TITLE PAGE

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

Protocol Number: RPT193-02

Amendment Number: 2.0

Product: RPT193

Short Title: An Efficacy and Safety Study of RPT193 in Adults with Atopic Dermatitis

Study Phase: Phase 2

Sponsor Name: RAPT Therapeutics, Inc.

Legal Registered Address:

561 Eccles Avenue
South San Francisco, CA 94080
United States

[redacted]

Date of Protocol: 07 July 2023

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 2.0	07 July 2023
Amendment 1	31 May 2022
Original Protocol	22 November 2021

Additions indicated with italicized text, deletions with strikethrough text.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	PK parameters at Week 2, 4, 8, *12,* 16, and 18.	Correction for consistency with Section 3.0.
1.1 Synopsis	Approximately ~~60~~ *80* sites in the US*, Canada, and Poland* are expected to participate in this study.	Additional sites and countries were added.
1.1 Synopsis; 5.1 Inclusion Criteria	6. Subject has a documented history of inadequate response to a ≥1 month treatment with topical medications, such as class I-V topical corticosteroids, *topical phosphodiesterase 4 (PDE4) inhibitor (e.g.,* crisaborole*)*, and/or calcineurin inhibitors in the 6 months prior to the Screening visit or subjects for whom topical treatments are otherwise medically inadvisable.	Clarification.
1.1 Synopsis; 5.1 Inclusion Criteria	6. Subject has an EASI score ≥16 at Screening and at Baseline. • Subjects may be screened with an EASI score ≥12 if the subject is administering class I-V topical corticosteroids, topical *PDE4 inhibitor (e.g.,* crisaborole*)*, and/or topical calcineurin inhibitors or is using systemic immunosuppressants (*e.g.,* methotrexate, cyclosporine A, mycophenolic acid, azathioprine, and/or systemic corticosteroids); eligibility for the study requires follow-up EASI score ≥16 at Baseline (after the relevant washout period for the index medication has been satisfied).	Clarification.
1.1 Synopsis; 5.2 Exclusion Criteria	6. Any of the following specific laboratory findings: • Alanine aminotransferase (ALT) >2.5× upper limit of normal (ULN) • Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 (Modification of Diet in Renal Disease [MDRD] equation) *Note: For subjects between the ages of 50 to 75 years old with an eGFR lower than 60 mL/min/1.73 m^2 but potentially within normal range for the subject's age, please contact the Medical Monitor to discuss the subject's eligibility*	Clarification.

Section # and Name	Description of Change	Brief Rationale
	• Platelet count <75,000 cells/mm^3 • Hemoglobin <10 g/dL • Absolute lymphocyte count <800 cells per mm^3 • Absolute neutrophil count <1500 cells per mm^3	
1.1 Synopsis; 5.2 Exclusion Criteria	11. Subject has received treatment with systemic immunosuppressive/ immunomodulating drugs (e.g., methotrexate, cyclosporine A, ~~systemic JAK inhibitors,~~ mycophenolic acid, ~~methotrexate,~~ or azathioprine), immunoglobulins, blood products and/or systemic corticosteroids (e.g., oral, intravenous, intraarticular, rectal) within 4 weeks prior to the Baseline visit. Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.	The washout period for systemic JAK inhibitors is 8 weeks per exclusion criterion 18.
1.1 Synopsis; 5.2 Exclusion Criteria	12. Subject has used any topical medicated treatment that could affect AD within 2 weeks prior to the Baseline visit, including, but not limited to, topical corticosteroids, *topical PDE4 inhibitor (e.g.,* crisaborole*)*, *topical* calcineurin inhibitors, *topical* JAK inhibitors (e.g., ruxolitinib), tars, *topical* antimicrobials, and medical devices.	Clarification.
1.2 Schema	Figure 1 (Study Schema) was revised to remove inclusion criteria related to BMI.	Correction for consistency with inclusion criteria.
1.3 Schedule of Activities (footnotes)	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 ~~27~~ *57*, Day 113, and on Days 141 and 169, if applicable.	Clarification that tape stripping will not be performed for subjects in Poland. Minor corrections.
1.3 Schedule of Activities (footnotes)	*p. The immunophenotyping sample is only required for subjects in the US and Canada; immunophenotyping samples should not be collected from subjects in Poland.* ~~p.~~ *q.* Blood sample will be collected from subjects who have consented to participate in the genetic analysis component of the study. Participation is optional. Please see Section 8.7 for further details.	Clarification that immunophenotyping will not be performed for subjects in Poland.

Section # and Name	Description of Change	Brief Rationale
2.2.1.2 Historical and Emerging Standard of Care	There are 2 key recent developments within the AD treatment landscape: (1) dupilumab, the biologic agent approved for moderate-to-severe AD, and (2) *recent approvals of* oral Janus kinase (JAK) inhibitors~~, which have completed Phase 3 studies and are currently under review by the Food and Drug Administration (FDA)~~.	Revision to reflect the current regulatory status of JAK inhibitors.
2.2.1.2 Historical and Emerging Standard of Care	~~Additionally, the FDA has placed black box warnings for JAK inhibitors approved in other indications due to the potential for serious infections, malignancies, and thromboembolic events.~~ *Approved JAK inhibitors have been associated with serious side effects (including serious infection, malignancy, and thromboembolic events), which is reflected in the US, EU, and Canadian labeling*.	Revision to reflect the product labeling in Canada and Poland in addition to the US.
5.4 Screen Failures	Subjects may be rescreened once provided the disqualifying reason is considered transient and is not related to disease activity status (i.e., vIGA, BSA, or EASI), if deemed acceptable by the Investigator. *The Investigator may consult with the* ~~and~~ Medical Monitor *on rescreening decisions if needed*.	Clarification.
6.3 Measures to Minimize Bias: Randomization and Blinding	The randomization list will be 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). (Note: Enrollment of subjects with a prior history of dupilumab or tralokinumab use will be capped at approximately 20%.)	Revision to incorporate stratification by region.
6.5 Prior Therapy	Eligible subjects will need to have had a documented history of inadequate response to a ≥1-month treatment with topical medication, such as corticosteroids (class I to V), calcineurin inhibitors, and/or *topical PDE4 inhibitor (e.g.,* crisaborole*)*.	Clarification.
6.6.3 Prohibited Therapies or Procedures	Table 3 (Prohibited Therapies or Procedures for Study Duration with Washout Periods) was revised to indicate that an 8-week washout period is required for systemic JAK inhibitors.	Correction for consistency with exclusion criterion 18.
6.6.4 Rescue Medications	Permitted rescue medications include ~~Mid-potency,~~ *low-to-moderate potency (*class IV-class VII*)*~~,~~ topical corticosteroids (Appendix 14) and should be applied only to problem areas. A topical calcineurin inhibitor, topical *PDE4 inhibitor (e.g.,* crisaborole*)*, or low-potency topical steroid may be used on the face if affected.	Correction for consistency with Appendix 14 and clarification.
8.1.5 Eczema Activity and Severity Index (EASI)	To be eligible for this study, subjects must have an EASI score of ≥16 at the Screening and Baseline visit, except for subjects who are administering class I-V topical corticosteroids, topical *PDE4 inhibitor (e.g.,* crisaborole*)*, and/or calcineurin inhibitors or is using systemic immunosuppressants (*e.g.,* methotrexate, cyclosporine A, mycophenolic acid, azathioprine, and/or systemic corticosteroids).	Clarification.

Section # and Name	Description of Change	Brief Rationale
8.6 Pharmacodynamics	Blood samples will be collected for pharmacodynamic analysis of RPT193 at the visits and time points specified in the SoA. The pharmacodynamic analysis of RPT193 will include but may not be limited to the assessment of CCR4 occupancy by flow cytometry, measurement of serum cytokines/chemokines levels by immune-assay, and blood cell immunophenotyping by flow cytometry. *Note: immunophenotyping will only be performed for subjects in the US and Canada; immunophenotyping will not be performed for subjects in Poland.*	Clarification that immunophenotyping will not be performed for subjects in Poland.
8.8 Biomarkers	Collection of samples for biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all subjects in this study as specified in the SoA: – Whole blood – Serum – Plasma – Skin tape strips – Skin swabs *Note: tape stripping is only required for subjects in the US and Canada; tape stripping should not be performed for subjects in Poland.*	Clarification that tape stripping will not be performed for subjects in Poland.
8.8.1 RNA Transcriptome Research	~~All subjects~~ *Subjects in the US and Canada* will have skin tape stripping samples collected at the visits specified in the SoA*; tape stripping should not be performed for subjects in Poland*. Tape strips will be collected from lesional and non-lesional skin at baseline. Tape strip samples will also be collected at the subsequent visits specified in SoA at the same sites sampled at baseline. For each sampled site, 16 tape-strip units will be placed and removed from the exact same site one after the other. All skin sampling (microbiome samples, and tape strips) should be collected from adjacent sites within the same lesion, whenever possible. Details about the collection, processing, handling, storage, and shipping of tape strip samples will be provided in the laboratory manual and/or the Study Reference Manual.	Clarification that tape stripping will not be performed for subjects in Poland.
9.6 Monitoring Committee	There will be no independent Data Monitoring Committee for this study. The safety of study participants will be closely monitored on an ongoing basis by [redacted] and ~~RAPT Therapeutics~~ *Sponsor* representatives.	Safety reporting responsibilities have been transitioned to [redacted].
Appendix 12 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	The appendix was revised to indicate that SAEs are to be reported to [redacted].	Safety reporting responsibilities have been transitioned to [redacted].

Section # and Name	Description of Change	Brief Rationale
Appendix 13 Contraceptive Guidance and Collection of Pregnancy Information	The table "Highly Effective Contraceptive Methods" was revised to include footnote b as follows: *b Female study participants who are women of childbearing potential using one of the highly effective, hormonal contraceptives described above (either birth control pills or implantable devices) will be required to also employ a barrier method of contraception (e.g., condom use by a male partner, diaphragm, or cervical cap) for a minimum of 30 days following the last dose of study drug.* *Male study participants with partners who are women of childbearing potential using one of the highly effective, hormonal contraceptives described above (either birth control pills or implantable devices) will be required to also employ a barrier method of contraception (e.g., condom use by a male partner, diaphragm, or cervical cap) for a minimum of 90 days following the last dose of study drug.*	Clarification for consistency with inclusion criteria 10 and 12.
Appendix 13 Contraceptive Guidance and Collection of Pregnancy Information	The appendix was revised to indicate that pregnancies are to be reported to [redacted]	Safety reporting responsibilities have been transitioned to [redacted]
Throughout the document	The protocol was revised to mention Research Ethics Boards (REBs) in addition to IRBs and IECs.	Revision to incorporate appropriate terminology for sites in Canada.
Throughout the document	Minor editorial and administrative changes.	Minor revisions were made for clarity, readability, consistency, and administrative purposes.

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

[redacted]

07-Jul-2023 | 11:30:06 PDT

Date

[redacted]
Chief Medical Officer
RAPT Therapeutics, Inc.

[redacted]

07-Jul-2023 | 12:46:03 PDT

Date

[redacted]
Medical Director
[redacted]

Medical Monitor name and contact information can be found in Appendix 2.

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

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

Short Title: An Efficacy and Safety Study of RPT193 in Adults with Atopic Dermatitis

Rationale:

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 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 sustained responses and/or further improvement in clinical parameters 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.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the clinical 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	• % 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.

Objectives	Endpoints
moderate-to-severe AD on subject reported symptoms associated with AD. Itch PP-NRS	• % 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 BSA 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: o Sleep quality (visual analog scale [VAS] from SCORAD) o Patient-oriented eczema measure (POEM) o Dermatology Quality of Life Index (DLQI) o Skin pain NRS o Patient global assessment (PtGA). o Atopic dermatitis sleep scale (ADSS) o [redacted]

Objectives	Endpoints
	○ 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 pharmacokinetics (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.

Objectives	Endpoints
Exploratory (Pharmacodynamic)	
• To evaluate the effect of multiple oral doses of RPT193 administered orally QD for 16 weeks to subjects with moderate-to-severe AD on serum cytokines and chemokines.	• Change in serum CCL17 levels • Change in serum CCL22 levels • Change in serum cytokines.
• To evaluate the effect of multiple oral doses of RPT193 administered orally QD for 16 weeks to subjects with moderate-to-severe AD on peripheral blood T cell subsets.	• Change in T cell subset numbers or proportion.
• To evaluate the effect of multiple oral doses of RPT193 administered orally QD for 16 weeks to subjects with moderate-to-severe AD on skin gene expression signatures and microbiome.	• Changes in skin gene expression signatures relative to baseline at Week 4, 8, 12, 16, and follow-up using skin tape strips. • Change in skin microbiome composition relative to baseline at Week 4, 8, 12, 16, and follow-up.

Overall Design:

This 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.

This study will assess RPT193 as monotherapy for the treatment of AD.

After the treatment period, there is a follow-up period ending at Day 169.

Number of Investigators and Study Centers:

Approximately 80 sites in the US, Canada, and Poland are expected to participate in this study.

Number of Subjects:

A total sample size of approximately 265 subjects (approximately 67 per treatment group) will be needed.

Treatment Groups and Duration:

RPT193-02 will consist of daily administration of 50, 200, or 400 mg of RPT193 or placebo for 16 weeks (112 consecutive days).

Inclusion/Exclusion Criteria:

Inclusion Criteria:

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Male or female subject aged 18 to 75 years, inclusive, at the time of consent.
2. Subject has clinically confirmed diagnosis of active AD, according to the revised Hanifin and Rajka criteria. [Eichenfield 2014]
3. Subject has at least a 12-month history of AD and had no significant flares in AD for at least 4 weeks before Screening, as determined by the Investigator through subject interview at the Screening visit or information obtained from medical chart or subject's physician.
4. Subject has a documented history of inadequate response to a ≥1 month treatment with topical medications, such as class I-V topical corticosteroids, topical phosphodiesterase 4 (PDE4) inhibitor (e.g., crisaborole), and/or calcineurin inhibitors in the 6 months prior to the Screening visit or subjects for whom topical treatments are otherwise medically inadvisable.

5. Subject has AD covering ≥10% of the BSA.
6. Subject has an EASI score ≥16 at Screening and at Baseline.
   - Subjects may be screened with an EASI score ≥12 if the subject is administering class I-V topical corticosteroids, topical PDE4 inhibitor (e.g., crisaborole), and/or topical calcineurin inhibitors or is using systemic immunosuppressants (e.g., methotrexate, cyclosporine A, mycophenolic acid, azathioprine, and/or systemic corticosteroids); eligibility for the study requires follow-up EASI score ≥16 at Baseline (after the relevant washout period for the index medication has been satisfied).
7. Subject has a Validated Investigator Global Assessment (vIGA) score ≥3.
8. Subject has been using one or more emollient(s) (except urea-containing emollients or medicated emollients that are regulated as a medical device) at least twice daily for 1 week prior to Baseline (except on visit day before the visit) and agrees to continue using the same emollient(s) daily at the same frequency (at least twice daily) throughout the study.
   Notes: On the day of scheduled visit, subjects cannot apply emollient before their scheduled visit, and every effort should be made to use the same emollient throughout the study for the same body region. However, the chosen emollient may differ depending on the body region (e.g., body vs face emollient may be different).
9. Female subject of childbearing potential has had a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline.
10. For female subject of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method from at least 4 weeks prior to Day 1 until at least 30 days after the last study drug administration. Highly effective contraceptive methods include hormonal contraceptives (e.g., combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s), tubal ligation or double barrier methods of contraception (e.g., male condom with cervical cap, male condom with diaphragm, and male condom with contraceptive sponge) in conjunction with spermicide.
    Notes:
    - For countries where double barrier methods are not accepted as highly effective contraception, then this option must not be considered.
    - A female subject of nonchildbearing potential is defined as follows:
      - Female subject who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)
      - Female subject who has had a cessation of menses for at least 12 months prior to the Screening visit without an alternative medical cause, and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).
    - Subjects must have been on a stable regimen of hormonal contraceptives for at least 4 weeks prior to Baseline.

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

11. Female subject agrees not to have egg retrieval during the study and for 30 days after the last study drug administration.
12. For male subject involved in any sexual intercourse that could lead to pregnancy, subject must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion #10, from Baseline (Day 1) until at least 90 days after the last study drug administration. If the female partner of a male subject uses any of the hormonal contraceptive methods listed above, this contraceptive method should be used by the female partner from at least 4 weeks before Baseline (Day 1) until at least 90 days after the last study drug administration.
13. Male agrees not to donate sperm during the study and for 90 days after the last study drug administration.
14. Subject has negative COVID-19 results at screening.
15. Subject is willing to comply with discontinuation of prohibited treatments for AD as described in Table 3 for the duration of the study, as directed by the Investigator.
16. Subject is willing to participate and is capable of giving informed consent.
    Note: Consent must be obtained prior to any study-related procedures.
17. Subject must be able and willing to comply with all study procedures and must be available for the duration of the study.

Exclusion Criteria:

Subjects are excluded from the study if any of the following criteria apply:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. Employee of the study center or RAPT.
3. Subject has any serious and/or uncontrolled medical condition (including cognitive impairment or signs/symptoms suspicious for a serious disease) or laboratory abnormality that would place subject's safety at risk or interfere with study participation, as judged by the Investigator including but not limited to the following:
   - Moderate-to-severe asthma that is uncontrolled
   - Subjects with uncontrolled diabetes (hemoglobin A1c [HbA1c] ≥9%)
   - Stage III or IV cardiac failure according to the New York Heart Association classification
   - Severe renal conditions (e.g., subjects on dialysis)
   - Active autoimmune disease (e.g., systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease)
4. Subject has had a major surgery in the past 8 weeks or has a major, elective surgery planned during the study.

5. Subject has any clinically significant medical condition or physical/laboratory/ECG (e.g., acute myocardial infarction, clinically significant arrythmia, or indications of serious underlying heart disease)/vital signs abnormality that would, in the opinion of the Investigator, be indicative of an underlying medical condition, put the subject at undue risk, and/or interfere with interpretation of study results.
6. Any of the following specific laboratory findings:
   - Alanine aminotransferase (ALT) >2.5× upper limit of normal (ULN)
   - Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 (Modification of Diet in Renal Disease [MDRD] equation)
     Note: For subjects between the ages of 50 to 75 years old with an eGFR lower than 60 mL/min/1.73 m^2 but potentially within normal range for the subject's age, please contact the Medical Monitor to discuss the subject's eligibility
   - Platelet count <75,000 cells/mm^3
   - Hemoglobin <10 g/dL
   - Absolute lymphocyte count <800 cells per mm^3
   - Absolute neutrophil count <1500 cells per mm^3
7. Subject has a history of drug and/or alcohol abuse in the last 12 months.
8. Subject has a history of skin disease or presence of skin condition that, in the opinion of the Investigator, would interfere with the study assessments.
   Note: Fungal infection of nail beds is allowed.
9. Subject has any state of immunodeficiency due to primary or secondary immunodeficiency syndromes, organ transplant (except corneal transplant), previous opportunistic infections, or any other state of immunodeficiency, as judged by the Investigator.
10. Subject has used tanning beds or phototherapy (narrowband ultraviolet B [NBUVB], UV-B, ultraviolet A1 [UVA1], or psoralen-UV-A [PUVA]) within 4 weeks prior to the Baseline visit.
11. Subject has received treatment with systemic immunosuppressive/immunomodulating drugs (e.g., methotrexate, cyclosporine A, mycophenolic acid, or azathioprine), immunoglobulins, blood products and/or systemic corticosteroids (e.g., oral, intravenous, intraarticular, rectal) within 4 weeks prior to the Baseline visit.
    Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
12. Subject has used any topical medicated treatment that could affect AD within 2 weeks prior to the Baseline visit, including, but not limited to, topical corticosteroids, topical PDE4 inhibitor (e.g., crisaborole), topical calcineurin inhibitors, topical JAK inhibitors (e.g., ruxolitinib), tars, topical antimicrobials, and medical devices.
13. Subject has used medicated emollients (regulated as a medical device) within 7 days prior to the Baseline visit.
14. Subject has received RPT193 in the past.
15. Subject has received an investigational oral, systemic agent within 8 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit.

16. Subject has received any marketed (other than dupilumab as described in exclusion criterion 17) or investigational biological therapeutic within 16 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit.
17. Subject has used dupilumab within 12 weeks or tralokinumab within 16 weeks prior to the Baseline visit OR has received dupilumab or tralokinumab at any time in the past and was considered to have no clinical response within 4 months of initiating dupilumab or tralokinumab treatment.
    Note: Lack of clinical response to dupilumab or tralokinumab may be defined by subject history alone.
18. Subject has used a systemic JAK inhibitor (e.g., tofacitinib, baricitinib, abrocitinib, upadacitinib) within 8 weeks prior to the Baseline visit OR has used a systemic JAK inhibitor at any time in the past and was considered to have no clinical response within 4 months of initiating JAK inhibitor treatment.
    Note: Lack of clinical response to a JAK inhibitor may be defined by subject history alone.
19. Subject is receiving a concomitant medication for condition(s) other than AD that require a change in dosing regimen within 7 days prior to the Baseline (Day 1) visit.
20. Subject has used a cell-depleting agent, including but not limited to rituximab within 6 months prior to the Baseline visit, or until lymphocyte counts return to normal, whichever is longer.
21. Subject has begun an allergen-specific immunotherapy regimen or had a clinically relevant change to their immunotherapy within 4 weeks prior to the Baseline visit.
22. Subject has used topical products containing urea within 1 week prior to the Baseline visit.
23. Subject has used systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks or topical antibiotics within 1 week prior to the Baseline visit.
24. Subject has received a live or live-attenuated vaccine within 4 weeks prior to the Baseline visit or plans to receive a live or live-attenuated vaccine during the study and up to 4 weeks after the last study drug administration.
25. Subject has a history of a clinically significant systemic infection or serious skin infection requiring parenteral antibiotic treatment within 4 weeks prior to the Baseline visit, or oral therapy within 2 weeks prior to the Baseline visit.
26. Subject has a known active bacterial, viral, fungal, helminth, or mycobacterial, or any other infection at the Baseline visit (non-complicated recurrent muco-cutaneous infections such as cold sores, tinea pedis, or disto-lateral mild to moderate onychomycosis are not considered exclusionary).
    Note: Subjects for whom infections have resolved and otherwise meet eligibility criteria may be rescreened up to once.
27. Active infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.
28. Subject has a diagnosis of, is suspected of having, or is at high risk for an endoparasitic infection unless clinical and laboratory assessment have ruled out active endoparasitosis prior to the Baseline visit.
29. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to the Baseline visit. Subjects with treated and completely resolved cutaneous basal cell carcinoma and/or cutaneous

squamous cell carcinoma in situ and/or cervical cancer in situ can be considered, as judged by the Investigator.

30. Subject has a positive tuberculosis (TB) infection test at screening. Subject will be evaluated for latent TB infection with a purified protein derivative (PPD) test, a QuantiFERON-TB Gold test, or a T-spot test. Subjects who demonstrate evidence of latent TB infection (either PPD ≥5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacilli Calmette-Guérin vaccination status) will not be allowed to participate in the study.
31. Subject has a positive screen for hepatitis B surface antigen (HbsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies. For HbsAg or HCV antibody positive screening, subjects may be enrolled if reflex testing (e.g., HBV-DNA or HCV-RNA) is negative and indicative that there is no active infection.
32. Subject has a known hypersensitivity to RPT193 or its excipients.
33. Subject is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided.
34. Subject is not willing to maintain their baseline skin care regimen (e.g., bathing) or use of herbals and/or supplements through the duration of the study.
35. Subject who is still participating in a clinical trial or who has participated in a clinical trial within 1 month prior to the Screening visit.
    Note: Please also refer to Exclusion Criteria 15 and 16 regarding those who participated in an investigational clinical trial.

Statistical methods:

Continuous endpoints will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum). Categorical endpoints will be summarized using frequency counts and percentages. All individual subject data will be present in listings.

Analysis sets will include a Full Analysis Set, a Per-Protocol Analysis Set, and a Safety Analysis Set.

The primary efficacy endpoint is the percent change from baseline in EASI score at Week 16. The primary analysis will be performed in FAS. The primary efficacy endpoint will be analyzed with analysis of covariance (ANCOVA) model. The model will include treatment group (each RPT193 dose vs. placebo), baseline vIGA scores, randomization stratification factors and study sites as factor, and baseline EASI score as a covariate. The least square (LS) mean and LS mean difference along with the 95% confidence interval (CI) and p-value will be reported.

For continuous secondary endpoints, the same model as discussed for the primary analyses will be followed. For binary secondary endpoints, a logistic regression model with treatment group, baseline vIGA scores, randomization stratification factors, study sites as factors and baseline score as a covariate will be used.

All safety analyses will be performed on the Safety Analysis Set. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are defined as AEs that first occurred or worsened in severity after the first dose of study treatment. The AE summaries will be primarily based on TEAEs. Descriptive statistics for the number and percentage of subjects with TEAEs will be summarized by treatment arm, system organ class, and preferred term for all TEAEs, treatment-related TEAEs, serious TEAEs, and TEAEs leading to discontinuation of study treatment. All TEAEs will be further summarized by maximum severity and causality. All AEs will be present in a by-subject listing. Serious AEs, and TEAEs leading to discontinuation of study treatment will be present in separate listings.

No interim analysis for efficacy is planned.

[redacted]

Data Monitoring Committee:

There will be no independent Data Monitoring Committee for this study.

1.2 Schema

Figure 1 Study Schema

AD=atopic dermatitis; BSA=body surface area; EASI=Eczema Activity and Severity Index; vIGA=Validated Investigator Global Assessment.

Note: As outlined in Inclusion Criterion #6, subjects may be screened with an EASI ≥12 under certain conditions.

1.3 Schedule of Activities

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								
SCORAD		X	X	X	X	X	X	X	X	X
Daily Pruritus (PP-NRS)		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
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]		X					X			X
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
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

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
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]; 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. Please see Appendix 11 for further details.
d. A negative COVID-19 test is required at Screening (see also Section 8.9.2).
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.

h. [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. Please see Section 8.7 for further details.

2.0 INTRODUCTION

2.1 Study Rationale

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 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.

2.2 Background

2.2.1 Atopic Dermatitis

Atopic dermatitis is a common, chronic, relapsing, inflammatory skin disease. It is characterized by intense itch, xerosis and acute (erythematous papules, vesicles, edema, exudation, crusting), subacute and chronic (scaly, erythematous papules and plaques, lichenification, excoriations, fissuring) eczematous skin lesions.[Bieber 2010; Bieber 2017; Boguniewicz 2017; Eichenfield 2014] Typically, AD presents with an age-related morphology and distribution.[Bieber 2017; Feldman 2019]

The global prevalence of AD is estimated to be ~15% to 30% in children and ~2% to 10% in adults. In children with AD, onset occurs in 45% during the first 6 months of life, 60% during the first year, and 90% are affected before the age of 5. [Bieber 2010; Bieber 2017; Boguniewicz 2017; Eichenfield 2014] Subjects can experience spontaneous disease remission later in adolescence but up to 50% will live with AD throughout adulthood. [Bieber 2010; Bieber 2017; Boguniewicz 2017; Feldman 2019]

There are a number of extracutaneous comorbid health problems that occur in subjects with AD. Atopic dermatitis is associated with and may predispose to higher risk of other atopic disorders, including food allergies, allergic conjunctivitis/rhinitis, and asthma (atopic march). Chronic pruritus and inflammation/pain can lead to sleep disturbances and mental health symptoms. Subjects with AD are at higher risk for multiple neuropsychiatric disorders, including attention deficit (hyperactivity) disorder, depression and suicidal ideation, speech disorders in childhood,

headaches, and seizures. [Patel 2019; Silverberg 2017; Silverberg 2018] There are also cardio-metabolic and musculoskeletal (osteoporosis, injuries, and fractures) comorbidities. [Silverberg 2017; Silverberg 2018; Ascott 2019] Each of these comorbidities negatively impacts subjects Quality of Life (QOL). In addition, AD, in particular moderate and severe AD, is associated with poor QOL independent of these comorbidities. [Silverberg 2018]

2.2.1.1 Pathophysiology of AD and the Role of Th2 Immune Cells

AD has complex pathophysiology characterized by epidermal barrier dysfunction and immune-mediated inflammation. It is driven by multiple interconnected genetic, environmental, and immunological factors. Damaged epidermal barrier allows penetration of allergens, followed by immunoglobulin E (IgE) and non-IgE mediated sensitization with predominant Type 2 helper T cell (Th2) response in the acute phase of AD. [Guttman 2017; Kim 2019] AD has a heterogeneous molecular fingerprint among different age groups and ethnicities, but with a dominant Th2/Th22 skewing and variable Th17/Th1 contributions. [Kim 2019; Renert-Yuval 2019]

Th2 cells express high levels of CCR4 and are clinically validated drivers of allergic diseases along the atopic march, which includes AD, food allergy, asthma, and allergic rhinitis/conjunctivitis. [Vestergaard 2003] When a pathogen comes into contact with the skin or mucosal lining of the nose or lungs, an immune response is triggered. It is believed that innate immune cells and antibodies that recognize the pathogen initiate a release of inflammatory cytokines, leading to the recruitment of other immune system components, including Th2 cells. Th2 cells secrete inflammatory cytokines, such as interleukin 4 (IL-4), IL-5, and IL-13. While this Th2 response may be highly effective against foreign pathogens, particularly parasites, sometimes the body overreacts to benign substances in this way, resulting in a significant and presumably unnecessary influx of Th2 cells, leading to conditions along the atopic march.

At a cellular and molecular level, the Th2 response is initiated and sustained when Th2 cells are recruited to the site of inflammation by the binding of CCL17 and CCL22 to CCR4. Subjects suffering from AD and other allergic disorders have significantly elevated levels of both CCL17 and CCL22. Additionally, elevated CCL17 in the blood is among the most tightly correlated biomarkers of AD severity and activity. All told, these data suggest that inhibiting the ability of these chemokines to bind to CCR4 may prevent migration of Th2 cells into these inflamed sites and promote clinical benefit.

2.2.1.2 Historical and Emerging Standard of Care

Emollients and topical therapies (including corticosteroids, calcineurin inhibitors and phosphodiesterase-4 [PDE4] inhibitors) phototherapy or systemic anti-inflammatory agents, are routinely used to manage skin inflammation in subjects with AD. Subjects who do not achieve sustained alleviation of symptoms with topical treatments are prescribed systemic steroids or other systemic immunosuppressive agents such as cyclosporine, azathioprine, methotrexate and

mycophenolate mofetil. [Boguniewicz 2017; Eichenfield 2014] While these can be effective as temporary treatments of flare-ups, extended use has been associated with many potential side effects or adverse events (AEs). Systemic steroids, such as prednisone, can lead to temporary symptom relief but their use is not recommended to induce stable remission due to numerous side effects and the propensity of severe disease flares upon treatment cessation. Cyclosporine is also not suitable for long-term use as it has been associated with renal toxicity, hirsutism, nausea and lymphoma, and subjects must discontinue use after 1 to 2 years. Topical immunosuppressive agents inadequately address the systemic nature of AD. Furthermore, safety issues associated with systemic immunosuppressants such as steroids and cyclosporine make them inappropriate for chronic administration. The treatment paradigm in AD is evolving given the inadequacies of the historical standard of care agents.

There are 2 key recent developments within the AD treatment landscape: (1) dupilumab, the biologic agent approved for moderate-to-severe AD, and (2) recent approvals of oral Janus kinase (JAK) inhibitors. [Traidl 2021]

Dupilumab is a recently approved biologic for AD targeting the Th2 pathway. Dupilumab prevents T-cell activation and amplification of proinflammatory signaling pathways by blocking the interleukin 4 receptor (IL-4R), preventing IL-4 and IL-13 binding. Approximately 36% of subjects receiving weekly or biweekly injections of dupilumab achieved significant improvement in disease symptoms. [Simpson 2016] Among the orally administered JAK inhibitors in development for AD, there are 3 that have completed Phase 3 trials: upadacitinib, baricitinib, and abrocitinib. JAK inhibitors block the signaling pathway to multiple proinflammatory cytokines, including IL-4 and IL-13, thereby preventing the downstream signaling of Th2 cells at the sites of inflammation. While JAK inhibitors have demonstrated comparable clinical efficacy to dupilumab and offer the advantage of oral dosing, these inhibitors are broadly immunosuppressive and therefore may not be suitable for long-term dosing. Approved JAK inhibitors have been associated with serious side effects (including serious infection, malignancy, and thromboembolic events), which is reflected in the US, EU, and Canadian labeling.

Despite the recent progress in the field, there is significant unmet medical need for a safe and efficacious agent for the treatment of AD. Inhibition of Th2 cell migration into inflamed tissues with an oral CCR4 antagonist represents a highly differentiated approach with the potential to compare favorably to dupilumab, which only blocks the downstream effects of 2 of the Th2-produced cytokines. An oral agent with a favorable safety and efficacy profile offers an attractive alternative for subjects compared to the biweekly injections associated with dupilumab.

2.2.2 RPT193

RPT193 is an antagonist of the CCR4 chemokine receptor that inhibits CCR4-mediated chemotaxis toward both CCL22 and CCL17.

2.2.2.1 Non-Clinical Pharmacology

RPT193 potently inhibits CCL22- and CCL17-induced CCR4-mediated chemotaxis with excellent selectivity over other chemokine receptors. Daily oral dosing of RPT193 resulted in reduced Th2-driven skin inflammation in multiple mouse models. In the ovalbumin (OVA)-induced model, daily oral dosing of RPT193 resulted in more than 50% decrease in ear thickness and IL-4 levels in inflamed tissue. In a fluorescein isothiocyanate (FITC)-induced model, daily oral dosing of RPT193 resulted in a significant reduction of ear thickness (~25%) and significantly less IL-13 in inflamed tissue (~80%). Taken together, these data suggest that RPT193 may inhibit recruitment of Th2 cells to inflamed tissue and reduce the ongoing allergic inflammation. Furthermore, RPT193 may provide therapeutic efficacy equivalent to that of biologics such as anti-IL-13 modulating agents. For more details on non-clinical studies, refer to the RPT193 Investigator's Brochure.

Daily oral dosing of RPT193 in preclinical models of pulmonary inflammation also reduced accumulation of T cells, eosinophils, and neutrophils in bronchoalveolar lavage fluid (BALF) of allergically inflamed lungs in mice by approximately 50%. There was a corresponding reduction in Th2-inflammatory cytokines (IL-5, IL-13) and chemokines (CCL17 and CCL22) in BALF. Reduction in eosinophils, IL-13, CCL17, and CCL22 was similar to that observed for treatment with the anti-IL-13 antibody. Importantly, RPT193 resulted in the reduction in number of lymphocytes and neutrophils and in IL-5 levels in BALF whereas anti-IL-13 treatment had no effect 24 hours after allergen challenge.

Consistent with the observation that CCR4 is not associated with any direct immune activation, RPT193 did not stimulate secretion of cytokines (granulocyte-macrophage colony-stimulating factor [GM-CSF], interferon [IFN]-γ, tumor necrosis factor [TNF]-α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-12p70, IL-13 or IL-18) from peripheral blood mononuclear cell (PBMC) in vitro at doses up to 5 μM.

2.2.2.2 Preclinical Pharmacokinetics

[redacted]

[redacted] It is predicted to have low clearance and a moderate half-life (from 9 to 20 hours) in humans.

RPT193 showed no significant competitive or time-dependent inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, or common drug transporters, nor did it cause induction of CYP1A2, CYP2B6, or CYP3A4 mRNA. Thus, at clinically relevant doses and exposures in humans, RPT193 is unlikely to inhibit or induce the activity of the major drug-metabolizing CYP450 enzymes or drug transporters.

2.2.2.3 Preclinical Toxicology

Nonclinical safety assessment of RPT193 comprised a series of studies that were conducted in compliance with Good Laboratory Practices, which include a battery of safety pharmacology studies, a battery of genotoxicology studies, photosafety evaluation, and repeated-dose toxicology studies with a treatment duration of up to 16 weeks. The safety pharmacology studies in dogs and mice showed that RPT193 did not induce any adverse effects on the central nervous, cardiovascular, and respiratory systems up to the highest dose tested, 30 mg/kg in dogs and 300 mg/kg in mice. RPT193 was not genotoxic in genotoxicology studies including Ames and micronucleus tests in vitro and a mouse micronucleus study in vivo. The in vitro 3T3 Neutral Red Uptake phototoxicity test has demonstrated that RPT193 has no phototoxic potential. Furthermore, RPT193 was well-tolerated with no adverse effects noted in the 4- and 16-week oral toxicology studies in dogs at doses up to 30 mg/kg/day, the highest dose tested. [redacted]

[redacted]

2.2.2.4 Clinical Pharmacokinetics and Pharmacodynamics

Clinical pharmacokinetics (PK) and pharmacodynamics data have been obtained from a Phase 1 study, RPT193-01, entitled: "A Phase 1, randomized, double-blind, placebo-controlled, single-dose escalation, multiple-dose escalation, and food effect study of RPT193 in healthy subjects and subjects with moderate-to-severe atopic dermatitis."

In the Phase 1 trial of heathy subjects, RPT193 has demonstrated increases in exposure following increasing single doses (5 to 400 mg) and up to approximately 2-fold accumulation following multiple doses (50 to 400 mg once daily [QD] for 7 doses), and minimal to no food effect, with a mean plasma half-life of approximately 24 hours.

Following administration of multiple doses of 400 mg RPT193 QD for 28 days in subjects with AD in either a fasted or fed state, the median time to maximum concentration [t_{max}] of RPT193 on Day 28 was ~6 hours. There was a substantial increase in C_{max} and AUC on Day 28 when compared to Day 1. Overall, the data indicate similar PK parameters in both healthy volunteers and AD following multiple doses of 400 mg QD.

Please refer to the Investigator's Brochure for a detailed description of the clinical PK and pharmacodynamics of RPT193.

2.2.2.5 Clinical Safety Data to Date

In RPT193-01, a first-in-human trial investigating RPT193 in healthy volunteers and subjects with AD, RPT193 was found to be well-tolerated at all tested doses (ranging from 5 to 400 mg) following single dose (Part A) and multiple-dose (Part B) administration to healthy subjects. RPT193 400 mg QD was also found to be well-tolerated following multiple-dose administration in subjects with AD (Part C). All treatment-emergent adverse events (TEAEs) were mild or moderate in severity and no severe TEAEs were reported in the study. Overall, TEAEs reported were generally equally represented across all treatment groups with no apparent relationship to

dose or severity. No serious adverse events (SAEs) or TEAEs leading to study discontinuation were reported. There were minimal changes from baseline in biochemistry, hematology, and quantitative urinalysis parameters, with no specific trends observed, and the majority of abnormal laboratory values were not clinically significant. There were minimal changes from baseline in vital signs and electrocardiograms (ECGs), and the majority of abnormal values were not clinically significant.

2.2.2.6 Effects of RPT193 on Signs and Symptoms of AD in Subjects with Moderate-to-Severe Disease Subjects

The effects of RPT193 as monotherapy on signs and symptoms of AD were explored in subjects with moderate-to-severe AD in the Phase 1 trial after a 4-week treatment period. Overall, the preliminary efficacy results and patient-reported outcomes (PROs) showed consistently higher improvement in the RPT193 400 mg QD group than the placebo group for most of the efficacy endpoints evaluated in this study during the treatment period up to Day 29. Only bland emollients were allowed with no rescue therapy during and after treatment discontinuation, and further improvements were observed up to Day 43 (which corresponded with the end of the study) for mean values of most efficacy parameters in the RPT193 group, whereas values were stable or decreased following cessation of treatment in the placebo group. Though the Phase 1b trial was signal-seeking and not powered for any specific endpoint, post-hoc statistical analyses conducted on Day 43 (2 weeks after the End-of-Treatment [ET]) revealed statistically significant differences between RPT193 and the placebo for several efficacy endpoints (% change in Eczema Activity and Severity Index [EASI], EASI-50, % change in SCORing Atopic Dermatitis [SCORAD], and % change in body surface area [BSA]).

The proportion of responders with at least a 4-point reduction from baseline in single daily 24-hour pruritus numerical rating scale (NRS) for subjects with a baseline ≥4 was numerically higher in the RPT193 400 mg QD group than placebo at all study visits. At Day 29, the proportion of responders was 45.0% in the RPT193 400 mg QD group, as compared to 22.2% in the group treated with placebo.

Differences in improvement in QOL, as measured by the Dermatology Quality of Life Index (DLQI), between RPT193 and placebo groups were limited. Notably, this study was conducted during the coronavirus disease of 2019 (COVID-19) pandemic, during which time changes in work and leisure activities may have influenced how subjects responded to PRO questionnaires, including the DLQI.

Despite the small sample size and short duration of treatment (4 weeks), clinically significant improvements in the signs and symptoms of AD were observed in this study following treatment with RPT193, with continued improvement even 2 weeks after the end of treatment.

A detailed description of the chemistry, pharmacology, efficacy, and safety of RPT193 is provided in the current Investigator's Brochure.

2.3 Benefit/Risk Assessment

2.3.1 Known Potential Risks and Benefits

RPT193 is under development and has not been marketed in any country. Clinical experience is limited to safety data from the Phase 1 study, RPT193-01. To date, review of laboratory, ECG, and clinical safety assessments has not identified any significant concerns.

Based on the Phase 1 clinical data in subjects with moderate-to-severe AD, subjects treated with RPT193 as monotherapy showed signs of improvement for both signs and symptoms of AD after 4 weeks of therapy compared to placebo-treated subjects. RPT193-treated subjects demonstrated continued improvement for 2 weeks after therapy suggesting unique kinetics of clinical improvement after CCR4 inhibition, which is an upstream mechanism to decrease the inflammatory response associated with AD. Subjects enrolled in this Phase 2 study may see benefit after treatment, particularly given the 16-week length of treatment in this study.

Participation in this study will help generate future benefit for larger groups of subjects with AD and possibly other inflammatory skin diseases if RPT193 proves to be safe, well tolerated, and successful in treating this condition.

2.3.2 Assessment of Risks and Benefits

The Phase 1 clinical and safety data in healthy volunteers and subjects with moderate-to-severe AD, the favorable safety and tolerability profile, convenience of an oral medication, PK, and preliminary efficacy results support further evaluation of RPT193 in studies with larger sample sizes and longer treatment periods for the development of RPT193 as a therapy for subjects with moderate-to-severe AD and other inflammatory diseases.

All quality, pharmacology and toxicology data, and satisfactory safety results demonstrated in non-clinical studies are considered sufficient to expect a positive benefit/risk ratio for the treatment of subjects with moderate-to-severe AD and thus initiate the study.

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, proper study design, and close monitoring.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of RPT193 may be found in the Investigator’s Brochure.

3.0 OBJECTIVES AND ENDPOINTS

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the clinical efficacy of RPT193 administered orally QD for 16 weeks to subjects with moderate-to-severe AD.	• % change in 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) [Yosipovitch 2019]).	• % 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. Itch PP-NRS (Yosipovitch, 2019).	• % 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:

Objectives	Endpoints
	○ % of subjects achieving ≥4-point reduction in PP-NRS from baseline at Week 2, 4, 8, 12, and 16. ○ Time to achieving ≥4-point reduction in PP-NRS from baseline. • For subjects with baseline PP-NRS ≥3: ○ % of subjects achieving ≥3-point reduction in PP-NRS from baseline at Week 2, 4, 8, 12, and 16. ○ 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 SCORAD from baseline at Week 2, 4, 8, 12, and 16. • % change in BSA 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) ○ 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.

Objectives	Endpoints
• 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.
Exploratory (Pharmacodynamic)	
• To evaluate the effect of multiple oral doses of RPT193 administered orally QD for 16 weeks to subjects with moderate-to-severe AD on serum cytokines and chemokines.	• Change in serum CCL17 levels • Change in serum CCL22 levels • Change in serum cytokines.
• To evaluate the effect of multiple oral doses of RPT193 administered orally QD for 16 weeks to subjects with moderate-to-severe AD on peripheral blood T cell subsets.	• Change in T cell subset numbers or proportion.
• To evaluate the effect of multiple oral doses of RPT193 administered orally QD for 16 weeks to subjects with moderate-to-severe AD on skin gene expression signatures and microbiome.	• Changes in skin gene expression signatures relative to baseline at Week 4, 8, 12, 16, and follow-up using skin tape strips. • Change in skin microbiome composition relative to baseline at Week 4, 8, 12, 16, and follow-up.

4.0 STUDY DESIGN

4.1 Overall Design

This 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).

This study will assess RPT193 as monotherapy for the treatment of AD.

After the treatment period, there is a follow-up period ending at Day 169.

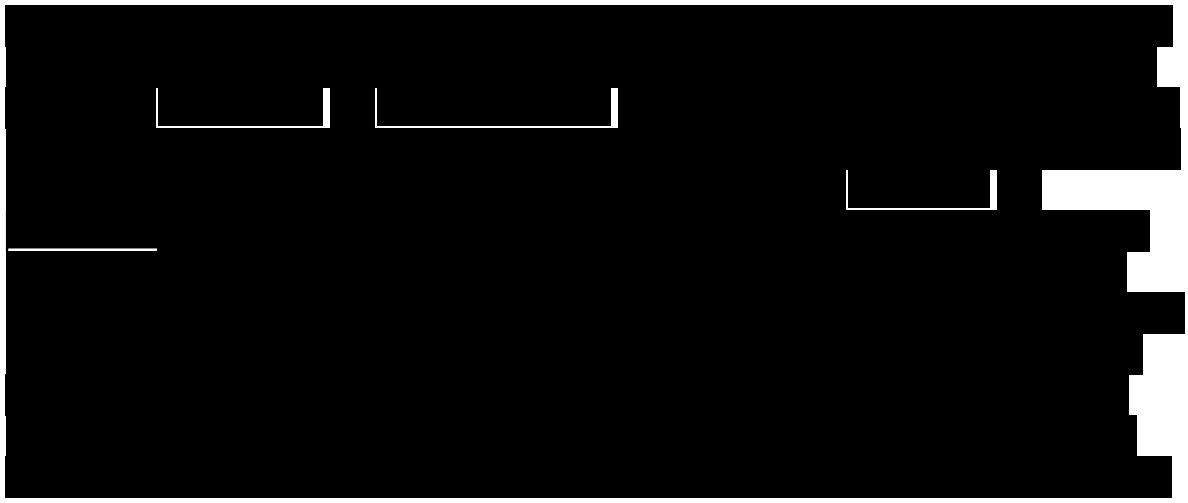
4.2 Scientific Rationale for Study Design

The proposed design is considered appropriate for assessing the efficacy and safety of RPT193 in subjects with moderate-to-severe AD.

This Phase 2 study will be randomized to ensure random allocation of subjects to treatment arms to reduce bias. Because efficacy assessments of AD can have a high degree of subjectivity, the study will be double-blinded. The highest degree of subject and assessor blinding should be sought to achieve credible inference. It is also important to have a placebo control to account for confounding factors, such as potential Investigator bias, and to ensure that the statistical procedures can be appropriately applied. The inclusion of 3 dose strengths of RPT193 across an 8-fold dosing range is designed to identify a sub-efficacious as well as a minimally effective dose.

4.3 Justification for Dose

RPT193-02 will investigate the efficacy and safety of RPT193 in subjects with moderate-to-severe AD. The study will assess 3 doses of RPT193 (50, 200, and 400 mg) taken orally QD for 16 weeks.



4.4 End of Study Definition

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 (Day -35 to Day -1), a 16-week double-blind treatment period (Day 1 to Day 113/Week 16) and an 8-week follow-up period (Day 113/Week 16 to Day 169/Week 24).

The end of the study is defined as the completion of the last visit or procedure shown in the SoA for the last enrolled subject in the trial for all sites.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Male or female subject aged 18 to 75 years, inclusive, at the time of consent.
2. Subject has clinically confirmed diagnosis of active AD, according to the revised Hanifin and Rajka criteria. [Eichenfield 2014]
3. Subject has at least a 12-month history of AD and had no significant flares in AD for at least 4 weeks before Screening, as determined by the Investigator through subject interview at the Screening visit or information obtained from medical chart or subject's physician.
4. Subject has a documented history of inadequate response to a ≥1 month treatment with topical medications, such as class I-V topical corticosteroids, topical PDE4 inhibitor (e.g., crisaborole), and/or calcineurin inhibitors in the 6 months prior to the Screening visit or subjects for whom topical treatments are otherwise medically inadvisable.
5. Subject has AD covering ≥10% of the BSA.
6. Subject has an EASI score ≥16 at Screening and at Baseline.
   - Subjects may be screened with an EASI score ≥12 if the subject is administering class I-V topical corticosteroids, topical PDE4 inhibitor (e.g., crisaborole), and/or topical calcineurin inhibitors or is using systemic immunosuppressants (e.g., methotrexate, cyclosporine A, mycophenolic acid, azathioprine, and/or systemic corticosteroids); eligibility for the study requires follow-up EASI score ≥16 at Baseline (after the relevant washout period for the index medication has been satisfied).
7. Subject has a Validated Investigator Global Assessment (vIGA) score ≥3.
8. Subject has been using one or more emollient(s) (except urea-containing emollients or medicated emollients that are regulated as a medical device) at least twice daily for 1 week prior to Baseline (except on visit day before the visit) and agrees to continue using the same emollient(s) daily at the same frequency (at least twice daily) throughout the study.
   Notes: On the day of scheduled visit, subjects cannot apply emollient before their scheduled visit, and every effort should be made to use the same emollient throughout the study for the same body region. However, the chosen emollient may differ depending on the body region (e.g., body vs face emollient may be different).
9. Female subject of childbearing potential has had a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline.
10. For female subject of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method from at least 4 weeks prior to Day 1 until at least 30 days after the last study drug administration. Highly effective contraceptive methods include hormonal contraceptives (e.g., combined oral

contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s), tubal ligation or double barrier methods of contraception (e.g., male condom with cervical cap, male condom with diaphragm, and male condom with contraceptive sponge) in conjunction with spermicide.

Notes:

- For countries where double barrier methods are not accepted as highly effective contraception, then this option must not be considered.
- A female subject of nonchildbearing potential is defined as follows:
  - Female subject who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)
  - Female subject who has had a cessation of menses for at least 12 months prior to the Screening visit without an alternative medical cause, and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).
- Subjects must have been on a stable regimen of hormonal contraceptives for at least 4 weeks prior to Baseline.
- The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Baseline (Day 1) and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

11. Female subject agrees not to have egg retrieval during the study and for 30 days after the last study drug administration.
12. For male subject involved in any sexual intercourse that could lead to pregnancy, subject must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion #10, from Baseline (Day 1) until at least 90 days after the last study drug administration. If the female partner of a male subject uses any of the hormonal contraceptive methods listed above, this contraceptive method should be used by the female partner from at least 4 weeks before Baseline (Day 1) until at least 90 days after the last study drug administration.
13. Male agrees not to donate sperm during the study and for 90 days after the last study drug administration.
14. Subject has negative COVID-19 results at Screening.
15. Subject is willing to comply with discontinuation of prohibited treatments for AD as described in Table 3 for the duration of the study, as directed by the Investigator.
16. Subject is willing to participate and is capable of giving informed consent.
    Note: Consent must be obtained prior to any study-related procedures.
17. Subject must be able and willing to comply with all study procedures and must be available for the duration of the study.

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. Employee of the study center or RAPT.
3. Subject has any serious and/or uncontrolled medical condition (including cognitive impairment or signs/symptoms suspicious for a serious disease) or laboratory abnormality that would place subject's safety at risk or interfere with study participation, as judged by the Investigator including but not limited to the following:
   - Moderate-to-severe asthma that is uncontrolled
   - Subjects with uncontrolled diabetes (hemoglobin A1c [HbA1c] ≥9%)
   - Stage III or IV cardiac failure according to the New York Heart Association classification
   - Severe renal conditions (e.g., subjects on dialysis)
   - Active autoimmune disease (e.g., systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease)
4. Subject has had a major surgery in the past 8 weeks or has a major, elective surgery planned during the study.
5. Subject has any clinically significant medical condition or physical/laboratory/ECG (e.g., acute myocardial infarction, clinically significant arrythmia, or indications of serious underlying heart disease)/vital signs abnormality that would, in the opinion of the Investigator, be indicative of an underlying medical condition, put the subject at undue risk, and/or interfere with interpretation of study results.
6. Any of the following specific laboratory findings:
   - Alanine aminotransferase (ALT) >2.5× upper limit of normal (ULN)
   - Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 (Modification of Diet in Renal Disease [MDRD] equation)
     Note: For subjects between the ages of 50 to 75 years old with an eGFR lower than 60 mL/min/1.73 m^2 but potentially within normal range for the subject's age, please contact the Medical Monitor to discuss the subject's eligibility
   - Platelet count <75,000 cells/mm^3
   - Hemoglobin <10 g/dL
   - Absolute lymphocyte count <800 cells per mm^3
   - Absolute neutrophil count <1500 cells per mm^3
7. Subject has a history of drug and/or alcohol abuse in the last 12 months.
8. Subject has a history of skin disease or presence of skin condition that, in the opinion of the Investigator, would interfere with the study assessments.
   Note: Fungal infection of nail beds is allowed.

9. Subject has any state of immunodeficiency due to primary or secondary immunodeficiency syndromes, organ transplant (except corneal transplant), previous opportunistic infections, or any other state of immunodeficiency, as judged by the Investigator.
10. Subject has used tanning beds or phototherapy (narrowband ultraviolet B [NBUVB], UV-B, ultraviolet A1 [UVA1], or psoralen-UV-A [PUVA]) within 4 weeks prior to the Baseline visit.
11. Subject has received treatment with systemic immunosuppressive/immunomodulating drugs (e.g., methotrexate, cyclosporine A, mycophenolic acid, or azathioprine), immunoglobulins, blood products and/or systemic corticosteroids (e.g., oral, intravenous, intraarticular, rectal) within 4 weeks prior to the Baseline visit.
    Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
12. Subject has used any topical medicated treatment that could affect AD within 2 weeks prior to the Baseline visit, including, but not limited to, topical corticosteroids, topical PDE4 inhibitor (e.g., crisaborole), topical calcineurin inhibitors, topical JAK inhibitors (e.g., ruxolitinib), tars, topical antimicrobials, and medical devices.
13. Subject has used medicated emollients (regulated as a medical device) within 7 days prior to the Baseline visit.
14. Subject has received RPT193 in the past.
15. Subject has received an investigational oral, systemic agent within 8 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit.
16. Subject has received any marketed (other than dupilumab as described in exclusion criterion 17) or investigational biological therapeutic within 16 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit.
17. Subject has used dupilumab within 12 weeks or tralokinumab within 16 weeks prior to the Baseline visit OR has received dupilumab or tralokinumab at any time in the past and was considered to have no clinical response within 4 months of initiating dupilumab or tralokinumab treatment.
    Note: Lack of clinical response to dupilumab or tralokinumab may be defined by subject history alone.
18. Subject has used a systemic JAK inhibitor (e.g., tofacitinib, baricitinib, abrocitinib, upadacitinib) within 8 weeks prior to the Baseline visit OR has used a systemic JAK inhibitor at any time in the past and was considered to have no clinical response within 4 months of initiating JAK inhibitor treatment.
    Note: Lack of clinical response to a JAK inhibitor may be defined by subject history alone
19. Subject is receiving a concomitant medication for condition(s) other than AD that require a change in dosing regimen within 7 days prior to the Baseline (Day 1) visit.
20. Subject has used a cell-depleting agent, including but not limited to rituximab within 6 months prior to the Baseline visit, or until lymphocyte counts return to normal, whichever is longer.

21. Subject has begun an allergen-specific immunotherapy regimen or had a clinically relevant change to their immunotherapy within 4 weeks prior to the Baseline visit.
22. Subject has used topical products containing urea within 1 week prior to the Baseline visit.
23. Subject has used systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks or topical antibiotics within 1 week prior to the Baseline visit.
24. Subject has received a live or live-attenuated vaccine within 4 weeks prior to the Baseline visit or plans to receive a live or live-attenuated vaccine during the study and up to 4 weeks after the last study drug administration.
25. Subject has a history of a clinically significant systemic infection or serious skin infection requiring parenteral antibiotic treatment within 4 weeks prior to the Baseline visit, or oral therapy within 2 weeks prior to the Baseline visit.
26. Subject has a known active bacterial, viral, fungal, helminth, or mycobacterial, or any other infection at the Baseline visit (non-complicated recurrent muco-cutaneous infections such as cold sores, tinea pedis, or disto-lateral mild to moderate onychomycosis are not considered exclusionary).
    Note: Subjects for whom infections have resolved and otherwise meet eligibility criteria may be rescreened up to once.
27. Active infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.
28. Subject has a diagnosis of, is suspected of having, or is at high risk for an endoparasitic infection unless clinical and laboratory assessment have ruled out active endoparasitosis prior to the Baseline visit.
29. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to the Baseline visit. Subjects with treated and completely resolved cutaneous basal cell carcinoma and/or cutaneous squamous cell carcinoma in situ and/or cervical cancer in situ can be considered, as judged by the Investigator.
30. Subject has a positive tuberculosis (TB) infection test at screening. Subject will be evaluated for latent TB infection with a purified protein derivative (PPD) test, a QuantiFERON-TB Gold test, or a T-spot test. Subjects who demonstrate evidence of latent TB infection (either PPD ≥5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacilli Calmette-Guérin vaccination status) will not be allowed to participate in the study.
31. Subject has a positive screen for hepatitis B surface antigen (HbsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies. For HbsAg or HCV antibody positive screening, subjects may be enrolled if reflex testing (e.g., HBV-DNA or HCV-RNA) is negative and indicative that there is no active infection.
32. Subject has a known hypersensitivity to RPT193 or its excipients.
33. Subject is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided.
34. Subject is not willing to maintain their baseline skin care regimen (e.g., bathing) or use of herbals and/or supplements through the duration of the study.

35. Subject who is still participating in a clinical trial or who has participated in a clinical trial within 1 month prior to the Screening visit.
    Note: Please also refer to Exclusion Criteria 15 and 16 regarding those who participated in an investigational clinical trial.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

RPT193 has been demonstrated to have similar PK and tolerability properties whether taken in a fasted or fed state. Thus, no restrictions related to food and ingestion of investigational product have been put in place. Investigational product should be taken with approximately 240 mL (8 ounces) of water. Subjects may discuss the pros and cons of taking the investigational product with food with the Investigator of their site.

5.3.2 Activity

Subjects should refrain from strenuous exercise or weightlifting within 96 hours (4 days) prior to screening and 48 hours prior to each subsequent visit as this could result in abnormal clinical laboratory values.

Subjects should try to limit exposure to the sun for the duration of the trial, but the use of sunscreen products and protective apparel are permitted when sun exposure cannot be avoided.

5.4 Screen Failures

Screen failures are defined as individuals who consent to participate in the clinical trial but are not subsequently randomly assigned to the study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Subjects may be rescreened once provided the disqualifying reason is considered transient and is not related to disease activity status (i.e., vIGA, BSA, or EASI), if deemed acceptable by the Investigator. The Investigator may consult with the Medical Monitor on rescreening decisions if needed. Rescreened subjects should be assigned a different identification number than the initial screening. All procedures planned at the Screening visit, including signature of a new consent form, will be performed.

5.5 Replacement of Subjects

The study assumes a drop-out rate of 10% with a goal of enrolling approximately 265 subjects and approximately 240 subjects completing the study. Thus, no replacement of subjects is anticipated.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a subject according to the study protocol.

The study consists of a screening period up to 35 days, a 112-day treatment period, and a 56-day follow-up period. Thus, the maximum duration of the study for an individual subject is 205 days (29 weeks). The study is anticipated to enroll approximately 265 subjects with 240 subjects completing the study (assuming a 10% drop out rate). The enrollment period is predicted to be 52 weeks. Thus, the duration of the study from initiation of Screening to the last Follow-up visit for the last subject enrolled is anticipated to be 81 weeks.

6.1 Study Treatment(s) Administered

RPT193-02 will consist of daily administration of 50, 200, or 400 mg of RPT193 or placebo for 16 weeks (112 consecutive days). The study drugs will be administered orally at approximately the same time of the day. On study days where PK samples are to be collected, the subject will administer the study drug at the study center, following the PK sample collection. The date and time of study drug administration will be collected daily via an electronic Diary (e-Diary) provided to the subject whether study drug is taken on- or off-site. The subject will be instructed to take the study drug at approximately the same time of the day when taken off-site. The subject will complete an e-Diary to document the time of each dose taken when off-site. Also, in the event of an adverse event of the gastrointestinal system organ class, the subject may be asked to indicate the timing of taking product in relation to food intake.

Further details regarding the study treatments can be found in Table 2.

Table 2 Study Treatment Details

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

The contents of the label will be in accordance with all applicable regulatory requirements. Details on study drug preparation by [redacted] can be found in the Manufacturing Batch Record. The active medication will be provided by the Sponsor.

6.2 Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study drug.
2. Only subjects enrolled in the study may receive study drug and only authorized study center staff may supply or administer study drug. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.
3. The study drug will be dispensed by the study site to the subject at the visits specified in Table 1.
4. Subjects are to return all study drug to the study site. The RPT193 tablets will be counted upon return, and the counts will be recorded in the source documents and electronic case report form (eCRF).
5. Each subject will be instructed on the importance of returning the study drug at the next visit and on taking the product as prescribed. If a subject does not return study drug, he or she will be instructed to return it as soon as possible.
6. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
7. The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study drug using the Drug Accountability Form, as per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP). These forms must be available for inspection at any time by the Sponsor, its designees, or by regulatory agencies.
8. Further guidance and information for the final disposition of unused study drug are provided in the Study Reference Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

At the study site, each screened subject will be assigned an identifier number during screening that will be used on all documentation. The identifier number will contain the site number (YYYY) and the subject number (SSSS) and will be assigned at the Screening visit (e.g., YYYY-4001).

Randomization will occur prior to first dosing, at the Baseline (Day 1) visit. Approximately 265 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 67 subjects are anticipated to complete the study in each group.

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

The randomization list will be 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). (Note: Enrollment of subjects with a prior history of dupilumab or tralokinumab use will be capped at approximately 20%.) The list will be 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.

Further guidance and information can be obtained in the Study Reference Manual.

This study will be double blind. At all times, treatment and randomization information will be kept confidential and will not be released to the Investigator, the study staff, the contract research organization (CRO), or the Sponsor study team until after the conclusion of the study. However, the laboratory where the PK samples will be analyzed will be provided with a copy of the randomization code since only samples of subjects who have received the active drug RPT193 will be analyzed.

The following controls will be employed to maintain the double-blind status of the study:

- The oral tablets containing active drug or placebo will be indistinguishable in appearance and taste.

Blinding codes should only be broken in emergency situations for reasons of subject safety. When the blind for a subject has been broken, the reason must be fully documented in the source document and eCRF. Whenever possible, the Investigator should contact the Sponsor or its designee before breaking the blind. If the blind is broken, the Investigator should promptly inform the Medical Monitor. Documentation of breaking the blind should be recorded with the date/time and reason why the blind was broken, and the names of the personnel involved.

The subject for whom the blind has been broken will be discontinued from the study and undergo the End-of-Treatment (ET)/Discontinuation procedures. In cases where there are ethical reasons to have the subject remain in the study, the Investigator must obtain specific approval from the Sponsor or its designee for the subject to continue in the study. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded.

6.4 Study Treatment and e-Diary Compliance

Study treatment and Diary compliance will be monitored at the visits specified in the Schedule of Activities (SoA) (Section 1.3). Adherence to treatment will be assessed by direct questioning and by maintaining adequate study drug dispensing and return records. Any deviation from the prescribed dosage regimen will be recorded in the source document. Adherence to Diary completion will be assessed by a review of compliance reports by the site monitors prior to each

site visit or contact. Subjects who are significantly noncompliant with e-Diary completion (i.e., missing >20% of Diary entries) will be counseled and could be discontinued from the study, at the discretion of the Investigator, following consultation with the Sponsor.

On visit days, the date and time of study drug administration and the number of units administered will be recorded. In addition, subjects will capture the date and time of dosing in a daily e-Diary when the study drug will be taken at the site or at home.

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

6.5 Prior Therapy

Eligible subjects will need to have had a documented history of inadequate response to a ≥1-month treatment with topical medication, such as corticosteroids (class I to V), calcineurin inhibitors, and/or topical PDE4 inhibitor (e.g., crisaborole). Medical history is sufficient but the medication and duration of treatment should be documented. Inadequate response should also be documented to have occurred within 6 months prior to the Screening visit. Additionally, subjects for whom topical treatments are considered medically inadvisable will be considered to have satisfied the requirements related to prior therapy.

6.6 Concomitant Therapy

6.6.1 Permitted Therapies

6.6.1.1 Emollients

Subjects must apply a basic, non-medicated emollient of their choice (except those containing urea) on their skin, including on AD lesions, at least twice a day. The emollient use must be initiated at least 7 days prior to Day 1 and subjects must continue using it at the same frequency (at least twice daily) throughout the study. However, on the day of scheduled visits, subjects should refrain from emollient use for at least 8 hours prior to each clinic visit.

Every effort should be made to use the same emollient throughout the study for the same body region. However, the chosen emollient may differ depending on the body region (e.g., body vs face emollient may be different). The commercial name of the selected emollient(s) will be recorded in the source document and the eCRF. No other products may be applied to the lesions during the study.

6.6.2 Prior Use of Dupilumab, Tralokinumab, or an Oral JAK Inhibitor

Prior use of dupilumab, tralokinumab, or an oral JAK inhibitor for the treatment of atopic dermatitis will be assessed at screening. Per the eligibility criteria, subjects with a history of dupilumab, tralokinumab, or an oral JAK inhibitor will be allowed in the study provided that they have achieved the relevant washout period and a history of a clinical response. This clinical response may be assessed by interview of the subject by the PI. Enrollment of dupilumab- or tralokinumab-exposed subjects will be capped at approximately 20% and randomization will be stratified by prior use.

6.6.2.1 Skin Care

Use of sunscreen products and protective apparel are permitted when sun exposure cannot be avoided.

Regular skin care (e.g., cleansing and bathing) is permitted during the study. New skin care regimens that are not present at baseline (e.g., bleach baths) should not be introduced through the course of the study.

6.6.2.2 Anti-infectives

Topical and systemic anti-infective medications are permitted during the study, independent of the location of the infection, should the Principal Investigator identify an acute infection requiring treatment.

6.6.2.3 Anti-histamines

Non-sedating anti-histamines (e.g., loratadine, cetirizine, or fexofenadine) are permissible. Sedating anti-histamines (e.g., doxepin, diphenhydramine) are permissible so long as these medications were on a stable dosing regimen within 7 days prior to the Baseline (Day 1) visit and remain on the stable dosing regimen through the duration of the treatment period (Day 113). Dose adjustments must be discussed with the Investigator prior to change.

6.6.2.4 Medications for Conditions Unrelated to AD

Subjects who are taking oral medications for conditions unrelated to AD should be on a stable dosing regimen within the 7 days prior to the Baseline (Day 1) visit. Adjustments to the regimen may be made after the Baseline visit if medically necessary. If a new medication is required to treat an emerging condition, these are allowable, provided the medication is not among the prohibited therapies. New concomitant medications should be discussed with the Medical Monitor prior to initiation.

6.6.2.5 Corticosteroids for Nose, Lungs, Eyes, and/or Ears

Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed when used as directed.

6.6.2.6 Herbals and supplements

Subjects may take herbals and/or supplements with the following conditions. First, subjects taking herbals and/or supplements at screening who wish to discontinue these may do so provided that they do the following for the duration of the study: 1) continue to refrain from taking the herbal/supplement and 2) do not introduce a new herbal and/or supplement. Second, subjects who intend to continue taking herbal products or supplements during the trial must agree to continue the regimen documented at Screening throughout the study unless discontinuation is considered medically necessary.

6.6.3 Prohibited Therapies or Procedures

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

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

Table 3 lists prohibited medications that are not to be used from the defined washout periods before the first administration of study treatment at the Day 1 visit through the last study visit.

Subjects who start prohibited medications or therapies as a treatment for AD or other reasons during the study may be withdrawn from study treatment for safety reasons. If in any doubt, Investigators are advised to discuss medications with the Medical Monitor.

Table 3 Prohibited Therapies or Procedures for Study Duration with Washout Periods

Prohibited Medications, Products, and Procedures	Washout Period Prior to First Dose (Day 1)
Cell-depleting agent (e.g., rituximab)	6 months
Any marketed or investigational biological therapeutic (other than dupilumab)	16 weeks or 5 half-lives (whichever is longer)
Dupilumab	12 weeks
Oral investigational drugs	8 weeks or 5 half-lives of the investigational drug (whichever is longer)
Major elective surgical procedures	8 weeks
Systemic JAK inhibitors	8 weeks
Parenteral antibiotic	4 weeks
Live-attenuated vaccine (including but not limited to adenovirus-based COVID-19 vaccines such as the Janssen COVID-19 vaccine)	4 weeks
mRNA-based COVID-19 vaccines (Pfizer-BioNTech or Moderna)**	2 weeks
Allergen-specific immunotherapy regimen (Note: subjects may continue on a stable dose of allergen immunotherapy if achieved 4 weeks prior to the Day 1 visit)	4 weeks
Systemic immunosuppressive/immunomodulating drugs (other than biologics) (e.g., methotrexate, cyclosporine A), immunoglobulins, blood products, and/or systemic corticosteroids (e.g., oral, intravenous, intraarticular, rectal)	4 weeks
Tanning beds or phototherapy (NBUVB, UV-B, UVA1, or PUVA)	4 weeks
Systemic antibiotics	2 weeks (oral) 4 weeks (parenteral)
Topical corticosteroids as these medications could affect AD*	2 weeks
Additional topical medicated treatment that could affect AD including, but not limited to phosphodiesterase 4 (PDE4) inhibitors, JAK inhibitors, calcineurin inhibitors, tars, antimicrobials, and medical devices.	2 weeks
Topical product containing urea	1 week
Topical antibiotics	1 week
Medicated emollient (regulated as medical device)	1 week

Abbreviations: AD=atopic dermatitis; COVID-19=coronavirus disease 2019; JAK=Janus kinase; NBUVB=narrowband ultraviolet-B; PDE4=phosphodiesterase 4; PUVA=psoralen-UV-A; UVA1=ultraviolet A1; UV-B=ultraviolet B.

*Please also refer to Section 6.6.4 regarding rescue medications for AD.

**mRNA-based COVID-19 vaccines (or boosters) are allowed after the end of the treatment period. See also refer to Section 8.9.2 for additional guidance.

6.6.4 Rescue Medications

Subjects who require topical corticosteroids, calcineurin inhibitors, or PDE4 inhibitor medications that could directly impact AD disease activity prior to Day 57 will be withdrawn from study drug and the study if requiring such topical therapies prior to Day 57.

Starting at Day 57, rescue medications for persistent, intolerable AD activity may be considered by the Investigator. Investigators must document evidence of continued active AD with EASI unchanged from or greater than the Baseline EASI score over 2 consecutive visits before initiating therapy. All subjects requiring rescue therapy between Day 57 (Week 8) and Day 113 (Week 16) will remain in the study and on study drug until Week 16.

After the end of treatment at Day 113 and during the follow-up phase, subjects may also initiate rescue if either the subject or investigator feels that there is persistent, intolerable AD activity.

Permitted rescue medications include low- to moderate-potency (class IV-class VII) topical corticosteroids (Appendix 14) and should be applied only to problem areas. A topical calcineurin inhibitor, topical PDE4 inhibitor (e.g., crisaborole), or low-potency topical steroid may be used on the face if affected. Subjects who require rescue therapy will be considered non-responders for all efficacy endpoints with data imputed for subsequent continuous endpoints for all time points as detailed in the Statistical Analysis Plan (SAP). Ideally, the specified medication for rescue treatment would be supplied by the clinic so that the tube could be weighed prior to administration. In addition, use of the specified medication should be recorded in the e-Diary, and the medication should be brought to clinic at subsequent visits to assess amount of medication used.

6.7 Dose Modification

No dosing modifications are permitted.

6.8 Treatment after the End of the Study

The Sponsor will not provide any additional care to subjects after they leave the study because such care should not differ from what is normally expected for subjects with moderate-to-severe AD.

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

See the SoA for data to be collected at the time of Early Termination/Treatment Discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary Discontinuation

In the event of an AE or clinically significant laboratory abnormality, study treatment of a subject may be temporarily discontinued based on the Investigator's judgment and preferably following a discussion with the Medical Monitor in accordance with the guidelines described in this section.

If during the course of treatment, a subject experiences a new (i.e., not existing at baseline) cardiovascular or hematologic AE (including laboratory abnormalities confirmed by repeat testing), consistent with Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [CTCAE 2017] of Grade 2 or higher, then the study drug should be temporarily discontinued for that subject. Treatment may be re-initiated if the abnormality resolves within 2 weeks of the onset of the AE.

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

The information pertaining to interruption or discontinuation of study drug and the reasons for it must be recorded in the case report form (CRF).

No dose reductions or modifications will be permitted in RPT193-02.

7.2 Subject Discontinuation/Withdrawal from the Study

Subjects have the right to withdraw from the study at any time for any reason without penalty. The Investigator also has the right to withdraw subjects from the study if he or she feels it is in the best interest of the subject or if he or she is uncooperative or noncompliant.

Should a subject decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible, particularly the examinations outlined in the Early Termination /Discontinuation (ET/Discon) visit.

The Investigator or one of his or her staff members should contact the subject to determine as accurately as possible the primary reason for the withdrawal.

A complete final evaluation at the time of withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.2.1 Discontinuation

Subjects who discontinue the study after the first dose will be asked, if they agree, to come for a last assessment (ET/Discon visit). Subjects who are discontinued for safety reasons may be asked to come for additional follow-up visits, at the Investigator's discretion, after the ET/Discon visit to ensure appropriate medical care and AE follow-up.

Reasons for discontinuation include the following:

- The Investigator decides that the subject should be withdrawn for any of the following reasons, but not limited to: difficulties in obtaining blood samples, violation of the protocol, severe AEs or SAEs, or for any other reason relating to the subject's safety or integrity of the study data. If this decision is made because of a SAE, the study drug is to be discontinued in that subject immediately and appropriate measures are to be taken. The Investigator will notify the Sponsor immediately.
- The attending physician requests that the subject be withdrawn from the study.
- The subject, for any reason, requires treatment with another systemic therapeutic agent that has been demonstrated to be effective for treatment of the study indication (e.g., oral corticosteroids, dupilumab, tralokinumab oral calcineurin inhibitor, oral immunosuppressive). In this case, discontinuation from the study occurs immediately upon introduction of the new agent.
- The subject is lost to follow-up. In this case, a reasonable attempt to contact the subject and ascertain his or her status must be made, and these attempts must be documented.
- The subject becomes pregnant at any time during the study.
- A clinically significant change in a laboratory parameter occurs (See Table 4),
- Onset of an opportunistic infection during the study.
- Other: the subject may withdraw from the study for any other reason, including withdrawal of consent.

- The Sponsor or regulatory authorities, for any reason, stop the study. In this case, all subjects will be discontinued from the study. The Investigator will immediately, on discontinuance of the study by the Sponsor, in its entirety or at a clinical trial site, inform both the subjects and the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of subjects or other persons.
- If during the course of treatment, a subject experiences a new onset cardiovascular adverse event consistent with Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 of Grade ≥2, such subjects should be discontinued from further dosing and, if applicable, followed for resolution.
- If a subject experiences a new onset adverse hematologic adverse event (including laboratory abnormalities) of Grade ≥2, such subjects should first have laboratory abnormalities verified by repeat measure, and if repeat measure confirms the new onset abnormality, such subjects should be discontinued from further dosing, and if applicable, followed for resolution.
- If a subject experiences an adverse event Grade ≥ 3 for any organ system, such subjects should be discontinued from further dosing and, if applicable, followed for resolution.
- The study drug should be discontinued in subjects who develop evidence of hepatocellular injury that may be caused by the study drug consistent with Hy's Law. Such an adverse event should be reported as a serious adverse event (SAE).

7.2.2 Laboratory Abnormalities

Table 4 Severe Laboratory Abnormalities Requiring Permanent Withdrawal from RPT193-02

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

7.2.3 Possible Case of Drug-Induced Liver Injury (DILI)

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

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

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

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

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

- The site will attempt to contact the subject and reschedule the missed visit. The site will then counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the last known mailing address of the subject, or local equivalent methods). These contact attempts should be documented in the medical record or study file of the subject.

If all attempts to contact the subject fail, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.0 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor and Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each subject over the duration of the study, not including any extra assessments that may be required, will be specified in the ICF. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Demographic information related to age and ethnicity will be collected at screening.
- In addition to a detailed history of AD, medical history of other non-AD conditions should be obtained including disease duration and current medications. A smoking history should also be obtained.

8.1 Efficacy Assessments

When subjects arrive at a visit requiring efficacy assessments, subjects should begin with subject-reported assessments (i.e., itch NRS, skin pain NRS, PtGA, DLQI, subject-oriented eczema measure [POEM], ADSS, subjective portion of the SCORAD), and as applicable, the ACQ-5 and [redacted] before evaluation by the Investigator. After completion of these subject-reported assessments, AD efficacy assessments will then be performed in a standardized order, starting with the vIGA, followed by the BSA, followed by the EASI score, and finished by the objective portion of the SCORAD.

8.1.1 Rater Qualifications and Training

Investigator assessments of AD will only be performed by trained Investigators or sub-investigators. Raters must complete the protocol-associated training for the vIGA, BSA, EASI, and SCORAD within 6 months prior to site activation. While Investigators or sub-investigators who are board-certified dermatologists are preferred, qualified non-dermatologist physician or

licensed medical professional (e.g., Nurse Practitioner) who has previously had documented experience in such assessments in AD clinical trials may be designated by the primary site Investigator to perform such evaluations. As with other raters in the study, these raters must complete all protocol-associated training.

Every effort should be made to have the same rater perform all AD efficacy assessments for an individual subject through the course of participation in the study.

8.1.2 Subject Questionnaires and Treatment Diaries

Subject questionnaires and treatment diaries will be completed via an electronic application on their personal electronic device or via site provisioned device if they choose not to use their own. If they choose to use their own device, the site will provide clear instructions on how to download and set up the application.

Subjects will complete daily e-Diaries including compliance with study drug and all questionnaires that are required listed in SoA. The e-Diary data will be reviewed regularly for compliance and queries by the monitors and study staff. Any queries identified will be managed by IQB and the clinical site.

8.1.3 Validated Investigator Global Assessment (vIGA)

[redacted]

8.1.4 Body Surface Area (BSA) of AD Affected Skin

The overall BSA affected by AD will be evaluated (from 0% to 100%) at the visits specified in the SoA. 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.

8.1.5 Eczema Activity and Severity Index (EASI)

[redacted]

corticosteroids, topical PDE4 inhibitor (e.g., crisaborole), and/or calcineurin inhibitors or is using [redacted]

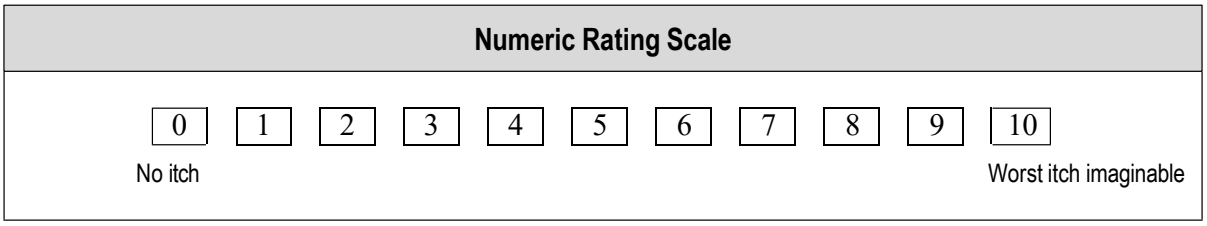
8.1.6 SCORing Atopic Dermatitis (SCORAD)

The SCORAD will be measured at the visits specified in the SoA. The SCORAD grading system [redacted]

8.1.7 Pruritus Numerical Rating Score

The intensity of pruritus will be recorded daily by the subject in an e-Diary using the pruritus NRS. 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 pruritus 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?". [Yosipovitch 2019] The daily (24-hour) pruritus NRS will be recorded and the weekly mean of the daily pruritus NRS will be calculated. The pruritus NRS is presented in Figure 2. Subjects should begin recording daily pruritus NRS scores starting at Day 1.

Figure 2 Pruritus Numeric Rating Scale



8.1.8 Patient-Oriented Eczema Measure (POEM)

[redacted]

8.1.9 Dermatology Life Quality Index Questionnaire (DLQI)

[redacted]

8.1.10 Skin Pain Numerical Rating Scale

The skin pain numerical rating scale was developed for AD subjects by Newton, et. al. [Newton 2019]. 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'.

8.1.11 Patient Global Assessment (PtGA)

[redacted]

8.1.12 Asthma Control Questionnaire (ACQ)

[redacted]

8.1.13 [redacted]

[redacted]

8.1.14 Atopic Dermatitis Sleep Scale

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 [Silverberg 2021]. 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 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.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the [Cardiovascular, Respiratory, Gastrointestinal, and Neurological] systems. Height and weight will also be measured and recorded. At screening only, skin tone should be assessed using the Fitzpatrick skin type scale (I to VI).
- A brief physical examination will include, at a minimum, assessments of the (skin, lungs, cardiovascular system, and abdomen [liver and spleen]).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Vital signs will consist of body temperature, pulse rate, blood pressure, and respiratory rate.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones) and with the subject in a seated or supine position.
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 blood pressure measurement with the subject in a seated or supine position.

8.2.3 Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.0 for QTc withdrawal criteria and any additional QTc readings that may be necessary.
- Triplicate 12-lead ECGs will be recorded with a maximum interval of 5 minutes between the first and the third ECG. The ECGs will be recorded after at least 10 minutes of rest in the

supine position using an automated device equipped with computer-based interval measurements (with no/minimal disturbance by procedures).

8.2.4 Clinical Safety Laboratory Assessments

- See Appendix 11 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- For the three visits requiring fasted labs (Baseline, Day 113, and Day 127), a subject should refrain from eating or drinking (except for water) for a period of at least 8 hours prior to the lab draw.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Medical Monitor and Sponsor notified.
  - All protocol-required laboratory assessments, as defined in Appendix 11, must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3 Adverse Events

The definitions of an AE or SAE can be found in Appendix 12.

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

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the subject to discontinue the study treatment or the study (see Section 7.0).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs will be collected 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.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of the Investigator's awareness of the event, as indicated in Appendix 12. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

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

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 12.

8.3.2 Method of Detecting AEs and SAEs

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 12.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/REBs/IECs, and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review

and then file it along with the Investigator's Brochure and will notify the IRB/REB/IEC, if appropriate according to local requirements.

8.3.5 Adverse Events of Clinical Interest

Events of clinical interest, whether serious or not, in the study include:

- malignancy
- major adverse cardiac events (MACE)
- tuberculosis (TB)
- inflammatory bowel disease (IBD)
- depression and suicidal ideation and behavior
- serious or opportunistic infection
- hypersensitivity reactions

RPT193 has not been associated with any of these events of clinical interest based on preclinical toxicology studies as well as clinical Phase 1 data from RPT193-01. These events of clinical interest will be evaluated on an ongoing basis. A separate analysis of these adverse events will also be performed at the end of the study.

8.3.6 Pregnancy

- Details of all pregnancies in female subjects and, if indicated, female partners of male subjects, will be collected after the start of study treatment and until 30 days after the last administration of study treatment.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 12.
- If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]), the Investigator will report according to the SAE reporting procedures described in Appendix 12.

8.4 Treatment of Overdose

Study drug overdose is any accidental or intentional use of study drug in an amount at least 2 times higher than the dose indicated per-protocol for a given subject. Study drug compliance (see Section 6.4) should be reviewed to detect potential instances of overdose (intentional or accidental).

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

In the event of overdose, the subject should be closely monitored for any potential AEs. All AEs associated with an overdose should be entered on the Adverse Event eCRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor or designee within 24 hours of awareness of the event. Any AEs or SAEs associated with an overdose will be reported using the procedures detailed in Appendix 12.

8.5 Pharmacokinetics

Blood samples will be collected for PK analysis of RPT193 at the visits and time points specified in the SoA.

The analysis of RPT193 in blood samples will be performed at [redacted] using (a) validated liquid chromatography-mass spectrometry/mass spectrometry method(s) (LC-MS/MS). The Bioanalytical Reports for the determinations will be included in the clinical study report (CSR). Exploratory analysis of RPT193 metabolites or related compounds in blood samples may be conducted at Sponsor laboratories.

At the time points defined in the SoA, blood samples will be taken for the analysis of RPT193 (and possibly for RPT193 metabolites or related compounds), in blood samples. The blood samples will be taken via an indwelling intravenous (IV) catheter or by direct venipuncture into K2 ethylenediaminetetraacetic acid [EDTA]-containing tubes.

The actual date and time of each blood sample collection will be recorded in the eCRF.

Details about the collection, processing, handling, storage, and shipping of PK samples will be provided in the laboratory manual.

PK variables will be the plasma concentrations of RPT193 and their PK parameters. A complete list of PK parameters will be provided in the SAP.

8.6 Pharmacodynamics

Blood samples will be collected for pharmacodynamic analysis of RPT193 at the visits and time points specified in the SoA. The pharmacodynamic analysis of RPT193 will include but may not be limited to the assessment of CCR4 occupancy by flow cytometry, measurement of serum cytokines/chemokines levels by immune-assay, and blood cell immunophenotyping by flow cytometry. Note: immunophenotyping will only be performed for subjects in the US and Canada; immunophenotyping will not be performed for subjects in Poland.

8.7 Pharmacogenomics

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

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

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

8.8 Biomarkers

Collection of samples for biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all subjects in this study as specified in the SoA:

- Whole blood
- Serum
- Plasma
- Skin tape strips
- Skin swabs

Note: tape stripping is only required for subjects in the US and Canada; tape stripping should not be performed for subjects in Poland.

Samples may be stored for a maximum of 25 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to RPT193.

8.8.1 RNA Transcriptome Research

Subjects in the US and Canada will have skin tape stripping samples collected at the visits specified in the SoA; tape stripping should not be performed for subjects in Poland. Tape strips will be collected from lesional and non-lesional skin at baseline. Tape strip samples will also be collected at the subsequent visits specified in SoA at the same sites sampled at baseline. For each sampled site, 16 tape-strip units will be placed and removed from the exact same site one after the other. All skin sampling (microbiome samples, and tape strips) should be collected from adjacent sites within the same lesion, whenever possible. Details about the collection, processing, handling, storage, and shipping of tape strip samples will be provided in the laboratory manual and/or the Study Reference Manual.

Transcriptome studies will be conducted using whole transcriptome RNA sequencing, which facilitates the simultaneous measurement of the relative abundances of thousands of ribonucleic acid (RNA) species resulting in a transcriptome profile for each skin sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to AD or the action of RPT193.

The same samples may also be used to confirm findings by application of alternative technologies.

8.8.2 Proteome Research

Plasma and serum proteome studies will be performed by immunoassay for specific proteins of interest. Multiplexed or individual immunoassays may be used to determine relative and/or quantitative changes in protein level because of treatment. Proprietary algorithms and standard statistical techniques, such as analysis of variance (ANOVA) and analysis of covariance (ANCOVA), may be used to identify individual proteins exhibiting statistically significantly different changes in their levels between samples and/or between groups of samples. Alternatively, differentially expressed proteins may be identified by mass spectrometry or equivalent technology. This will enable the evaluation of changes in proteome profiles that may correlate with biological response relating to disease and medically related conditions or the results of treatment. Details about the collection, processing, handling, storage, and shipping of plasma and serum samples will be provided in the laboratory manual.

The samples may also be used to confirm findings by application of alternative technologies.

8.8.3 Skin Microbiome Swab

All subjects will have collection of skin microbiome samples at the visits specified in the SoA. Skin microbiome sampling is a non-invasive procedure that involves passing a swab along the skin. Two skin microbiome samples will be collected at baseline, one from lesional and one non-lesional skin. A skin microbiome sample will also be collected at the subsequent visits specified in the SoA at the same lesional site sampled at Baseline.

All skin sampling (microbiome samples and tape strips) should be collected from adjacent sites within the same lesion, whenever possible.

Details about the collection, processing, handling, storage, and shipping of skin microbiome samples will be provided in the laboratory manual and/or the Study Reference Manual.

8.9 Other Study Procedures

8.9.1 Medical Photography

Medical photographs will be performed at selected sites at the visits specified in the SoA. One or more most affected body regions, per Investigator's judgment, may be photographed.

Photographs will be identified with the following information: study number, subject number, and visit name and date. Digital images will be uploaded [redacted] via the secure website for Sponsor review.

Details about the medical photography will be provided in the Study Reference Manual.

8.9.2 COVID-19-Related Considerations

COVID-19 Vaccination Guidance

Investigators and subjects should consider the schedule of their COVID-19 booster vaccine (if applicable) when planning the timing of their study participation. Where possible, the timing of vaccination should be planned so that a booster vaccination is not administered during the study treatment period. Ideally, administration of a COVID-19 booster vaccine (if applicable) should be given at least 4 weeks prior to the first dose of study treatment for live, attenuated vaccines and 2 weeks prior to the first dose of study treatment for mRNA vaccines. If unavoidable, vaccination with mRNA-based vaccines can proceed during the study, but every effort should be made to avoid administration during the final month of the treatment period, if possible. These events will not be considered major protocol deviations, but are considered prohibited therapies. It should be noted that the effect of RPT193 on the response to COVID-19 vaccination is unknown. The COVID-19 vaccine may lead to AEs (fever, chills, etc.), which will need to be captured and distinguished as related to the vaccine versus RPT193.

COVID-19 Testing Guidance

At the Screening visit (Visit 1) and Baseline visit (Visit 2) prior to the first dose of study treatment, all subjects must have a nasopharyngeal swab, or oropharyngeal swab, nasal swab, or saliva sample collected to test for the presence of the SARS-CoV-2 virus. The sample will be sent to the study's central laboratory or local laboratory, if necessary, for analysis by an acceptable diagnostic assay. Subjects with positive test results at Screening (Visit 1) will be considered screen failures and will not be allowed to enroll per the exclusion criteria for the study. Such screen failed subjects may be considered for rescreening at a later date following consultation with the study Medical Monitor. If results from the COVID-screening at the Baseline visit are immediately available and positive, the subject should be screen failed and may be considered for rescreening at a later date following consultation with the study Medical Monitor. If results from COVID-screening at the Baseline visit are not immediately available at the time of randomization, subjects are allowed to dose with study treatment at the Baseline visit

(Visit 2) provided the Screening test was negative and as long as there is no clinical suspicion of COVID-19 infection or subject recent exposure to an individual with a confirmed, active infection at the time of the Baseline visit.

If the subject's results are positive for SARS-CoV-2 following sample collection at Baseline (Visit 2), the subject will need to be notified immediately upon receipt of the results. The subject should be advised to begin self-isolation and self-monitoring procedures according to any applicable local, state, and/or country-specific health recommendations. Referral to an appropriate health care provider for management of the subject's COVID-19 diagnosis should also be made. The subject's COVID-19 diagnosis will be reported as medical history unless the subject's clinical course progresses such that criterion for SAE reporting is met (see Appendix 12), in which case, all applicable safety reporting procedures will be followed by the site. Sites will also have the option to perform an unscheduled test for the SARS-CoV-2 virus at any time during the treatment phase of the study should a subject's clinical presentation necessitate it, in the Investigator's opinion. The same notification and referral procedures, as outlined in the preceding paragraphs, should be followed by the site. However, it is expected that any COVID-19 diagnosis made from a sample collected after the initiation of study treatment administration be reported as an AE per the requirements of Appendix 12 of this protocol. In the event that a subject tests positive for the SARS-CoV-2 virus at or after Baseline (Visit 2), the Investigator must consult with the study Medical Monitor to determine if the subject should continue with study drug treatment or discontinue from treatment. Determinations will be made on a case-by-case basis with the intent to minimize any increased risk for the subject.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Considerations

The comprehensive SAP with detailed description of all statistical analyses will be developed and finalized before database lock.

All statistical analyses, including summary tables and data listings will be performed using SAS® software (version 9.4 or higher). Continuous endpoints will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum). Categorical endpoints will be summarized using frequency counts and percentages. All individual subject data will be present in listings.

9.2 Sample Size Determination

[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 approximately 265 subjects (approximately 67 per treatment group) will be needed.

9.3 Populations for Analyses

For purposes of analysis, the analysis sets in Table 5 are defined.

Table 5 Analysis Sets

Analysis Set	Description
Full Analysis Set (FAS)	All subjects who have been randomized to a study treatment group. FAS will be the primary analysis set for all efficacy analyses. Subjects will be analyzed according to their randomized treatment.
Per-Protocol (PP) Analysis Set	All subjects in FAS with no major protocol deviation that would have an impact on the primary and key secondary efficacy assessments. Major protocol deviations will be reviewed and determined prior to database lock. Subjects to be excluded from the PP analysis set will be determined based on a blinded data review meeting prior to database lock. Subjects will be analyzed according to their randomized treatment.
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 treatment they received.

9.4 Statistical Analyses

9.4.1 Subject Disposition and Demographics

Subject disposition events as well as the number of subjects in each analysis sets will be summarized using frequency counts and percentages by treatment arms.

Demographic and baseline characteristic will be summarized as appropriate.

9.4.2 Primary Efficacy Analysis

The primary efficacy endpoint is the percent change from baseline in EASI score at Week 16.

The primary estimand is defined as

- Population of interest: adult subjects with moderate-to-severe AD as defined by the inclusion/exclusion criteria
- Variable/endpoint of interest: percent change from baseline in EASI score at Week 16.
- Intercurrent event handling strategy:
  - 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 will be included in analysis.
  - Use of rescue medications: subjects who use rescue medication during the 16-week treatment period will be analyzed by the hypothetical strategy. All EASI scores collected after the start of rescue medication will be set to missing and imputed.
- Population-level summary measure: difference in mean percent change from baseline in EASI score between RPT193 and placebo.

The primary analysis will be performed in FAS. The primary efficacy endpoint will be analyzed with ANCOVA model. The model will include treatment group (each RPT193 dose vs. placebo), baseline vIGA scores, randomization stratification factors and study sites as factor, and baseline EASI score as a covariate. The least square (LS) mean and LS mean difference along with the 95% confidence interval (CI) and p-value will be reported.

The following sensitivity analysis will be planned for the primary estimand:

- In FAS, including only the observed data regardless of rescue medication uses and without missing data imputation.
- In PP analysis set, following the same model as described for the primary estimand.

9.4.2.1 Secondary Efficacy Analysis

For continuous secondary endpoints, the same model as discussed for the primary analyses will be followed. For binary secondary endpoints, a logistic regression model with treatment group, baseline vIGA scores, randomization stratification factors, study sites as factors and baseline score as a covariate will be used.

9.4.2.2 Multiplicity

For the primary efficacy endpoint, 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 vs. placebo. The order of the testing will be performed from the highest RPT193 dose to the lowest dose. Testing will stop if non-significance (2-sided p-value ≥ 0.05) is observed.

9.4.3 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). A TEAE is any condition that was not present prior to treatment with the study drug but appeared following treatment, 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).

The AE summaries will be primarily based on TEAEs. Descriptive statistics for the number and percentage of subjects with TEAEs will be summarized by treatment arm, system organ class, and preferred term for all TEAEs, treatment-related TEAEs, serious TEAEs, and TEAEs leading to discontinuation of study treatment. All TEAEs will be further summarized by maximum severity and causality.

All AEs will be present in a by-subject listing. Serious AEs, and TEAEs leading to discontinuation of study treatment will be present in separate listings.

Adverse Events of Clinical Interest

A separate analysis focused on the following events of clinical interest will also be performed: malignancy, major adverse cardiac events (MACE), tuberculosis (TB), inflammatory bowel disease (IBD), depression and suicidal ideation and behavior, serious or opportunistic infection (e.g., infection resulting in hospitalization, requiring IV antibiotics, or considered life-threatening), and hypersensitivity reactions.

Clinical Laboratory Tests

Laboratory data will be summarized using descriptive statistics for each parameter, including change baseline at each assessment time by treatment arm. Frequency tables or shift tables will be used to present the number and percentages of subjects with laboratory values within/outside normal reference ranges. All laboratory data will be present in the listings. A by-subjects listing will also be provided for subjects with abnormal laboratory results.

12-Lead Electrocardiogram (ECG) and Vital Signs

Descriptive statistics will be used to summarize the observed and change from baseline values of the ECG and vital signs parameters at each assessment time point by treatment group. All ECG and vital signs data will be present in listings.

9.4.4 Other Analyses

Pharmacokinetic (PK), pharmacodynamic, exploratory endpoints and skin microbiome analyses will be summarized using descriptive statistics and will be listed and summarized in a tabular and/or graphical form.

9.4.5 Missing Data

For the primary and key secondary efficacy endpoints, the efficacy data collected after the start of rescue medication will be set to missing. All missing data up to Week 16 will be imputed using a multiple imputation (MI) technique as follows:

- Intermittent missing data will first be imputed using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS PROC MI procedure and imputed datasets with monotone missing pattern will be generated. This applies to intermittent missing data prior to the intercurrent events including early termination of the study treatment as well as initiation of rescue medications.

- The monotone missing values will then be imputed with the imputation model estimated from subjects in the placebo group using the SAS PROC MI procedure with MNAR statement. This approach is based on the missing not at random (MNAR) assumption. This assumes that the missing data in

the RPT193 doses post treatment discontinuation and/or the start of rescue medication follow similar profile as the placebo group.

- Response status (Yes, No) will be derived from the imputed scores in each MI datasets for binary endpoints. The results of the multiple MI datasets will then be combined into a single analysis using PROC MIANALYZE.

As a sensitivity analysis, all missing continuous data up to Week 16 will also be imputed by using last observation carried forward (LOCF). Missing data for responder endpoints will be imputed as treatment failures (TF). Additional sensitivity analyses under different assumptions for missing data handling may be explored in the SAP.

9.5 Interim Analyses

No interim analysis for efficacy is planned.

9.6 Monitoring Committee

There will be no independent Data Monitoring Committee for this study. The safety of study participants will be closely monitored on an ongoing basis by [redacted], [redacted], and Sponsor representatives.

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11.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
ACQ	Asthma Control Questionnaire
AE	Adverse event
AD	Atopic dermatitis
ADSS	Atopic Dermatitis Sleep Scale
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the plasma concentration-time curve at 0 to 24 hours
BALF	Bronchoalveolar lavage fluid
BSA	Body surface area
CI	Confidence interval
C_{max}	Maximum concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease of 2019
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	Cytochrome P450
DLQI	Dermatology Quality of Life Index
EASI	Eczema Activity and Severity Index
ECG	Electrocardiogram
eCRF	Electronic case report form
e-Diary	Electronic Diary
EDTA	Ethylenediaminetetraacetic acid
eGFR	Glomerular filtration rate

Abbreviation	Definition
ET	Early Termination
FAS	Full Analysis Set
FCS	Full conditional specification
FDA	Food and Drug Administration
FITC	Fluorescein isothiocyanate
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HbA1c	Hemoglobin A1c
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C
HIV	Human immunodeficiency virus
IC_{90}	Concentration of an inhibitor where the response is reduced by 90%
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
IgE	Immunoglobulin E
IL	Interleukin
IL-4R	Interleukin 4 receptor
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
JAK	Janus kinase
LC-MS/MS	Liquid chromatography-mass spectrometry/mass spectrometry
LOCF	Last observation carried forward
LS	Least square
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MI	Multiple imputation
NBUVB	Narrowband ultraviolet B
NOAEL	No-observed-adverse-effect-level
NRS	Numerical rating scale
OVA	Ovalbumin
PBMC	Peripheral blood mononuclear cell
PDE4	Phosphodiesterase-4
P-gp	P-glycoprotein
PK	Pharmacokinetics
POEM	Patient-oriented eczema measure
PP	Per-Protocol
PPD	Purified protein derivative
PP-NRS	Peak pruritus numerical rating scale
PRO	Patient-reported outcome
PT	Prothrombin time
PtGA	Patient global assessment
PUVA	Psoralen-UV-A
QD	Once daily
QOL	Quality of Life
RBC	Red blood cell
REB	Research Ethics Board
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCORAD	SCORing Atopic Dermatitis
SD	Standard deviation
[redacted]	[redacted]
SoA	Schedule of Activities
sRO	Surface receptor occupancy
SUSAR	Suspected unexpected serious adverse reactions
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TF	Treatment failure

Abbreviation	Definition
Th2	Type 2 helper T cell
t_{max}	Time to maximum concentration
TNF	Tumor necrosis factor
ULN	Upper limit of normal
UVA1	Ultraviolet A1
VAS	Visual analog scale
vIGA	Validated Investigator Global Assessment
vIGA-AD	Validated Investigator Global Assessment for atopic dermatitis
WOCBP	Women of childbearing potential

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/REB/IEC by the Investigator and reviewed and approved by the IRB/REB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/REB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/REB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/REB/IEC.
  - Notifying the IRB/REB/IEC of SAEs or other significant safety findings as required by IRB/REB/IEC procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 CFR, ICH guidelines, the IRB/REB/IEC, European regulation 536/2014 for clinical studies, other country-specific requirements, as applicable, and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 15). The study will not start at any study center at which the Investigator has not signed the protocol.

Protocol Adherence and Deviations

The Investigator and site personnel should conduct the study in compliance with the protocol and should use continuous vigilance to identify and report protocol deviations. A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol that may be on the part of the Investigator, site personnel, or the subject. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include

enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study. The Investigator should not implement any deviation from the protocol without agreement from the Sponsor and prior review and approval from the IRB/REB/IEC of an amendment, except where necessary to eliminate an immediate hazard to a study subject, or when the change involves only logistical or administrative aspects of the study, such as a change in a monitor or telephone number. If a large number of protocol deviations are noted at a site, the Investigator shall implement corrective actions and evaluate the effectiveness of the corrective actions as they pertain to protocol deviations. Issues of non-compliance with the study protocol (repeated protocol deviations) may result in a corrective action plan or non-use of study data (depending on the quantity and content of protocol deviations). In the event of an important protocol deviation, the Investigator will discuss the deviation with the Sponsor's medical monitor and will come to an agreement as to whether the subject should be withdrawn from the study due to the important protocol deviation.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the Sponsor files.

Informed Consent Process

- The Investigator or a person designated by the Investigator (if acceptable by local regulation), will explain the nature of the study (i.e., purposes, procedures, potential risk, and his or her rights as a research subject) to the subject or his/her legally authorized representative and answer all questions regarding the study. In addition, insurance coverage provided during the study will be explained.
- Subjects must be informed that their participation is voluntary and that they may withdraw from the study at any time for any reason, without prejudice. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/REB/IEC or study center.

- Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.
- The subject will sign the informed consent document prior to any procedures being done specially for the study. The study source must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative for their records.
- If new safety information results in significant changes in the risk benefit assessment, or if any new information becomes available that may affect the willingness of a subject to continue to participate the consent form should, if necessary, be reviewed and updated by the Sponsor and approved by the IRB/REB/IEC. All subjects should be informed of the new information, given a copy of the revised form and asked to give their consent to continue in the study. When the ICF is revised, re-consent is required for subjects to continue on study.
- Subjects who are rescreened are required to sign a new ICF.

Clinical Monitoring and Inspections

The CRO monitor is responsible for visiting sites at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH Good Clinical Practice (GCP) and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

The monitor will communicate deviations from the protocol, SOPs, GCP, and applicable regulations to the Investigator and will ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and documented.

In accordance with ICH GCP and the Sponsor's audit plans, the study may be selected for audit by representatives from the Sponsor. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories etc.) and review of study-related records (e.g., eCRFs, source data, and other pertinent documents) will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/REB/IEC members, and by inspectors from regulatory authorities.
- The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

Administrative Structure

Table 6 Study Administrative Structure

Function	Responsible Organization
Study Operations Management Medical Monitoring	CRO
Study Master File	CRO
Randomization Code	Sponsor/CRO
Data Management	CRO
Clinical Supply Management	Sponsor/CRO
Quality Assurance Auditing	CRO
Biostatistics Medical Writing	Sponsor/CRO
Laboratory Assessments	Sponsor/ICON
Electrocardiogram Collection, Review, and Analysis	[redacted]
Pharmacokinetic Sample Testing	[redacted]
Management of Event Adjudication	Not applicable
Adjudication Committee	Not applicable
Steering Committee	Not applicable
Safety Monitoring Committee (see Section 9.6)	Sponsor/CRO

Medical Monitor

Dissemination of Clinical Study Data

A clinical study report will be prepared detailing the outcomes of this study and provided to health authorities in the countries where the study is being conducted. The Sponsor will ensure that this report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).

Data Quality Assurance

- All subject data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/REB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to

source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Study Center Closure

The Sponsor/ designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/REB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

Appendix 3 Validated Investigator Global Assessment (vIGA)

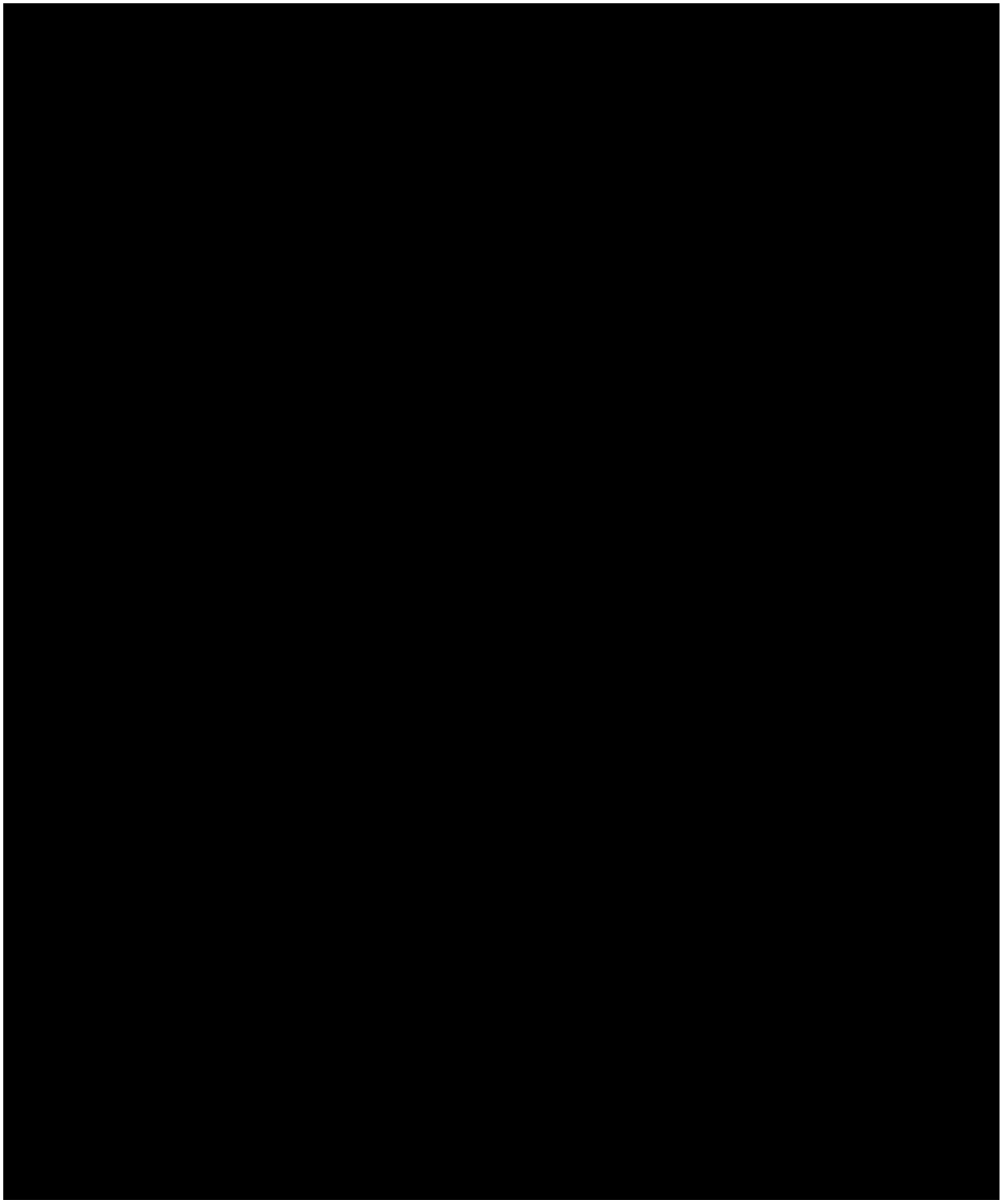
[redacted]

[redacted]

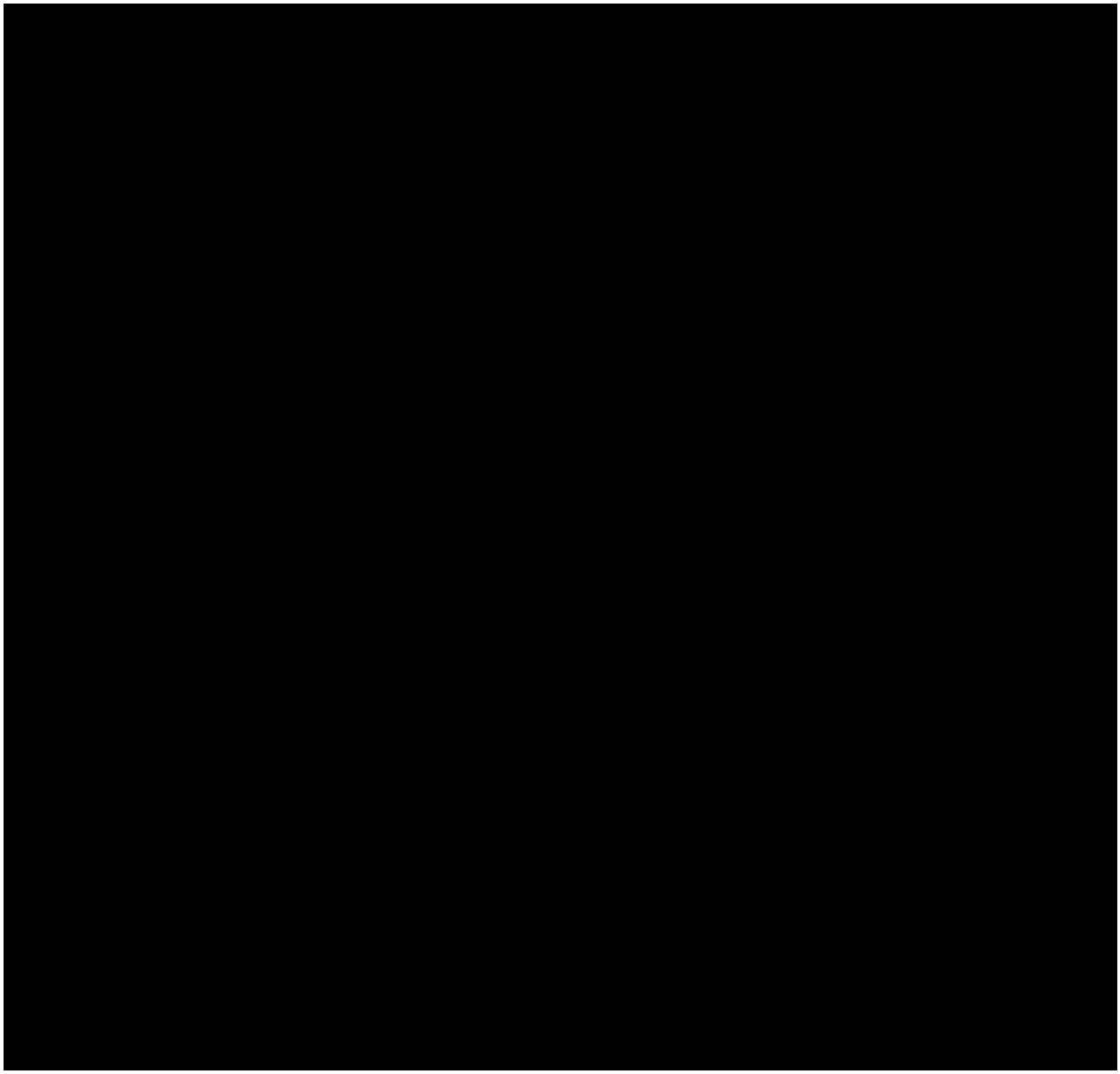
[redacted]

[redacted]

Appendix 4 Eczema Activity and Severity Index (EASI)



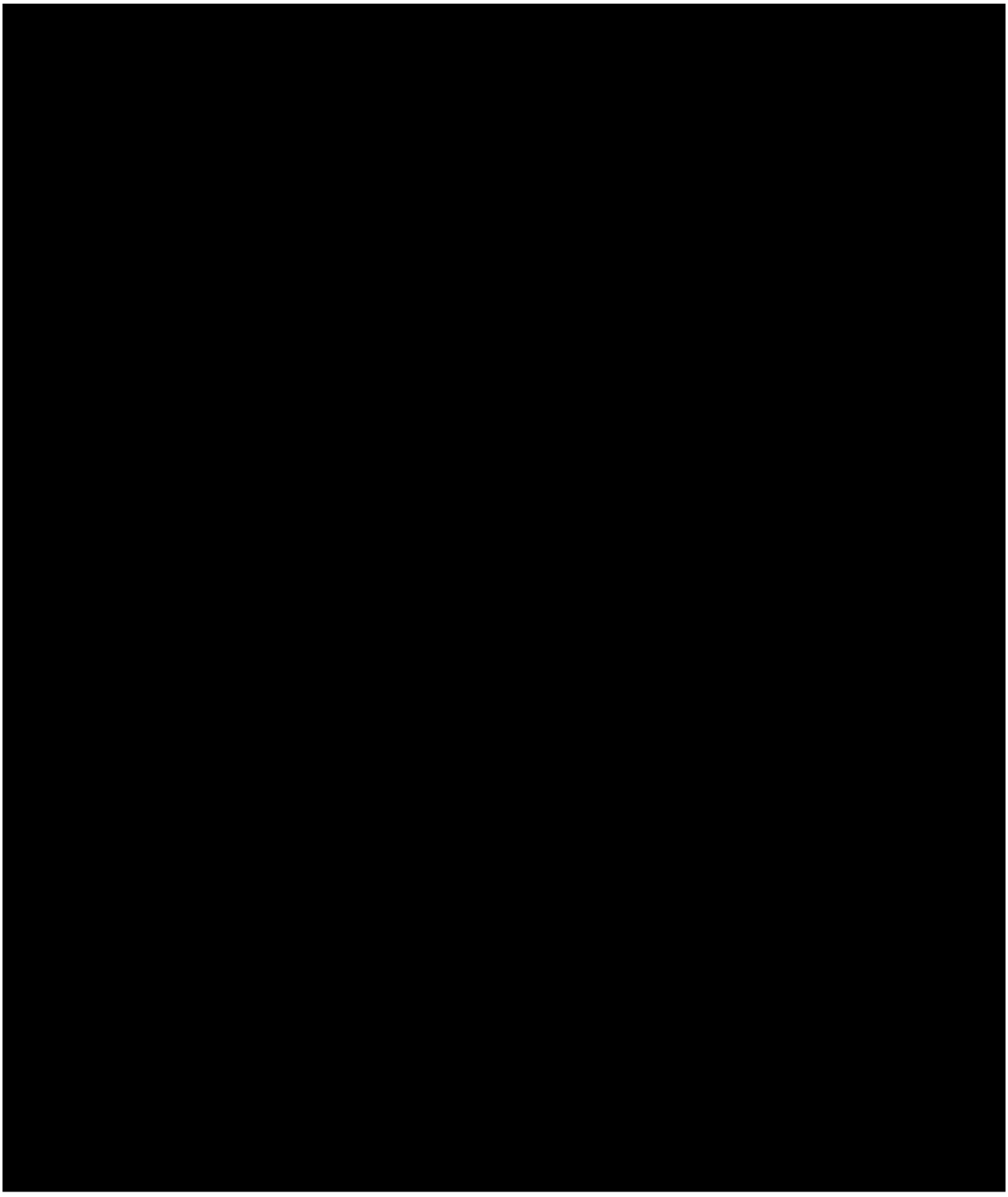
EASI guidance December 14



EASI guidance December 14

Appendix 1: Eczema Area and Severity Index (EASI) - Extent of eczema per body region

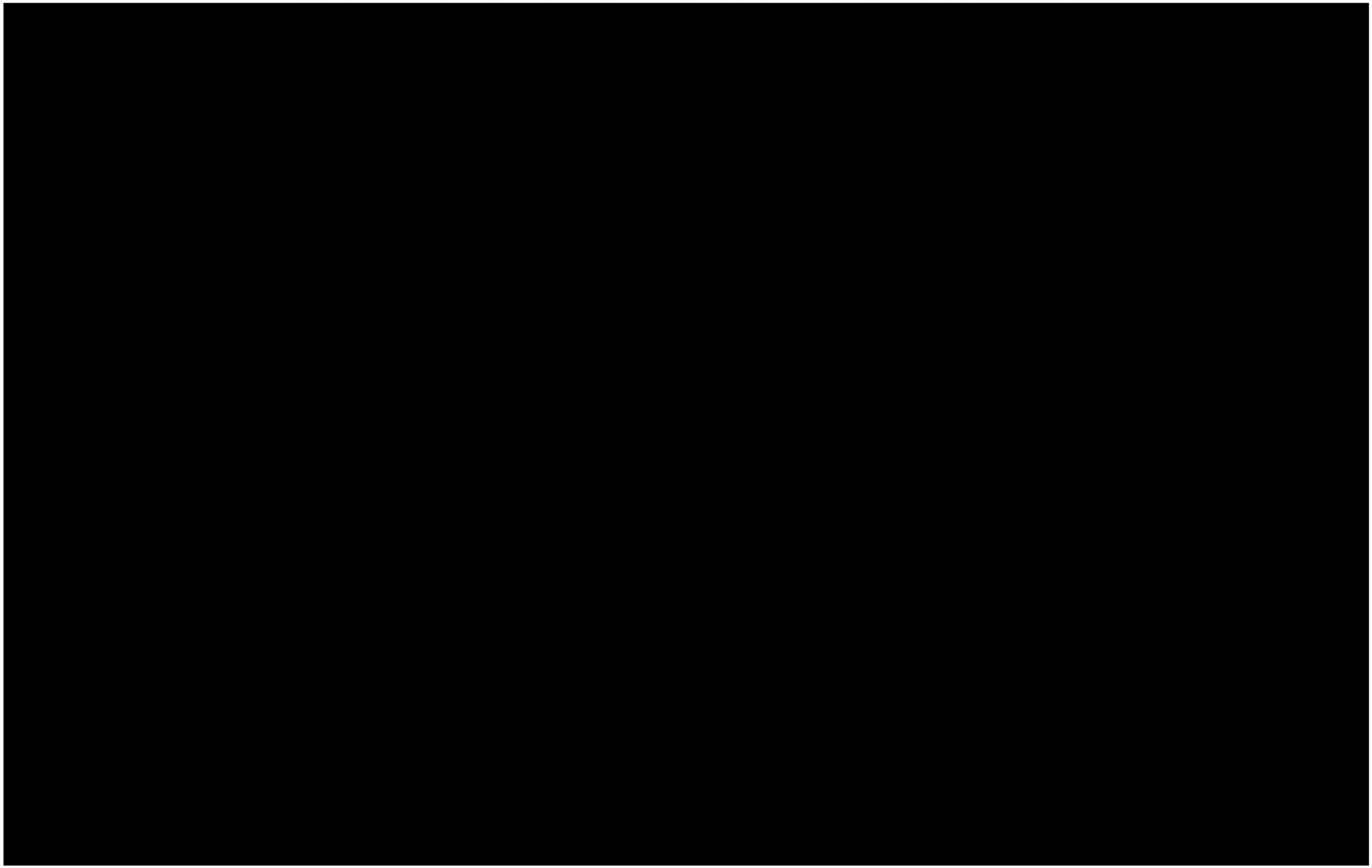
Appendix 2: Eczema Area and Severity Index (EASI) –lesion severity atlas



Appendix 3.1: Eczema Area and Severity Index (EASI) case report form – age <8 years

[redacted]

Appendix 3.2: Eczema Area and Severity Index (EASI) case report form - age≥8 years



Appendix 4 - Frequently Asked Questions

What is the difference between edema/papulation and lichenification?
Consider edema/papulation as corresponding to the acute signs of atopic dermatitis that reflect histological spongiosis. Lichenification are more firm thickened plaques with accentuation of the skin markings that develop as a result of prolonged scratching or rubbing in chronic disease. In darker skin types, follicular lichenification may present as firm flat-topped discrete papules. Grade these chronic lesions as lichenification.

How do I grade prurigo nodules?
Prurigo nodules are larger, deeper lesions as a result of chronic scratching and are graded as areas of lichenification.

How do I grade erythema in darker skin?
To avoid underestimating inflammation in patients with darker skin tones, take into account the underlying skin pigment when grading erythema. Often this means increasing your erythema grade by one level.

Can half-steps be used to assess lesion severity?
The original EASI validation study allowed for half steps. These may be helpful when trying to average the severity of a parameter over a region. For example, if there are some areas with an erythema grading of 2 and some areas more consistent with a severity of 3, 2.5 may be a good choice.

What if most areas in a region are a severity grade of 1, but there are some areas that are a grade 3?
Attempt to average the severity across the involved areas in that region. If these areas are close to equal in size, a score of 2 would be most appropriate. If the majority of involved areas are a grade 1, a score of 1 or 1.5 is more appropriate. Be careful not to score the highest severity in a region but the average one.

How do I grade xerosis (dryness), ichthyosis and hyperlinear palms?
Unless there is active acute or chronic eczema overlying these findings, they are not included in the EASI assessment.

How precise should my assessment of eczema extent be?
The *region scores*, which reflect the extent of eczema, were designed and validated as rough estimates of the percentage of involved skin. Each region is given a *score* ranging from 0 to 6, based on a "ballpark" estimation of extent (see region score table in page 1). If you find it difficult to provide a rough estimate of disease extent, you can use the schematics in Appendix 1 to guide you. More time-consuming methods for evaluating disease extent such as the rule of nines or the 'palm' method are generally unnecessary, as the EASI was designed to be...easy.

EASI guidance December 14

My patient has responded well to treatment and significantly improved since the last visit. Should I adjust the grading based on the patient's relative improvement?
No. The EASI is a static score, meaning that it is done independently at each time point to reflect current severity. You should grade the EASI per visit regardless of the previous status. Studies have shown that the EASI score has good responsiveness, meaning that overall it is sensitive to change and the improvement will be reflected in the total score.

Can the EASI be used in children?
Yes. The EASI is performed in the same method in all age groups, but the calculation of the final EASI score differs by age. When calculating the EASI, each of the 4 region scores is multiplied by a constant which reflects the relative contribution of that region to the total body surface area. For patients 8 years and older the multipliers are 0.1 for the head/neck, 0.2 for the upper extremities, 0.3 for the trunk and 0.4 for the lower extremities. Below 8 years of age the head/neck multiplier is increased to 0.2 while the lower extremities multiplier decreases to 0.3, consistent with the proportions of these regions in childhood. Refer to Appendix 3 for EASI forms by age.

What happens if a child turns 8 during the course of the study? Which EASI formula should I use?
There are no clear-cut definitions for this situation. In general, if the study is a short term study such as an RCT lasting a few months – using the same formula throughout the trial is preferred, even if the child turns 8 during these months. Keeping the EASI formula consistent in this scenario can serve to preserve the EASI sensitivity to change (e.g. its change in response to treatment) without compromising the validity of the score.
In long term studies such as cohort studies lasting a year or longer, it is important to update the EASI formula based on the physical changes children go through. Switching to the age 8+ formula once a child is older is preferred in that scenario.

What do the terms erythema, edema/papulation, excoriation and lichenification mean?
These are key signs of atopic dermatitis. Recognizing and grading them properly requires training on the visual and physical exam consistent with these signs. Generally speaking, erythema is skin redness; edema/papulation refers to an elevation or swelling of the skin (that should be differed from lichenification below); excoriations are scratch marks that have broken the skin surface; and lichenification is a leathery thickening of the skin with exaggerated skin markings.

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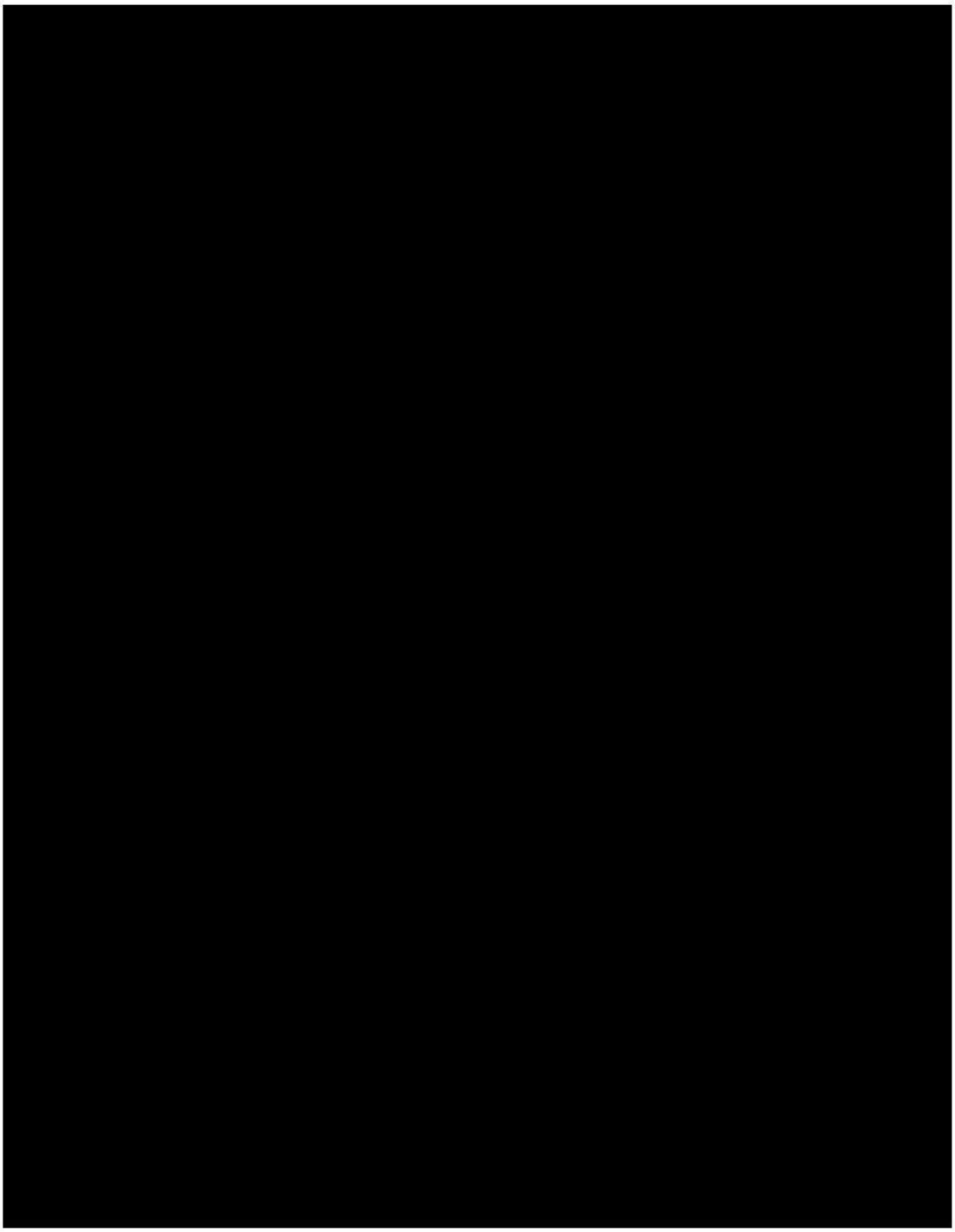
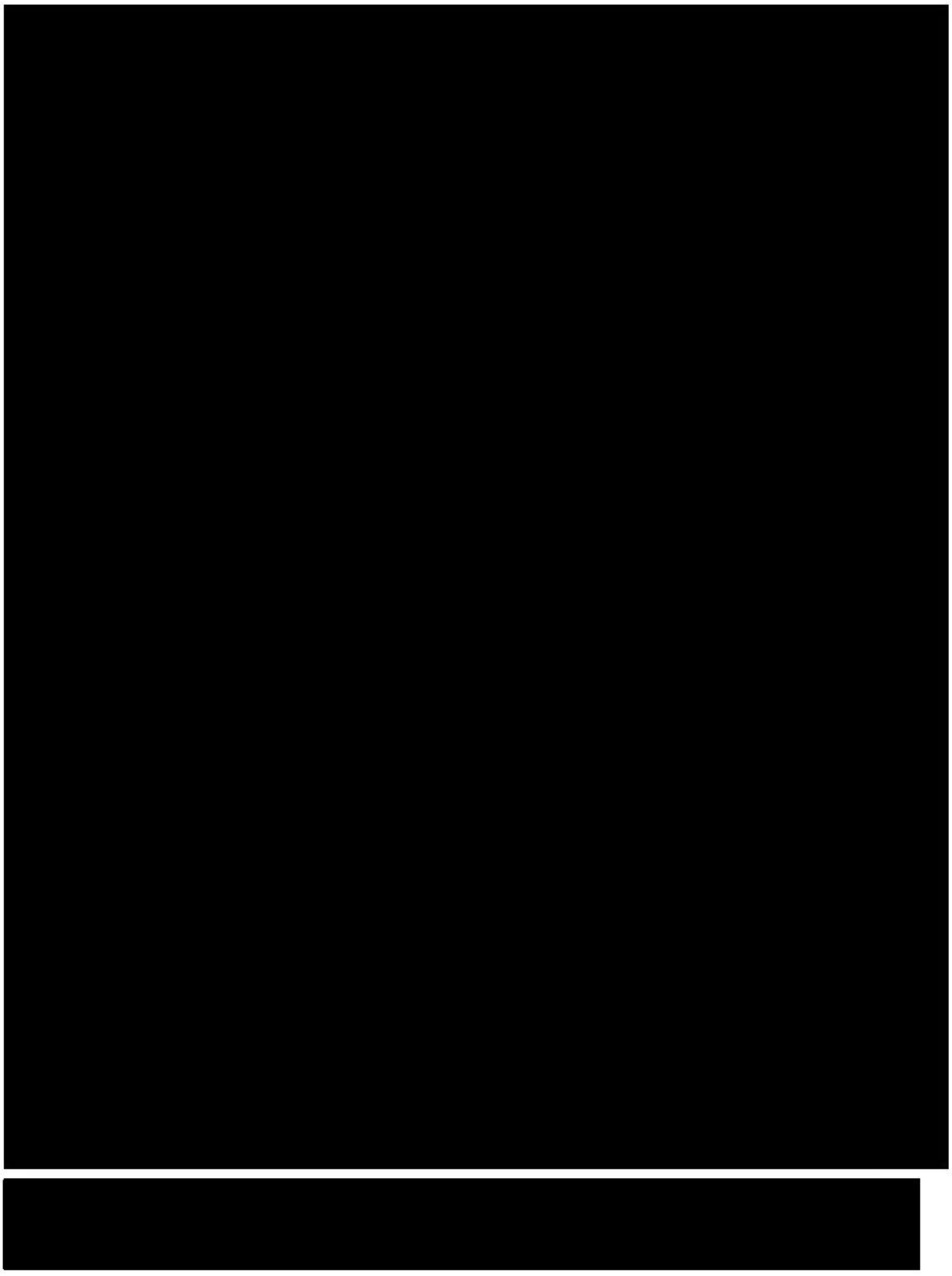
Appendix 5 SCORing Atopic Dermatitis (SCORAD)

[redacted]

26 European Task Force on Atopic Dermatitis/SCORAD

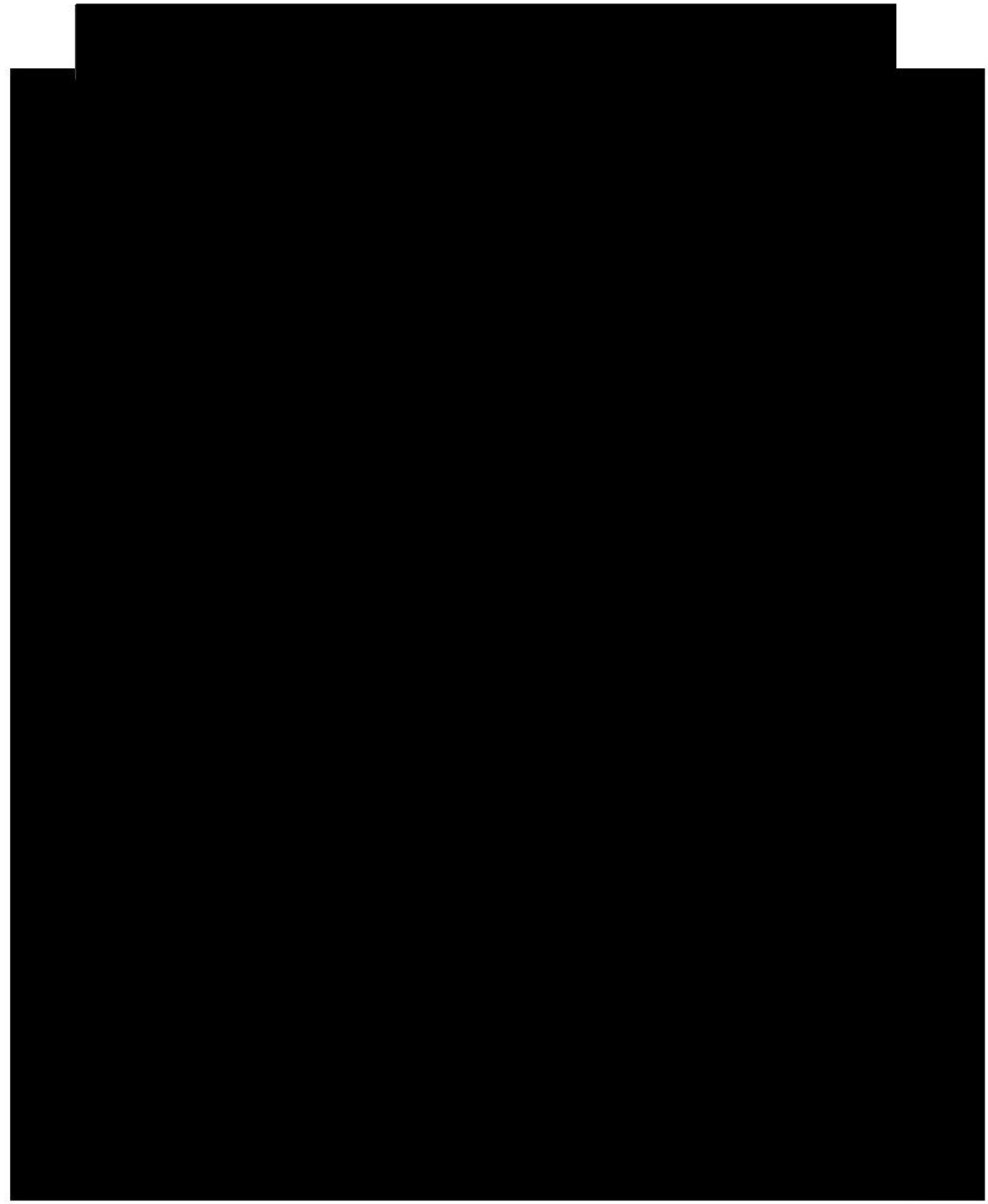
Appendix 6 Patient-Oriented Eczema Measure (POEM)





Appendix 7 [redacted]

[redacted]



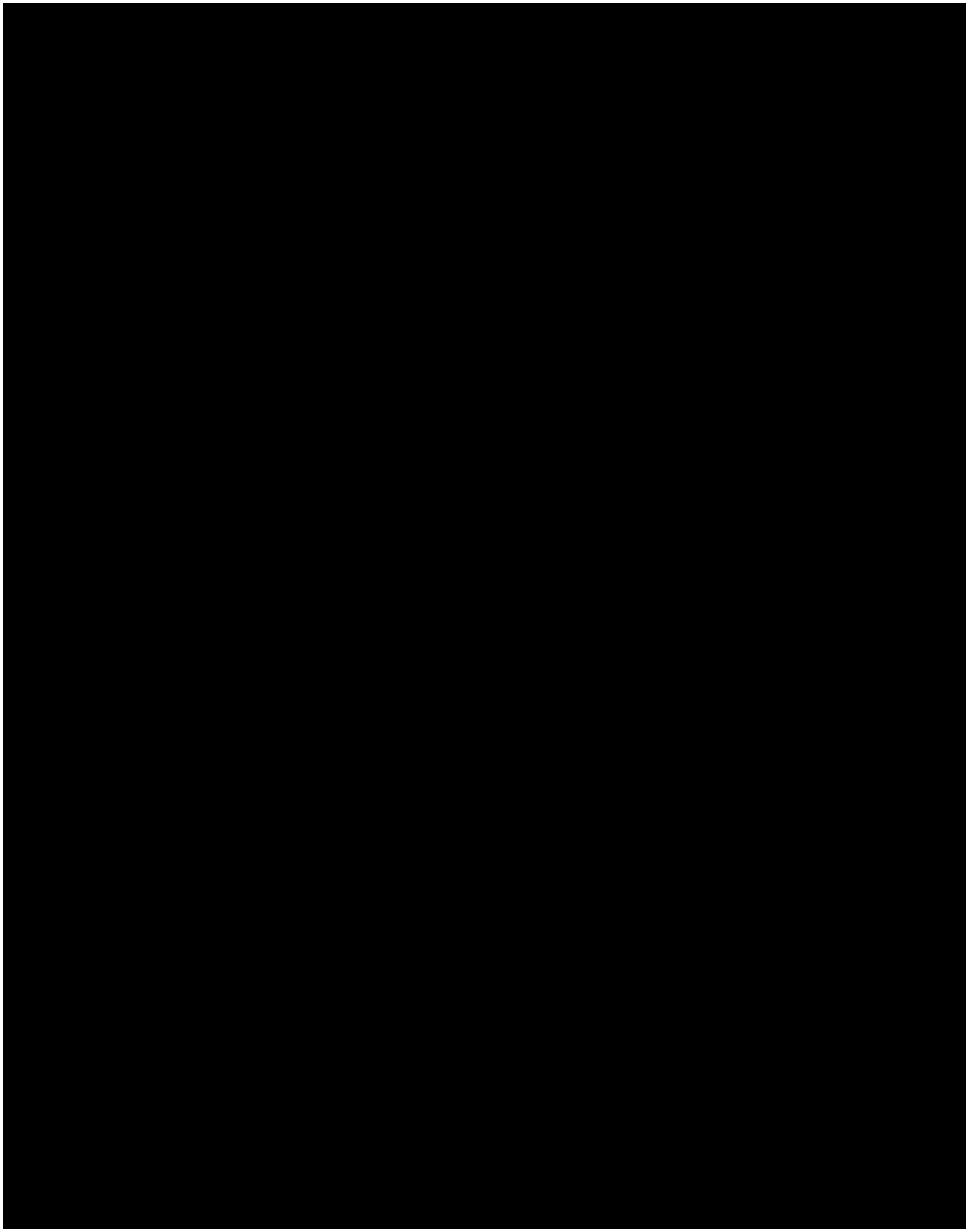
Appendix 8 Patient Global Assessment (PtGA)

[redacted]

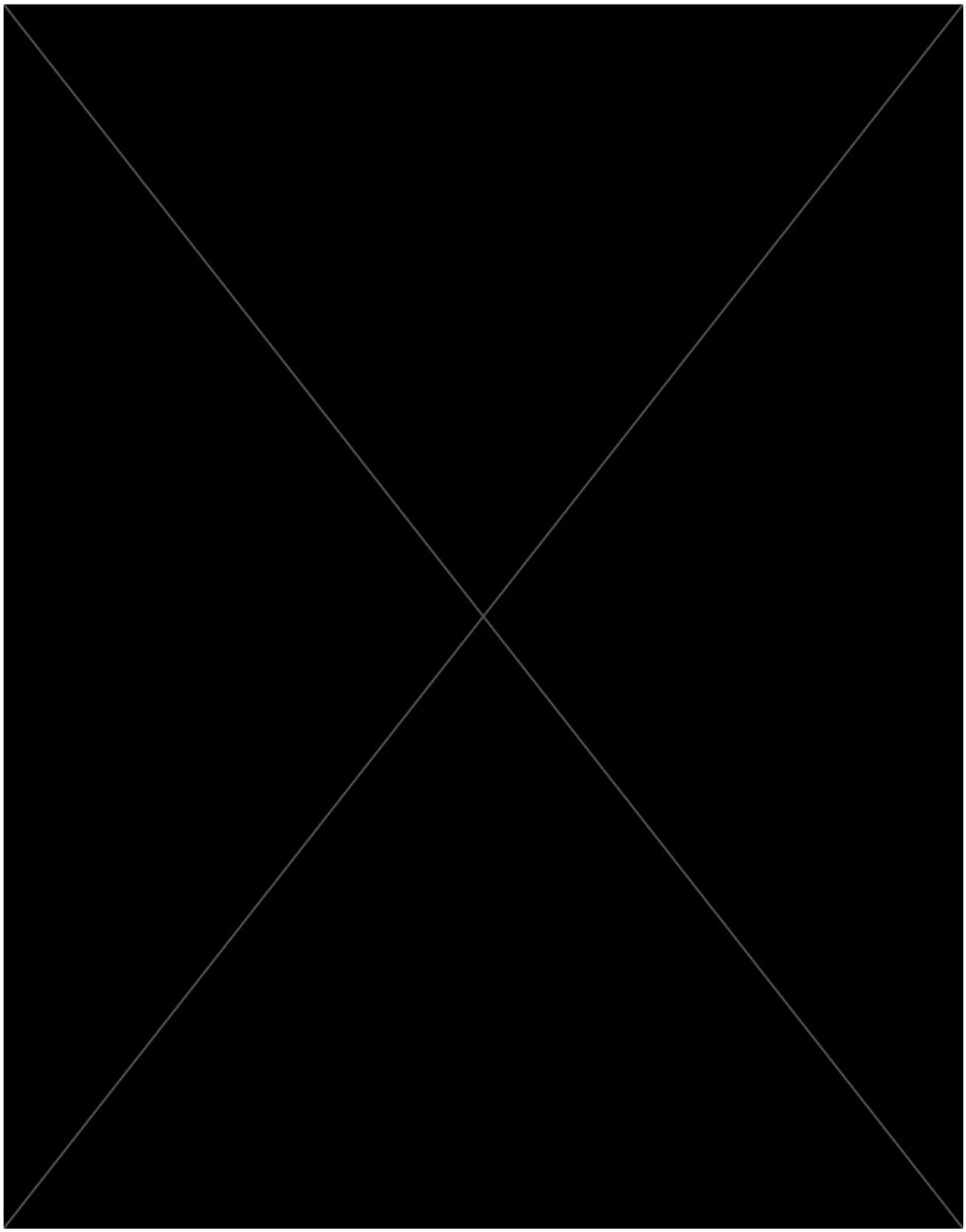
[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Appendix 9 Asthma Control Questionnaire (ACQ)



Appendix 10 [redacted]



Appendix 11 Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.0 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 7 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	White Blood Cell Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Red Blood Cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
	White Blood Cell Count			
Clinical Chemistry[a]	Blood Urea Nitrogen	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [fasting]	Calcium	Alkaline phosphatase	Cholesterol (Total, HDL, LDL)[1]
	Albumin	Chloride	GGT	LDH
	Triglycerides	Uric Acid	Coagulation panel	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum human chorionic gonadotropin (hCG) pregnancy test at screening and urine at baseline and during study (as needed for women of childbearing potential)[b] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody or specify other tests)			

Laboratory Assessments	Parameters
	• Tuberculosis test (PPD or QuantiFERON-TB Gold or T-spot) The results of each test must be entered into the (e)CRF.
NOTES: [a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis). [b] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/REB/IEC.	

[1] 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.

Investigators must document their review of each laboratory safety report.

Pharmacokinetics results that could unblind the study will not be reported to study centers or other blinded personnel.

Appendix 12 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

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

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

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

Definition of TEAE

TEAE Definition
• A TEAE is any condition that was not present prior to treatment with the study product but appeared following treatment, 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).

Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d) Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other medically important serious event: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

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

Assessment of Intensity

The intensity of an AE is an estimate of the relative severity of the event made by the Investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- Mild: The symptom is barely noticeable to the subject and does not influence performance of daily activities. Treatment is not ordinarily indicated.
- Moderate: The symptom is sufficiently severe to make the subject uncomfortable, and performance of daily activities is influenced. Treatment may be necessary.
- Severe: The symptom causes severe discomfort, and daily activities are significantly impaired or prevented. Treatment may be necessary.

Please note that the severity of cardiovascular and hematologic adverse events only will also be graded according to the CTCAE Version 5.0.

Assessment of Causality

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

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

- Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or

other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- Potentially Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be Related: A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related: The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

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

Follow-up of AEs and SAEs

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

Reporting of SAEs

Safety Event Reporting to [redacted] via Paper CRF
• Email transmission of the paper Safety Event Report Form is the preferred method to transmit safety event information to [redacted] Safety with facsimile as a back-up method, if necessary. • Safety events should be reported to [redacted] at: • [redacted] [redacted]

Appendix 13 Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.
   Note: Documentation can come from the study center personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male subjects

- Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following [during the protocol-defined time frame in Section 5.1]:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
  - Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
- In addition, male subjects must refrain from donating sperm for the duration of the study and for 90 days after the last dose of study treatment.

- Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and 90 days after the last dose of study treatment.

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation[b] • Oral. • Injectable.
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). • Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: [a] Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. b Female study participants who are women of childbearing potential using one of the highly effective, hormonal contraceptives described above (either birth control pills or implantable devices) will be required to also employ a barrier method of contraception (e.g., condom use by a male partner, diaphragm, or cervical cap) for a minimum of 30 days following the last dose of study drug. Male study participants with partners who are women of childbearing potential using one of the highly effective, hormonal contraceptives described above (either birth control pills or implantable devices) will be required to also employ a barrier method of contraception (e.g., condom use by a male partner, diaphragm, or cervical cap) for a minimum of 90 days following the last dose of study drug.

Pregnancy Testing:

- WOCBP should only be included after a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing should be performed at the times specified in the SoA during the study period after the last dose of study treatment and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive RPT193.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor or designee within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]), the investigator will report according to the SAE reporting procedures described in Appendix 12.

- Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor or designee as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study treatment.

Reporting Pregnancy Information

Email transmission of the paper Pregnancy Report Form is the preferred method to transmit safety event information to [redacted] with facsimile as a back-up method, if necessary.

Safety events should be reported to [redacted] at:

Email: [redacted]

Fax: [redacted]

Appendix 14 Table of Topical Corticosteroid Potencies

Category	Drug	Formulation
Ultra High (I)	Clobetasol proprionate	Cream 0.05% Ointment 0.05% Lotion 0.05%
	Fluocinonide	Cream 0.1%
	Diflorasone diacetate	Ointment 0.05%
	Halobetasol proprionate	Cream 0.05% Ointment 0.05%
High (II)	Amcinonide	Ointment 0.1%
	Betamethasone diproprionate	Ointment 0.05%
	Desoximetasone	Cream 0.05% Ointment 0.05%
	Fluocinonide	Cream 0.05% Ointment 0.05%
	Halcinonide	Cream 0.1% Ointment 0.1%
High (III)	Betamethasone diproprionate	Cream 0.05%
	Betamethasone valerate	Ointment 0.1%
	Dicflorasone diacetate	Cream 0.05%
	Triamcinolone acetonide	Ointment 0.1%
Moderate (IV and V)	Betamethasone dipropionate	Lotion 0.02%
	Betamethasone valerate	Cream 0.1% Lotion 0.1%
	Desoximetasone	Cream 0.05%
	Fluocinolone acetonide	Cream 0.025% Ointment 0.025%
	Fluticasone proprionate	Cream 0.05%
	Fludroxycortide	Ointment 0.05%
	Hydrocortisone butyrate	Ointment 0.1% Cream 0.1%
	Hydrocortisone probutyrate	Cream 0.1%
	Hydroxycortisone valerate	Cream 0.2% Ointment 0.2%
	Mometasone furoate	Cream 0.1% Ointment 0.1%
	Triamcinolone acetonide	Cream 0.025% Lotion 0.025% Cream 0.1% Lotion 0.1%

Category	Drug	Formulation
Low (VI)	Betamethasone valerate	Lotion 0.05%
	Desonide	Cream 0.05% Ointment 0.05% Lotion 0.05%
	Fluocinolone acetonide	Cream 0.01%
Low (VII)	Dexamethasone sodium phosphate	Cream 0.1%
	Hydrocortisone	Cream 1% Lotion 1% Ointment 1% Cream 2.5% Lotion 2.5% Ointment 2.5%
	Hydrocortisone acetate	Cream 1%
	Methylprednisolone acetate	Cream 0.25%

Appendix 15 Signature of Principal Investigator

PROTOCOL TITLE: A Phase 2 study to evaluate the efficacy and safety of RPT193 as monotherapy in adults with moderate-to-severe atopic dermatitis

PROTOCOL NO: RPT193-02

VERSION: Amendment 2.0

This protocol is a confidential communication of RAPT Therapeutics, Inc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to the CRO.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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