorded daily by the subject in the e-Diary. At the visits specified in the SoA, the pruritus NRS will be completed by the subject at the study center using the e-Diary and should be assessed at about the same time each day.

The PP-NRS will ask subjects “On a scale of 0 to 10, with 0 being “no itch” and 10 being “worst itch imaginable”, how would you rate your itch at the worst moment during the previous 24 hours?”.

The daily and weekly average PP-NRS scores will be presented in a data listing.

4. Patient Global Assessment (PtGA)

The PtGA is a subject assessment that is collected at Baseline/ Visit 2, Visit 3/ Week 2, Visit 4/ Week 4, Visit 5/ Week 8, Visit 6/ Week 12, Visit 7/ Week 16, Visit 8/ Week 18, Week 9/ Week 20 and Visit 10/Week 24 using the e-Diary.

The PtGA will capture a global assessment of the current state of their disease. Subjects will use a 5-point assessment of overall disease severity ranging from 0-Clear, 1-Almost clear, 2-Mild, 3-Moderate, and 4-Severe.

The PtGA scores will be presented in a data listing.

5. Atopic Dermatitis Sleep Scale (ADSS)

The ADSS will be recorded daily by the subject in an e-Diary.

The three-item ADSS captures the self-reported impact of itch on sleep disturbance each day, including: difficulty falling asleep (Item 1); number of night-time awakenings (Item 2), and difficulty falling back asleep after waking (Item 3) during the previous night. Each ADSS item is scored individually. For items 1 and 3, subjects will be asked to select a score ranging from 0 ("not at all") to 4 ("very difficult"). For item 2, subjects will select the number of times they woke up each night, ranging from 0 to 29 times. Subjects are only to answer item 3 if their answer to item 2 is greater than 0.

The daily and average/worst weekly scores for the individual items of the ADSS results will be presented in a data listing.

6. SCORing Atopic Dermatitis (SCORAD)

The SCORAD is a clinical assessment collected Baseline/ Visit 2, Visit 3/ Week 2, Visit 4/ Week 4, Visit 5/ Week 8, Visit 6/ Week 12, Visit 7/ Week 16, Visit 8/ Week 18, Week 9/ Week 20 and Visit 10/Week 24 using the e-Diary.

The Scoring Atopic Dermatitis (SCORAD) is a standard tool to assess AD severity. The overall BSA affected by AD will be evaluated (from 0% to 100%) and will contribute to the extent (A) portion of the score. Six signs (erythema, edema/papulation, oozing/crusts, excoriation, lichenification, and dryness) will be evaluated to assess the intensity of AD. These assessments will contribute to the intensity (B) portion of the score. Loss of sleep and pruritus will be evaluated by the subjects on a visual analog scale (0 to 10) and will be based on the average of the last 3 days/nights. These assessments will contribute to the symptoms (C) portion of the score.

The SCORAD score is calculated in the ADaM when all assessments are completed and as following:

$$(A/5 + 7B/2 + C)$$

The SCORAD score can range from 0 to 103, higher score reflecting the worse severity of AD. The components of SCORAD (A, B and C) will be summarized descriptively. The individual questions, the components of SCORAD (A, B and C) and the SCORAD score will be presented in a data listing.

7. Patient-oriented Eczema Measure (POEM)

The POEM is a subject assessment that will be collected at Baseline/ Visit 2, Visit 3/ Week 2, Visit 4/ Week 4, Visit 5/ Week 8, Visit 6/ Week 12, Visit 7/ Week 16, Visit 8/ Week 18, Week 9/ Week 20 and Visit 10/Week 24 using the e-Diary.

The POEM is a self-assessment of disease severity by the subject. The POEM has total score ranging from 0 (absent disease) to a maximum value of 28 (severe disease) based on the summation of subject's response to all 7 questions scored from 0 to 4. The total score will be calculated in the analysis dataset and only if all assessments are collected.

The individual items of the POEM as well as the total score will be presented in a data listing.

8. Dermatology Life Quality Index (DLQI)

The DLQI is a subject assessment that is collected at Baseline/ Visit 2, Visit 3/ Week 2, Visit 4/ Week 4, Visit 5/ Week 8, Visit 6/ Week 12, Visit 7/ Week 16, Visit 8/ Week 18, Week 9/ Week 20 and Visit 10/Week 24 using the e-Diary.

The DLQI is a simple 10-question validated questionnaire. For question 1 and 2, the responses will be scored as very much = 3; alot = 2; a little = 1; not at all = 0. For questions 3, 4, 5, 6, 8, 9 and 10, the responses will be scored as very much = 3; a lot = 2; a little = 1; not at all = 0, not relevant=0. For question 7 the response will be scored as yes=3, no=0, not relevant=0. For question 7a, the response will be score as a lot=2, a little=1, not at all=0. Question 7a will only be considered if 'no' was the response for 7.

The DLQI is calculated by adding the score of each question, resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. A score higher than 10 indicates that the subject's life is being severely affected by their skin disease. If one question is unanswered, it is allocated a score of 0 and the DLQI score is summed in the usual way, out of 30. If two or more questions are unanswered, the questionnaire is not scored.

The individual items of the DLQI as well as the total score will be presented in a data listing.

[redacted]

10. Asthma Control Questionnaire (ACQ-5)

The ACQ-5 is a subject assessment that is collected at Baseline/ Visit 2, Visit 5/ Week 8, Visit 7/ Week 16, and Visit 10/Week 24 using the e-Diary. The ACQ-5 will only be assessed in subjects reporting a history of ongoing asthma at Screening.

The ACQ-5 is a questionnaire scoring five symptoms on a 7-point scale (0=no problem, 6=problem as bad as it can be).

The total score will be the mean of the five symptoms. If an assessment is missing then the total score will not be calculated.

The individual items of the ACQ-5 will be presented in a data listing.

11. Body Surface Area (BSA) of AD Affected Skin

The BSA is a clinical assessment that is collected at Screening/ Visit 1, Baseline/ Visit 2, Visit 3/ Week 2, Visit 4/ Week 4, Visit 5/ Week 8, Visit 6/ Week 12, Visit 7/ Week 16, Visit 8/ Week 18, Week 9/ Week 20 and Visit 10/ Week 24 using the e-Diary.

The overall BSA affected by AD will be evaluated (from 0% to 100%). The palmar surface of one hand represents ~1% of a subject's total BSA. To be eligible, subjects must have a BSA of ≥10% at the Screening and Baseline visits.

The BSA will be presented in a data listing.

12. Skin Pain Numerical Rating Scale (Pain NRS)

The PP-NRS will be recorded daily by the subject in an e-Diary. At the visits specified in the SoA, the pain NRS will be completed by the subject at the study center using the e-Diary and should be assessed at about the same time each day.

Subjects will be asked about the "worst skin pain" over the prior 24-hour period and respond on an 11-point scale between 0 = 'no pain' to 10 = 'worst imaginable pain'.

The daily and weekly average Pain NRS will be presented in a data listing.

B. Analysis of Efficacy Variables

The following table outlines the primary and secondary efficacy analyses planned with the corresponding analysis sets and imputations.

Efficacy Endpoint	Primary Analysis: Analysis Set, imputation method	Sensitivity Analysis: Analysis Set, imputation method
Primary		
• Percent change in Eczema Area Severity Index (EASI) from baseline at Week 16.	• FAS, PMM-MI (MNAR)	• FAS, MI (MAR) • FAS, PMM-MI (including site as a factor) • FAS, MMRM • PP, MI • FAS, LOCF • FAS, WOCF

		• FAS, OC
Efficacy Endpoint	**Primary Analysis: Analysis Set, imputation method**	**Sensitivity Analysis: Analysis Set, imputation method**
Key Secondary		
• Percent of subjects achieving a vIGA score of 0 or 1 at Week 16. • Percent of subjects achieving EASI-75, defined as a 75% reduction in EASI from baseline to Week 16.	• FAS, PMM-MI (MNAR)	• PP, MI • FAS, TF • FAS, OC
• Percent change from baseline in PP-NRS from an itch daily e-Diary at Week 16.	• FAS, PMM-MI (MNAR)	• FAS, MI (MAR) • FAS, PMM-MI (including site as a factor) • FAS, MMRM • PP, MI • FAS, LOCF • FAS, WOCF • FAS, OC
Other Secondary		
• Change from baseline in PP-NRS at Week 16	• FAS, MI (MAR)	• FAS, LOCF • FAS, OC

• Percent of subjects achieving EASI-50 at Week 2, 4, 8, 12, 16. • Percent of subjects achieving EASI 90 at Week 2, 4, 8, 12, 16. • Percent of subjects achieving at least 2-point reduction in vIGA score from baseline to Week 2, 4, 8, 12, 16. Percent of subjects achieving EASI-75 from baseline to Week 2, 4, 8, 12, 16. • Percent of subjects achieving ≥4-point reduction in PP-NRS from baseline at Week 2, 4, 8, 12, 16. • Percent of subjects achieving ≥3-point reduction in PP-NRS from baseline at Week 2, 4, 8, 12, 16	• FAS, MI (MAR)	• FAS, TF • FAS, OC
• Time to achieving ≥4-point reduction in PP-NRS from baseline • Time to achieving ≥3-point reduction in PP-NRS from baseline • Time to achieving EASI-50 from baseline • Time to achieving EASI-75 from baseline • Time to achieving EASI-90 from baseline	• FAS, OC	N/A

C. Primary Efficacy Analysis

The primary endpoint is the percent change in EASI from baseline to Week 16. The primary analysis will be based on the FAS and will use control-based PMM-MI to handle missing data.

The primary efficacy endpoint will be analyzed with an ANCOVA model. The model will include treatment group (each RPT193 dose vs. placebo), the randomization stratification factors of baseline vIGA score (3,4), and prior dupilumab or tralokinumab use (yes or no), and baseline EASI score as a covariate.

For each imputed dataset the least square (LS) mean, and LS mean difference in the percent change from baseline between each RPT193 dose level and placebo along with the corresponding estimated standard error will be reported. These results will be combined in PROC MIANALYZE using Rubin's formula and the resulting p-value will be used for inference at the 0.05 level of significance. The LS mean and LS mean difference along with the 95% confidence interval (CI) and p-value will be reported.

Sensitivity Analyses

Similar to control-based PMM-MI under MNAR, missing EASI 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 Week 16 data of each of the 100 complete imputed datasets will be analyzed using an ANCOVA model with treatment, randomization strata, and baseline EASI value included in the model, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 100 analyses using Rubin's formula. The example code can be found in Appendix II.

In addition to the MI method described previously, sensitivity analyses for the percent change in EASI will also be conducted using Mixed-effect Model for Repeated Measures (MMRM) without imputation. The model will include factors (fixed effects) for treatment, randomization strata, visit, treatment-by-visit interaction, and baseline EASI score. An unstructured covariance matrix will be used to model the within-patient errors. Denominator degrees of freedom will be estimated using approximation of SATTERTH. The efficacy data will be set to missing after rescue medication or procedure is used or after study withdrawal. Afterwards no imputation will be made.

The MMRM model will provide baseline adjusted least-squares (LS) means at Week 16 and at other time points for each treatment group with the corresponding standard error and the confidence interval, as well as the p values for treatment comparisons. The graph of LS-mean +/- SE by visit will be provided.

Other following sensitivity analyses will be planned for the primary estimand using the ANCOVA model mentioned above:

- In FAS, using PMM-MI and including site as a factor in the ANCOVA model.
- PP analysis set, using MI for handling missing data.
- In FAS, the LOCF and WOCF methods to handle missing data.
- In FAS, the Observed-Cases (OC) approach. No imputation for missing data at any time point. Data collected after the start of rescue will be set to missing.

D. Secondary Efficacy Analyses

1. Key Secondary Efficacy Analysis

The key secondary analysis will be based on the FAS and will use control-based PMM-MI for both categorical and continuous endpoints to handle missing data. The key secondary analysis endpoints are as following:

- Percent of subjects achieving a vIGA score of 0 or 1 at Week 16. Analyzed as a binary

endpoint.

- Percent of subjects achieving EASI-75, defined as a 75% reduction in EASI from baseline to Week 16. Analyzed as a binary endpoint.
- Percentage change from baseline in PP-NRS from an itch daily e-Diary at Week 16. Analyzed as a continuous endpoint.

Binary endpoints

The key secondary efficacy binary endpoint will be analyzed with a logistic model. The model will include treatment group, the randomization stratification factors of baseline vIGA scores (3 or 4) and prior dupilumab or tralokinumab use (yes or no), and the baseline score as covariate (if not previously included).

The estimate and standard error of the log odds ratio will be evaluated for each of the imputed datasets and combined in PROC MIANALYZE using Rubin's formula. The combined results will be back transformed such that the odds ratio, 95% CI and p- value are reported.

Continuous endpoint

The continuous endpoint will be analyzed in a similar manner as the primary efficacy endpoint.

Sensitivity Analyses

Similar to primary efficacy endpoint, missing PP-NRS will be imputed using the multiple imputation (MI) with analysis of covariance (ANCOVA) model. MI will be performed under missing at random (MAR) assumption.

The Week 16 data of each of the 100 complete imputed datasets will be analyzed using an ANCOVA model with treatment, randomization strata, and baseline PP-NRS value included in the model, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 100 analyses using Rubin's formula.

The percent change from baseline in PP-NRS will also be analyzed using MMRM without imputation. The model will include factors (fixed effects) for treatment, randomization strata, visit, treatment-by-visit interaction, and baseline PP-NRS score. An unstructured covariance matrix will be used to model the within-patient errors. Denominator degrees of freedom will be estimated using approximation of SATTERTH. The efficacy data will be set to missing after rescue medication or procedure is used or after study withdrawal. Afterwards no imputation will be made.

The MMRM model will provide baseline adjusted least-squares (LS) means at Week 16 and at other time points for each treatment group with the corresponding standard error and the confidence interval, as well as the p values for treatment comparisons. The graph of LS-mean +/- SE by visit will be provided.

Other following sensitivity analyses will be planned for the key secondary using the ANCOVA or logistic model mentioned above, as applicable:

- In FAS, using PMM-MI and including site as a factor in the ANCOVA model.
- PP analysis set, using MI for handling missing data for all key secondary endpoints.
- In FAS, the LOCF and WOCF methods for handling missing data for continuous endpoints.

- In FAS, the TF method for handling missing data for binary endpoints.
- In FAS, the Observed-Cases (OC) approach for all endpoints. No imputation for missing data at any time point.

2. Other Secondary Endpoints

The other secondary endpoints will be summarized descriptively.

The analysis will be based on FAS and will use MI, LOCF for the imputation of continuous endpoints and TF for categorical endpoints. The data will additionally be summarized using the OC.

- Change from baseline in PP-NRS at Week 16
- Percent of subjects achieving EASI-50 from baseline to Week 2, 4, 8, 12, 16.
- Percent of subjects achieving EASI-75 from baseline to Week 2, 4, 8, 12, 16
- Percent of subjects achieving EASI-90 from baseline to Week 2, 4, 8, 12, 16.
- Percent of subjects achieving at least 2-point reduction in vIGA score from baseline to Week 2, 4, 8, 12, 16.
- Percent of subjects achieving ≥4- point reduction in PP- NRS from baseline at Week 2, 4, 8, 12, 16.
- Percent of subjects achieving ≥3- point reduction in PP- NRS from baseline at Week 2, 4, 8, 12, 16.

Time to Events Endpoints

The following endpoints are considered time to event endpoints and the analysis will be based on the FAS using OC;

- Among subjects with baseline PP-NRS ≥4, time to achieving ≥4-point reduction in PP-NRS from baseline
- Among subjects with baseline PP-NRS ≥3, time to achieving ≥3-point reduction in PP-NRS from baseline
- Time to achieving first occurrence of EASI-50 from baseline
- Time to achieving first occurrence of EASI-75 from baseline
- Time to achieving first occurrence of EASI-90 from baseline

The time to achieving is defined as:

(first occurrence – first treatment date) + 1.

If the subject does not achieve the event, then the subject will be censored at their last non-missing assessment. If a subject uses rescue medication, then the subject will be censored at their last assessment prior to use of rescue medication. Estimates of medians and quartiles with 95% confidence intervals using the Kaplan-Meier (K-M) methods and unstratified and stratified log-rank tests will be reported.

E. Exploratory Efficacy Analysis

All exploratory efficacy analysis will be based on the FAS. Descriptive summary statistics will be provided by treatment and visit for exploratory endpoints listed below. No imputation will be utilized for missing data.

- Percent change in SCORAD from baseline at Week 2, 4, 8, 12, and 16
- Percent change in BSA from baseline at Week 2, 4, 8, 12, and 16
- Change from baseline to Week 16 in sleep loss from the SCORAD VAS
- Change from baseline to Week 16 in POEM
- Change from baseline to Week 16 in DLQI
- Change from baseline to Week 16 in Skin pain NRS
- Change from baseline to Week 16 in PtGA

  A shift table from baseline will be provided.
- Change from baseline to Week 16 in ADSS

  For item 1 and 3 a shift table will be provided to display the change from baseline. The change from baseline for item 2 will be presented descriptively.

[redacted]

- Change from baseline to Week 16 in ACQ-5

  A shift table from baseline will be provided for each question
- Percent of subjects achieving a PtGA score of 0 or 1 and a ≥2 point reduction from baseline at Week 2, 4, 8, 12, and 16. The assessment at each specific timepoint will be independently considered.
- Subgroup analysis of the primary efficacy endpoint as outlined in section IV.I
- Proportion of subjects maintaining responder status at Weeks 18, 20, 24 among those achieving the corresponding responder status at Week 16 and not receiving rescue therapy from Week 8 to Week of interest. The endpoint at Week 20 will not consider Week 18 status and will include subjects that do not use rescue from Week 8 to Week 20. Similarly, Week 24 will not consider responder status at Week 18 and Week 20 and will only include subjects that did not use rescue from Week 8 to Week 24 An additional analysis will be conducted without consideration of the use of rescue medication after Week 16. The following responder status will be analyzed separately.
  - EASI-50
  - EASI-70
  - EASI-90
  - vIGA score of 0 or 1
- Percent change in EASI at Weeks 18, 20, and 24 compared to Week 16 among those not receiving rescue therapy from Week 8 to Week of interest. In other words, the analysis at Week 20 will only include subjects who do not use rescue from Week 8 to Week 20.
- Percent change in SCORAD at Weeks 18, 20, and 24 compared to Week 16 among those not receiving rescue therapy from Week 8 to week of interest.

VII. Safety Analyses

All safety analysis will be based on the safety analysis set. The safety analyses which need analysis window, eg. change from baseline, will follow the analysis window for efficacy data, unless it is specified in each section below.

A. Exposure

Study drug administration data will be listed by subject. The following exposure parameters will be summarized by treatment group and overall using descriptive statistics:

- Total duration of exposure (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. There are 32 tablets in a bottle.
- 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 therefore 224 tablet.
- The total number of tablets taken, is number of dispensed tablets minus total number of tablets returned.
- Treatment compliance, defined as the (total number of tablets taken/ total number of tablets planned)*100%

Treatment compliance will be summarized as a continuous variable as well as a categorical variable for the categories of <80% and ≥ 80%, <90% and ≥ 90%, <120% and ≥ 120%

B. Adverse Events

Adverse events and SAEs will be documented on the "Adverse Event" eCRF page from the signing of the ICF until Follow-up/ Visit 10 or 28 days after the last dose of study treatment if subject is terminated early.

Treatment-Emergent AEs (TEAEs) is any condition that was not present prior to treatment with the study product but appeared following treatment, or was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment regardless of the intensity of the AE when the treatment was initiated. TEAE will be programmatically identified as AEs with an onset date on or after the first dose of study drug, and within 30 days after end of treatment.

When the AE start date is complete missing, adverse events will be assumed to be treatment-emergent. If AE start date is partially missing, please see AE data imputation in Section IV.D Missing Data, before determining TEAEs.

All adverse events will be coded according to MedDRA version 24.1.

Severity of AEs are graded as 'Mild", "Moderate" and "Severe". If the severity of the AE is missing it will be imputed as "Severe" for analysis purposes. Relationship to study drug will be categorized for analysis purposes as 'Related' or 'Not Related'. 'Related" include "Potentially Related", Probably Related" and "Definitely Related". AEs missing relationship status will be imputed as 'Related' in the related TEAE tables and listings.

An overall summary of number and percentage of subjects with at least one of the categories described below will be provided by treatment group and overall.

- Any AE
- Any TEAE
- Any TEAE of clinical interest
    - Malignancy
    - Major adverse cardiac events (MACE)
    - Tuberculosis (TB)
    - Inflammatory bowel disease (IBD)
    - Depression and suicidal ideation and behavior
    - Serious or opportunistic infection
    - Hypersensitivity reactions
- Any treatment-related TEAE
- Any serious TEAE
- Any serious treatment-related TEAE
- Any severe TEAE
- Any TEAE leading to study drug withdrawal
- Any treatment-related TEAE leading to study drug withdrawal
- Any TEAE leading to study drug interruption
- Any treatment-related TEAE leading to study drug interruption
- Any TEAE leading to death

The counts and percentages will be summarized for each PT and SOC by treatment group and overall. Additional summaries will also be provided by relationship to study drug and severity. A subject reporting multiple cases of the same TEAE will be counted once within

each system organ class, preferred term and will be counted once under the strongest relationship to study drug and worst severity.

- All TEAEs
- TEAEs with PT ≥5% in any treatment groups
- Treatment-related TEAE
- Serious TEAEs
- Serious treatment-related TEAEs
- TEAE leading to study drug withdrawal
- TEAE leading to study drug interruption
- TEAEs by strongest relationship to study drug
- TEAEs by worst severity

All AEs will be present in a by-subject listing. serious AEs, and TEAEs leading to study drug withdrawal will be present in separate listings.

C. Adverse Events of Clinical Interest

A separate analysis focused on adverse events of clinical interest will also be performed. Adverse events of clinical interest are as follows and identified by the eCRF page "Adverse Events":

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

The counts and percentages will be summarized for each PT and SOC by treatment group and overall. Additional summaries will also be provided by strongest relationship to study drug and worst severity.

The time to first TEAE of clinical interest during the week 16 treatment period will be assessed by Kaplan-Meier estimates (K-M plot) by each AECI category. The time is defined as the date of first event – the date of first dose + 1. Subjects without an event will be censored at the last AE assessment date within the 16 week of treatment period.. Graphs of cumulative incidence rate over time will be presented by treatment group.

The adverse events of clinical interest will be present in a separate listing.

D. Clinical Laboratory Test

All laboratory measurements include hematology, clinical chemistry, and urinalysis results, and will be converted to standard international (SI) units and US conventional units. Laboratory data will be summarized using descriptive statistics for the observed and change from baseline by treatment arm and overall. Worst post-baseline CTCAE grade shift from baseline tables will also be provided for hematology, clinical chemistry and urinalysis for lab test with available grading. Shift tables will be used to present the number and percentages of subjects with laboratory values within/outside normal reference ranges for parameters that do not have a CTCAE grading. Clinically significant changes will be reported as AE.

All laboratory data, including serology, pregnancy and other lab test, will be present in the listings. A by-subjects listing will also be provided for subjects with abnormal laboratory results.

E. Vital Signs

Vital sign tests will include sitting systolic and diastolic blood pressure (mmHg), pulse rate (beats/minute), respiratory rate (breaths/minute), body temperature (C), weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Vital sign parameters will be summarized using descriptive statistics at each assessment timepoint by treatment arm and overall. Change from Baseline will also be summarized descriptively by treatment arm and overall. Clinically significant changes will be reported as AE.

All vital sign data will be displayed in a by-subject listing.

F. Physical Examination

Physical examinations will consist of general appearance, skin, eyes/ ears/ nose/ throat, head/ neck, cardiovascular, respiratory, gastrointestinal, abdomen, extremities, lymph nodes, musculoskeletal, neurologic function and other. Abnormal physical examination findings may be reported as an adverse event.

The 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.

G. Prior and Concomitant Medications

Prior medications are defined as any medication that stopped before the date of the first dose of study drug. These medications will be recorded on both the "Prior Dupilumab and/or Tralokinumab Meds" and the "Prior and Concomitant Medications" eCRF form. Concomitant medications are defined as any medication that was ongoing or ended at the date of first dose, or any medication that started on or after the date of first dose. These medications will be recorded on the "Prior and Concomitant Medications" eCRF form.

All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) version B3 Global September 2021. Prior and concomitant medications will be summarized separately by Anatomical-Therapeutic-Chemical (ATC) level 4 classification and PT by treatment group and overall.

Medications that are indicated as rescue medications will also be summarized. Detailed information of rescue medications/procedures including duration of use and incidence of use will be summarized by topical and systemic groups. Kaplan-Meier (K-M) curves for time to first rescue use will be generated. The duration of use will be calculated based on the first start date and end date by topical and systemic groups. Missing dates will be imputed following Section IV.D.

All medications will be presented in a listing. A separate listing will be presented to include the rescue medications.

H. Concurrent Procedure

All concurrent procedures will be coded according to MedDRA version 24.1. Concurrent

[redacted] procedures will be summarized by SOC and PT by treatment group and overall.

All concurrent procedures will be presented in a listing.

I. ECG

12-lead electrocardiogram (ECG) in triplicate are performed at the visits designated in the SOA.

ECG measurements include mean heart rate (msec), PR interval (msec), RR interval (msec), QRS interval (msec), QT uncorrected (msec), QT corrected with Bazzett's formula (msec) and QT corrected with Fridericia formula (msec). The average of the triplicate assessments will be used for summary purposes. The actual value and change from baseline will be summarized using descriptive statistics at each assessment visit by treatment group and overall.

Absolute QTcF interval prolongation will be summarized by counts and percentages across all post-baseline assessments using the following criteria:

- QTcF interval >450 ms
- QTcF interval >480 ms
- QTcF interval >500 ms
- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms

The frequency count and percentage of the worst overall ECG evaluation among the triplicate will be summarized at each assessment visit by treatment group and overall. The best to worst overall assessment will be order as: normal, abnormal not clinically significant, abnormal clinically significant.
Clinically significant ECG abnormalities will be reported as AE.

All ECG data will be presented in listing.

J. COVID-19 Pandemic Impacted Subjects Assessment

Subjects who are impacted by COVID will be excluded in the Per-protocol Set.

The number of subjects who missed visits due to COVID-19 and the impacts ("Quarantined", "Site temporarily closed", "Unable to commute to clinic", "Other") due to the missing visits will be summarized by treatment and overall, and a by-subject listing will be provided. Moreover, the number of subjects who have COVID-19 related TEAEs or COVID-19 related protocol deviations will be reported in the disposition table. Any major COVID-19 related protocol deviations will be summarized and listed.

Appendix I

Visit	Screening	Baseline	Treatment (Day 1 to Day 113)					Follow-up (Day 127 to Day 169)		
Study Day	**Day -35 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 127/ET/ Discon**	**Day 141**	**Day 169**
Week Number			**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 18**	**Week 20**	**Week 24**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Window (day)			±2	±3	±3	±3	±3	±3	±3	±3
Informed consent	X									
Eligibility check for randomization	X	X								
Medical history	X									
Demographics	X									
Physical examination[a]	X	X	X	X	X	X	X	X	X	X
Height, weight, and BMI[b]	X							X		
TB screening	X									
Pregnancy test (females only)[c]	X	X		X	X	X	X	X		X
COVID-19 test[d]	X	X								
Clinical laboratory tests[e], including FSH at screening[f]	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X		X			X	X		
Triplicate 12-lead ECG	X	X		X			X	X		
Vital signs	X	X	X	X	X	X	X	X	X	X
Fitzpatrick skin type	X									
EASI	X	X	X	X	X	X	X	X	X	X
vIGA	X	X	X	X	X	X	X	X	X	X
BSA (palm method to be used for both EASI and SCORAD)	X	X	X	X	X	X	X	X	X	X
Randomization		X								

Visit	Screening	Baseline	Treatment (Day 1 to Day 113)					Follow-up (Day 127 to Day 169)		
Study Day	**Day -35 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 127/ET/ Discon**	**Day 141**	**Day 169**
Week Number			**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 18**	**Week 20**	**Week 24**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Window (day)			±2	±3	±3	±3	±3	±3	±3	±3
SCORAD		X	X	X	X	X	X	X	X	X
Daily Pruritus (PP-NRS)		X —	—	—	—	X				
Daily Skin Pain NRS		X —	—	—	—	X				
ADSS		X —	—	—	—	X				
Patient Global Assessment (PtGA)		X	X	X	X	X	X	X	X	X
DLQI		X	X	X	X	X	X	X	X	X
POEM		X	X	X	X	X	X	X	X	X
ACQ-5[g]		X			X		X			X
[redacted]										
Photographs[i]		X		X	X	X	X			X
Provisioning Subject e-Diary Device or Application[j]		X						X		X
Study drug dosing at study center[k]		X	X	X	X	X				
Study drug dosing daily at home[k]		X ----------	----------	----------	----------	----------	---------- X			
Daily subject e-Diary for drug dosing at home		X ----------	----------	----------	----------	----------	---------- X			
PK sampling – Blood[l]		X	X	X	X		X	X		
Tape stripping[m]		X		X	X		X		X	X
Skin microbiome samples (swab)[n]		X		X	X		X		X	X

Visit	Screening	Baseline	Treatment (Day 1 to Day 113)					Follow-up (Day 127 to Day 169)		
Study Day	**Day -35 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 127/ET/ Discon**	**Day 141**	**Day 169**
Week Number			**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 18**	**Week 20**	**Week 24**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Window (day)			±2	±3	±3	±3	±3	±3	±3	±3
Plasma Sample Collection for Biomarker Exploration[o]		X		X			X			X
Serum cytokines/ chemokines and biomarker levels		X	X	X	X		X	X		X
Immunophenotyping – Blood[p]		X			X		X	X		X
Pharmacogenomics Cell Pellet[q]		X								
Study drug distribution		X	X	X	X	X				
Study drug collection/review			X	X	X	X	X			
Rescue therapy collection/review (on or after Day 57 if applicable)					X	X	X	X	X	X
Application of rescue therapy in e-Diary (if applicable)					X	X	X	X	X	X
Prior and concomitant medication	Ongoing from screening									
AE/SAE reporting	Ongoing from the time of signing the ICF (non-treatment and treatment- emergent adverse events)									

Abbreviations: ACQ=asthma control questionnaire; ADSS=atopic dermatitis sleep scale; AE=adverse event; BMI=body mass index; BSA=body surface area; DLQI=Dermatology Quality of Life Index; EASI=Eczema Activity and Severity Index; ECG=electrocardiogram; ET=Early Termination; FSH=follicle-stimulating hormone; ICF=Informed Consent Form; PK=pharmacokinetics; POEM=Patient-oriented eczema measure; PP-NRS=Peak Pruritus Numerical Rating Scale; PtGA=Patient's Global Assessment; SAE=serious adverse event; SCORAD=SCORing Atopic Dermatitis; [redacted] 22; TB=tuberculosis; vIGA=Validated Investigator Global Assessment.

Baseline assessments to be obtained pre-dose.

There are no post-dose blood draws.

a. Full physical examination at Screening, partial physical examination at all other visits.
b. Height and weight will be collected, and BMI calculated at Screening. Weight will be collected at follow-up.
c. Serum pregnancy test at Screening, and urine pregnancy test at other visits.
d. A negative COVID-19 test is required at Screening.
e. Fasting required for labs at Baseline, Day 113 (Week 16), and Day 127/ET/Discon (Week 18). A subject should refrain from eating or drinking (except for water) for a period of at least 8 hours prior to the lab draw.
f. FSH at Screening only for females of non-childbearing potential.
g. The ACQ-5 instrument will only be assessed in subjects reporting a history of ongoing asthma at Screening.

[redacted]

i. Photographs will be taken at the selected sites. One or more most affected body regions, per Investigator's judgement, may be photographed.
j. The e-Diary will be dispensed to the subject or the e-Diary application will be loaded to the subject's device at Baseline. Collection or removal of application will occur at EOS or at ET/Discon. Subjects enter e-Diary information on a daily basis for their compliance with study treatment starting Baseline/Day 1, recording daily pruritus, daily skin pain NRS, and ADSS starting at Baseline/Day 1.
k. On Day 1, Day 15, Day 29, Day 57, and Day 85, the study drug will be administered at the study center after all other assessments are performed. All other daily drug intake will be self-administered by the subject, at home, at approximately the same time of the day through Day 112.
l. PK blood sampling will be done pre-dose on Day 1, Day 15, Day 29 and Day 57.
m. Tape stripping is only required for subjects in the US and Canada; tape stripping should not be performed for subjects in Poland. Tape strips will be collected from lesional and non-lesional skin pre-dose at Baseline. Tape strip samples will also be collected at the same sites sampled at Baseline on Day 29, Day 57, Day 113, and on Days 141 and 169, if applicable.
n. Two skin microbiome samples will be collected at Baseline, one from lesional and one non-lesion skin. A skin microbiome sample will also be collected at subsequent visits at the same lesional site sampled at Baseline.
o. Plasma blood sampling will be done pre-dose.
p. The immunophenotyping sample is only required for subjects in the US and Canada; immunophenotyping samples should not be collected from subjects in Poland.
q. Blood sample will be collected from subjects who have consented to participate in the genetic analysis component of the study. Participation is optional.

Appendix II

SAS example code for ANCOVA:

```
proc glm data=data_in;
     by avisitn avisit;
     class trtp(ref="vehicle")  prioruse;
     model chg = trtp base_EASI  base_VIGA prioruse / solution ss3;
     lsmeans trtp / stderr pdiff=all cov cl;
ods output lsmeancl=lsm lsmeandiffcl=diff parameterestimates=pp;
run;
```

SAS example code for MMRM:

```
proc mixed order=internal data = data_in;
     class usubjid trt01pn avisitn avisit  prioruse;
     model pchg = base_EASI trt01pn avisitn avisit trt01pn*avisit  base_VIGA prioruse/noint
    solution ddfm=kenwardroger;
     repeated /type=un subject=usubjid;
     lsmeans trt01pn*avisit /cl pdiff ;
 ods output lsmeans=lsmeans diffs=diffs;
run;
```

SAS example code for MI (MAR):

```
proc mi data =data_in out=data_out seed =1277282 nimpute=100 min= 0; by trt01p;
   mcmc impute = monotone; var week2-16;
 run;
```

SAS example code for PMM-MI (NMAR):

EASI, PP-NRS

```
proc mi data =data_in out =data_out seed=1277282 nimpute = 1 min=0 by _imputation_;
   class trt01p  base_VIGA prioruse;
   var base_EASI week2-16;
   monotone reg(week16 = base_EASI week2-12 trt01p  base_VIGA prioruse);
   mnar model(week16/ modelobs=(trt01p='placebo'));
run;
```

vIGA

```
proc mi data =data_in out =data_out seed=1277282 nimpute = 1 min=0 max=4
    by _imputation_;
     class trt01p  base_VIGA prioruse;
     var base_VIGA week2-16;
     monotone logistic(week16 = week2-12 trt01p  base_VIGA prioruse);
     mnar model(week16/ modelobs=(trt01p='placebo'));
run;
```

SAS example code for imputed results combinations:

```
proc glm data = data_mi;
  model week16 = base_EASI week2-12 trt01p  base_VIGA prioruse;
  by _imputation_;
  ods output ParameterEstimates=mxparms;
run;

proc mianalyze parms=mxparms;
    class trt01p;
    modeleffects Intercept base_EASI week2-12 trt01p  base_VIGA prioruse;
run;
```