Received: 12 May 2023 | Revised: 27 September 2023 | Accepted: 14 October 2023

DOI: 10.1111/all.15949

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

ORIGINAL ARTICLE

Clinical and molecular effects of oral CCR4 antagonist RPT193 in atopic dermatitis: A Phase 1 study

Robert Bissonnette[1] | Janet DuBois[2] | Paola Facheris[3] | Ester Del Duca[3] | Madeline Kim[3] | Joel Correa Da Rosa[3] | Damian L. Trujillo[4] | Swaroop Bose[3] | Angel D. Pagan[3] | David Wustrow[4] | Dirk G. Brockstedt[4] | Brian Wong[4] | Paul D. Kassner[4] | Jasmina Jankicevic[4] | William Ho[4] | Laurence E. Cheng[4] | Emma Guttman-Yassky[3]

[1]Innovaderm Research Inc., Montreal, Quebec, Canada

[2]DermResearch, P.A., Austin, Texas, USA

[3]Laboratory of Inflammatory Skin Diseases, Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[4]RAPT Therapeutics, Inc., South San Francisco, California, USA

Correspondence
Emma Guttman-Yassky, Laboratory of Inflammatory Skin Diseases, Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
Email: emma.guttman@mountsinai.org

Present address
Paola Facheris, Dermatology Unit, IRCCS Humanitas Research Hospital, Milan, Italy

Funding information
RAPT Therapeutics, Inc.

Abstract

Background: RPT193 is an orally administered small molecule antagonist of the human C-C motif chemokine receptor 4 (CCR4) that inhibits the migration and downstream activation of T-helper Type 2 (Th2) cells. We investigated single- and multiple-ascending doses of RPT193 in healthy subjects, and multiple doses of RPT193 in subjects with moderate-to-severe atopic dermatitis (AD).

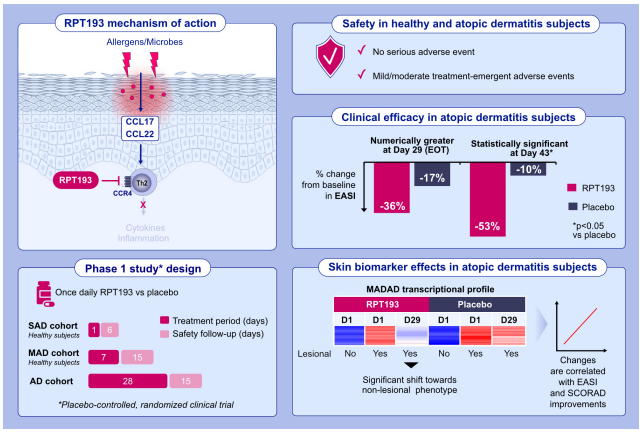
Methods: This was a first-in-human randomized, placebo-controlled Phase 1a/1b monotherapy study (NCT04271514) to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and CCR4 surface receptor occupancy in eligible healthy subjects and subjects with moderate-to-severe AD. Clinical efficacy and skin biomarker effects of RPT193 monotherapy were assessed as exploratory endpoints in AD subjects.

Results: In healthy ($n = 72$) and AD subjects ($n = 31$), once-daily RPT193 treatment was generally well tolerated, with no serious adverse events reported and all treatment-emergent adverse events reported as mild/moderate. In AD subjects, numerically greater improvements in clinical efficacy endpoints were observed with RPT193 monotherapy versus placebo up to the end of the treatment period (Day 29), with statistically significant improvement, compared to Day 29 and placebo, observed 2 weeks after the end of treatment (Day 43) on several endpoints ($p < .05$). Moreover, significant changes in the transcriptional profile were seen in skin biopsies of RPT193-treated versus placebo-treated subjects at Day 29, which were also significantly correlated with improvements in clinical efficacy measures.

Abbreviations: CCL17, C-C motif chemokine ligand 17; CCL22, C-C motif chemokine ligand 22; CCR4, C-C motif chemokine receptor 4; EASI, Eczema Area and Severity Index; EOT, end of treatment; MAD, multiple ascending dose; MADAD, meta-analysis derived atopic dermatitis; NL, non-lesional; SAD, single ascending dose; SCORAD, SCORing Atopic Dermatitis; Th, T-helper cell.

Conclusions: To our knowledge, this is the first clinical study with an oral CCR4 antagonist that showed clinical improvement coupled with modulation of the cutaneous transcriptomic profile in an inflammatory skin disease.

KEYWORDS
atopic dermatitis, biomarkers, chemokines, dermatology



GRAPHICAL ABSTRACT

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease that is estimated to affect ~15%–20% of children and up to 10% of adults worldwide, with growing prevalence.[1,2] AD negatively impacts overall quality-of-life, with sleep disturbance related to pruritus and pain, and other social, emotional/mental, and financial challenges for patients and their families/caregivers.[3–5] Given its high-prevalence, AD poses significant public health and economic burdens due to considerable disease-related morbidity and disability, increased healthcare resource utilization, impacts on work productivity, and high cost of care for payers and patients.[6–10] These clinical and economic burdens highlight the importance of optimal disease management.

AD has complex pathophysiology driven by multiple interconnected factors including genetics, microbial imbalance, immune dysregulation, and environmental triggers leading to skin inflammation and epidermal barrier dysfunction.[2,11] Upregulation of the Type 2 helper T cell (Th2) pathway has been demonstrated to play a central role in the pathogenesis of AD and contributes substantially to the aberrant immune activation, skin barrier dysfunction, and propagation of inflammation and itch.[11–19] Molecular profiling studies in lesional and non-lesional skin biopsies,[20–22] as well as blood,[23–25] of subjects with AD have revealed upregulated expression of Th2 markers and found strong correlations with disease severity.

The Th2 immune response is initiated and sustained when Th2 cells are recruited to the site of inflammation. This recruitment of Th2 cells is driven by the binding of two principal human C-C motif chemokine receptor 4 (CCR4) ligands: thymus and activation-regulated chemokine (TARC) also known as C-C motif chemokine ligand 17 (CCL17), and macrophage-derived chemokine (MDC) also known as CCL22.[26] Individuals with AD and other allergic disorders have significantly elevated levels of both TARC/CCL17 and MDC/CCL22 in blood plasma.[27] Circulating TARC/CCL17 has been shown to correlate with AD disease severity and has been described as a biomarker for AD treatment response.[28] CCR4, which is highly expressed on Th2 cells, has been shown to be critical for homing of Th2 cells to skin following cutaneous antigen challenge in mice.[29–31] In pre-clinical models of AD, Th2-dominated allergic skin inflammation characteristic of acute AD skin lesions was observed following cutaneous antigen challenge in wildtype mice, but not in Ccr4$^{-/-}$ mice. Furthermore, adoptive transfer of T cells from orally immunized wildtype but not Ccr4$^{-/-}$ mice transferred allergic skin inflammation to naïve recipients. CCR4 was not found to be required for systemic immune response to oral antigen challenge, demonstrating that CCR4 is a nonredundant component of lymphocyte trafficking that is skin-specific.[31] These findings suggest that inhibiting the ability of CCR4 ligands to bind to CCR4 may prevent migration of Th2 cells into these inflamed tissues and makes CCR4 a potential target for the treatment of AD.

RPT193 is an orally administered small molecule CCR4 antagonist that is currently being investigated as a potential treatment for AD and other allergic disorders including asthma. In preclinical assessments, RPT193 exhibited high selectivity for CCR4 and decreased cell surface expression of CCR4 in cellular assays.[32] CCR4 antagonists have previously been shown to ameliorate AD-like skin lesions in an AD mouse model.[33] Here, we present the findings of

the first-in-human, Phase 1a/1b, multi-center, randomized, double-blind, placebo-controlled study (RPT193-01; NCT04271514) that investigated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of RPT193 monotherapy in healthy subjects and subjects with moderate-to-severe AD. Clinical efficacy of RPT193, and the biological effects of RPT193 on the skin tissue, were also assessed as exploratory endpoints in AD subjects.

2 | METHODS

2.1 | Study design

The RPT193-01 study was divided into 3 parts (Appendix Table 1): (1) single ascending dose (SAD) and food effect in healthy subjects; (2) multiple ascending dose (MAD) in healthy subjects; and (3) multiple doses in subjects with AD.

In the SAD and MAD cohorts (Phase 1a), following the 28-day screening period, eligible healthy subjects were randomized (3:1) at baseline (Day 1) to receive oral RPT193 (50, 100, 200, or 400 mg) or matching placebo under fasted conditions. Subjects in the SAD cohort received a single RPT193 or placebo dose on Day 1, and subjects in the MAD cohort received once daily (QD) doses from Day 1 to 7. In the SAD cohort, food effect on the PK of RPT193 was also examined in subjects who received the 200 mg dose, and the PK and PD of lower doses of RPT193 (5 and 20 mg, administered in an open-label fashion) were assessed (Supplementary Methods).

In the AD cohort (Phase 1b), following a 35-day screening period, eligible subjects with AD were randomized (2:1) on Day 1 to receive oral RPT193 400 mg or matching placebo QD from Day 1 to 28. Randomization was stratified based on validated Investigator's Global Assessment (vIGA) score at baseline (vIGA of 3 vs. 4). The use of rescue medications was prohibited during the course of the study. The 28-day treatment period was followed by a 15-day safety follow-up period (blinded); only bland emollients were allowed with no rescue therapy during this follow-up period after treatment discontinuation. The Phase 1b trial was not powered to achieve statistical significance for any particular endpoint.

The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in accordance with the protocol, International Council for Harmonization Good Clinical Practice, and applicable local regulations. A signed informed consent form was obtained from all participants prior to the start of any screening procedures.

2.2 | Study participants

The SAD and MAD cohorts included healthy subjects aged 18–55 years (inclusive) at the time of consent (aged 18–54 years inclusive for the SAD 5 and 20 mg groups); body mass index (BMI) 18.0–30.0 kg/m^2 and weight ≥ 50 kg at screening. Key inclusion criteria for the AD cohort were: subjects aged 18–65 years (inclusive) at the time of consent, with ≥12-month history of AD; BMI ≥18 and < 40 kg/m^2 at screening; AD covering ≥10% of the body surface area (BSA); Eczema Area and Severity Index (EASI) score ≥ 12; and vIGA score ≥3. Full eligibility criteria for the Phase 1 study are described in the Supplementary Methods.

2.3 | Study objectives and assessments

The primary objective for all three parts of the Phase 1 study was to evaluate the safety and tolerability of RPT193. Secondary objectives were to evaluate the PK of RPT193 (SAD, MAD, AD) and the food effect on the PK (SAD). Exploratory objectives included assessment of CCR4 surface receptor occupancy (sRO; SAD and MAD cohorts); and PD analysis of RPT193, as assessed by whole blood immunophenotyping (AD cohort) and measurement of plasma cytokines/chemokines levels (TARC/CCL17, MDC/CCL22; MAD and AD cohorts). Exploratory objectives for the AD portion also included clinical efficacy of RPT193 assessed by vIGA,[34] EASI,[35] SCORing Atopic Dermatitis (SCORAD),[36] BSA, pruritus numeric rating scale (NRS),[37] and subject-oriented SCORAD[36] symptoms (sleep loss and pruritus/itch). The effects of RPT193 on the skin were also evaluated as exploratory endpoints by collecting skin biopsies for gene expression analyses. Assessment timepoints and methodology details are provided in Supplementary Methods.

2.4 | Statistical analyses

Details of statistical analysis methods are described in the Supplementary Methods.

3 | RESULTS

3.1 | RPT193 mechanism of action

The chemical structure of RPT193 is shown in Figure 1A; its discovery and molecular characterization were described previously.[32] In an in vitro chemotaxis assay assessing RPT193 inhibition of the migration of Th2 cells differentiated from naïve CD4+ T-cells from healthy individuals, RPT193 inhibited CCL22- and CCL17-induced CCR4-mediated chemotaxis by over 90% in 100% serum (Figure 1B,C; Supplementary Methods).

3.2 | Subject disposition and baseline characteristics

In the SAD cohort, all 32 randomized healthy subjects and 8 healthy subjects receiving open-label RPT193 5 or 20 mg completed the study (Appendix Figure 1). In the MAD cohort, of the 32 randomized subjects, one subject in the RPT193 200 mg QD group did

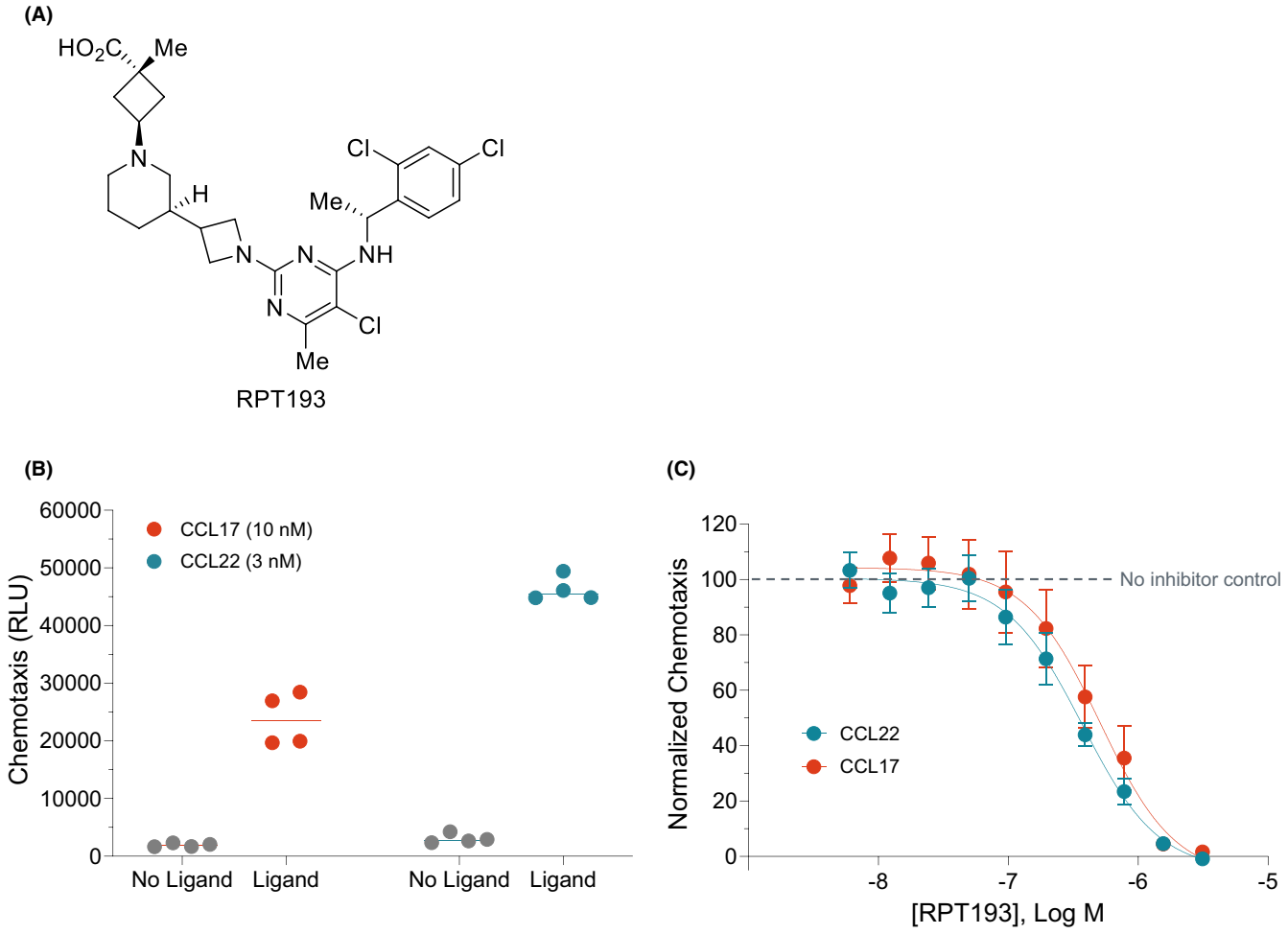


FIGURE 1 (A) Chemical structure of RPT193, (1*R*,3*r*)-3-((*R*)-3-(1-(5-chloro-4-(((*R*)-1-(2,4-dichlorophenyl)ethyl)amino)-6-methylpyrimidin-2-yl)azetidine-3-yl)piperidin-1-yl)-1-methylcyclobutane-1-carboxylic acid. (B) In vitro assessment of Th2 chemotaxis toward CCR4 ligands. Th2 cells differentiated from naive CD4+ T cells were assessed for chemotaxis. Technical replicates ($n=4$) are shown for one of two representative experiments. (C) In vitro assessment of potency of RPT193 in human Th2 chemotaxis with CCL22 and CCL17. Mean +/− SD for four technical replicates are shown for one of two representative experiments for CCL22 and the single CCL17 experiment.

not complete the study (reason: withdrawal by subject; Appendix Figure 2). Subject demographics and baseline characteristics were similar for all treatment groups (Appendix Table 2).

In the AD cohort, of the 31 randomized subjects, 1 of 21 subjects (4.8%) in the RPT193 group (reason: withdrawal by subject) and 1 of 10 subjects (10.0%) in the placebo group (reason: other) discontinued the study (Appendix Figure 3). Baseline demographics and disease characteristics were similar for both groups (Table 1).

3.3 | Safety and tolerability in healthy subjects and subjects with AD

In healthy subjects receiving single (SAD) or multiple doses (MAD) of RPT193, all treatment-emergent adverse events (TEAEs) were mild or moderate in severity and no severe TEAEs were reported in the study at all tested doses (Appendix Tables 3–5). The majority of TEAEs were considered not related to the study treatment and were resolved at the end of the study. The most common TEAE reported in the SAD and MAD cohorts was headache. In the SAD cohort, 6 of 32 subjects (18.8%) receiving RPT193 reported headache (vs. 2 of 8 [25.0%] receiving placebo). Six of 24 subjects (25.0%) receiving RPT193 in the MAD cohort reported headache (vs. 6 of 8 [75.0%] receiving placebo). The proportion of subjects reporting TEAEs was similar under fasted and fed conditions (Appendix Table 4). No serious adverse events (SAEs), or TEAEs leading to study discontinuation were reported in the SAD and MAD cohorts.

In the AD cohort receiving RPT193 400 mg or placebo QD for 28 days, 11 subjects (35.5%) experienced at least one TEAE ($n=9$ [42.9%] in the RPT193 group and $n=2$ [20.0%] in the placebo group; Table 2). All TEAEs were of mild or moderate severity and no severe TEAEs were reported. No SAEs or TEAEs leading to study discontinuation were reported in the AD cohort after Day 1. One subject receiving RPT193 in the AD cohort had the study drug withdrawn for a TEAE (generalized rash of moderate severity, considered possibly treatment-related). Six subjects (19.4%) experienced TEAEs that were considered treatment-related ($n=5$ [23.8%] in the RPT193 400 mg QD group and $n=1$

TABLE 1 Baseline characteristics for the AD subject cohort (safety analysis set). Subjects in the AD cohort were males or females, aged 18–65 years, with a BMI ≥18 and <40 kg/m^2, diagnosed with active AD according to the revised Hanifin and Rajka criteria.

	RPT193 400 mg QD ($n=21$)	Placebo ($n=10$)
Age (years), mean (range)	41.1 (19–63)	35.8 (22–64)
Female, *n* (%)	12 (57.1%)	4 (40.0%)
Ethnicity, *n* (%)		
Hispanic/Latino	3 (14.3%)	3 (30.0%)
Race, *n* (%)		
White	12 (57.1%)	5 (50.0%)
Asian	2 (9.5%)	0
Black or African American	7 (33.3%)	5 (50.0%)
BMI (kg/m^2), mean (range)	28.4 (20.8–39.4)	26.8 (20.3–35.6)
Baseline AD characteristics[a]		
EASI, mean (range)	18.49 (12.0–30.0)	21.07 (13.6–45.5)
BSA, mean (range)	23.29 (11.0–55.0)	24.50 (10.0–61.0)
vIGA 3, *n* (%)	18 (85.7%)	8 (80.0%)
Total SCORAD, mean (range)	56.98 (36.6–82.4)	56.62 (41.0–81.4)
SCORAD subj, mean (range)	11.99 (5.0–18.0)	10.77 (2.0–16.3)
Peak NRS, mean (range)	6.9 (3–10)	7.3 (3–10)
Peak NRS ≥4, *n* (%)	20 (95.2%)	9 (90.0%)

Abbreviations: AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; EASI, Eczema Area and Severity Index; NRS, numeric rating scale; SCORAD, SCORing Atopic Dermatitis; vIGA, validated Investigator's Global Assessment.

[a]mITT analysis set.

[10.0%] placebo). The most common treatment-related TEAE was nausea. All treatment-related TEAEs were resolved by the end of the study.

Overall, no observations of clinically significant changes from baseline in the laboratory parameters (including hematology assessments, shown in Appendix Table 6), vital signs, and electrocardiogram were noted to suggest a clear relationship to RPT193 treatment. No AEs related to specific hematologic subsets that are covered by Common Terminology Criteria for Adverse Events (CTCAE) were reported in the SAD, MAD, and AD cohorts.

3.4 | RPT193 PK/PD in healthy subjects and subjects with AD

Following RPT193 QD administration for 7 days in healthy subjects in the fasted state in the MAD cohort, the median time to attain maximum observed plasma concentration (t_{max}) of RPT193 on Day 7 was between 2.0 and 4.0 h across the multiple dose regimens. Dose-proportional exposure was observed in plasma with QD oral dosing of RPT193 over 7 days (Figure 2A). On Day 7, a dose-proportional increase was observed for the geometric mean terminal elimination half-life ($t_{1/2}$; from 22.6 to 27.3 h); the mean terminal half-life of RPT193 was ~25 hours across all dose levels. Findings in the MAD cohorts were consistent with those observed in the SAD cohort. Further, no clear evidence for an effect of food was observed in the food effect group receiving a single dose of RPT193 200 mg after a high-fat breakfast. The median t_{max} increased from 4.0 h (fasted state) to 8.0 h (fed state), whereas the geometric mean $t_{1/2}$ was not affected by food.

The effect of RPT193 on CCR4 sRO was assessed in the SAD and MAD cohorts via ex vivo analysis of human whole blood samples (Supplementary Methods). This sRO assay displayed good intra-donor as well as inter-assay reproducibility (Appendix Figure 4A). In the SAD cohort, 23 out of 24 RPT193-dosed healthy subjects showed ≥80% sRO at 4 h post-dose (76%–101%; Figure 2B). At 24 h, subjects in the RPT193 50 and 100 mg groups dropped to 63%–85% and 68%–96% sRO, respectively; subjects in the RPT193 200 and 400 mg groups remained at 86%–108% and 81%–98% sRO, respectively. In the RPT193 5 and 20 mg groups, a dose- and time-dependent CCR4 target engagement was observed (Appendix Figure 4B,C). Peak sRO for both doses was reached at either 4 or 24 h-post-dose, subsequent to which there was a notable decline in sRO. While peak sRO for the RPT193 5 mg group varied between 30% and 45%, peak sRO for the RPT193 20 mg group ranged from 75% to 95%, with two of the four subjects achieving the targeted 80% sRO at 24 hours following the dose. Data from the MAD cohort corroborated the results in the SAD cohort (Figure 2C). Moreover, sRO correlated with RPT193 plasma concentrations (Figure 2D). These data from the SAD and MAD cohorts demonstrated that RPT193 at the dose of 50 mg was sufficient to achieve the targeted sRO of 80%.

PD was assessed in healthy and AD subjects by whole blood immunophenotyping and plasma cytokines and chemokines (Supplementary Methods). In both the SAD and MAD cohorts, RPT193-dosed subjects (50, 100, 200, 400 mg) exhibited a statistically significant decrease in CCR4 cell surface expression, as determined by mean fluorescence intensity (MFI), relative to placebo subjects ($p<.0001$). While subjects receiving placebo showed stable levels of CCR4 cell surface expression, a ≥ 30% decrease in CCR4 surface levels was observed in ~61% of RPT193-dosed subjects at 24 h-post-dose in the SAD cohort, and in ~42% and ~37% of the RPT193-dosed subjects at 24 h (Day 8) and 72 h (Day 10), respectively, after the final RPT193 dose in the MAD cohort. Similar significant decreases in cell surface CCR4 expression were observed in the SAD 20 mg cohort at Day 4 ($p=.0047$ vs. pre-dose), but not in the 5 mg cohort ($p=.1754$), potentially suggesting a RPT193 dose-dependent decrease in surface CCR4. In subjects with AD, a statistically significant decrease in cell surface CCR4 MFI was also observed following RPT193 400 mg QD treatment for 28 days, including an average of 40%–50% decrease in cell surface expression on Th1, Th2, and Th17 subtypes of CD4+ T cells (Appendix Figure 5).

TABLE 2 Adverse events profile in the AD cohort (safety analysis set).

N (%) [E]	RPT193 400 mg QD (*n* = 21)	Placebo (*n* = 10)
Subjects with at least one AE	10 (47.6) [17]	2 (20.0) [4]
Subjects with at least one TEAE	9 (42.9) [16]	2 (20.0) [4]
Mild	4 (19.0) [7]	1 (10.0) [1]
Moderate	6 (28.6) [9]	1 (10.0) [3]
Severe	0	0
Subjects with at least one serious AE	0	0
Subjects with at least one serious TEAE	0	0
Subjects with at least one TEAE leading to study drug discontinuation	1 (4.8) [1]	0
Subjects with at least one TEAE leading to study discontinuation	0	0
Subjects with at least one AE leading to death	0	0
Treatment-related TEAEs by PT (≥2 subjects in RPT193 group)		
Nausea	3 (14.3)	0

Note: Treatment-emergent adverse events were defined as 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). Treatment-related TEAEs were defined as any TEAE that was assessed by the investigator as definitely, probably, or potentially related to study treatment. Not treatment-related TEAEs were defined as any TEAE that was assessed by the investigator as unlikely to be related or not related. Subjects experiencing multiple AEs within the same preferred term were counted only once within that preferred term under the greatest reported relationship.

Abbreviations: AE, adverse event; E, number of events; PT, preferred term; TEAE, treatment-emergent adverse event.

Results suggest that RPT193 has a two-fold mechanism of action to reduce CCR4-mediated functions in that treatment results in both prevention of ligand binding but also in decreased CCR4 surface expression.

A statistically significant increase in circulating levels of MDC/CCL22 was observed at all RPT193 doses tested in the MAD cohort; this increase was not dose dependent, and the observed increase in MDC/CCL22 was sustained throughout the dosing period (Appendix Figure 6A). A similar trend towards an increase in circulating MDC/CCL22 was observed in subjects with AD, though this increase did not reach statistical significance versus placebo (Appendix Figure 6B). There were no statistically significant changes in levels of circulating TARC/CCL17 following RPT193 treatment versus placebo both in healthy subjects in the MAD cohort and in the AD cohort (Appendix Figure 6). In the AD cohort, circulating levels of immunoglobulin E remained unchanged during the 28-day treatment period and the 15-day safety follow-up visit, and were not statistically different versus placebo ($p > .25$).

3.5 | Efficacy in subjects with moderate-to-severe AD

Numerically greater improvements in EASI, BSA, vIGA, and SCORAD were observed with RPT193 400 mg QD treatment as compared to placebo at all visits during the 28-day treatment period (Figure 3 and Appendix Table 7). At Day 29, the percent improvement from baseline in mean EASI score in subjects treated with RPT193 was 36.3% (vs. 17.0% in the placebo group). The proportion of subjects achieving EASI-50 at Day 29 was 42.9% in the RPT193 group and 10.0% in the placebo group. The proportion of subjects in the RPT193 group achieving ≥1-grade reduction from baseline in vIGA score and ≥2-grade reduction from baseline in vIGA score to clear (0) or almost clear (1) were 33.3% (vs 20.0% placebo) and 4.8% (vs. 0% placebo), respectively, at Day 29. Results from BSA, SCORAD total score, subject-oriented SCORAD[36] symptoms (sleep loss and pruritus/itch), and proportion of subjects with 3-point and 4-point decrease in pruritus NRS also showed numerically greater improvements over time up to Day 29 in the RPT193 group compared to placebo (Figure 3 and Appendix Table 7).

At 2 weeks after the end of treatment (Day 43), subjects treated with RPT193 400 mg QD showed further improvement in several efficacy endpoints (Figure 3 and Appendix Table 7). Although the study was not designed/powered to detect statistical significance for any given endpoint, a statistically significant difference ($p < .05$ vs. placebo) was observed in a post-hoc analysis in subjects treated with RPT193 400 mg QD in the following efficacy endpoints at Day 43: change from baseline in mean EASI, proportion of subjects achieving EASI-50, BSA, and SCORAD total scores and subject-oriented symptoms scores.

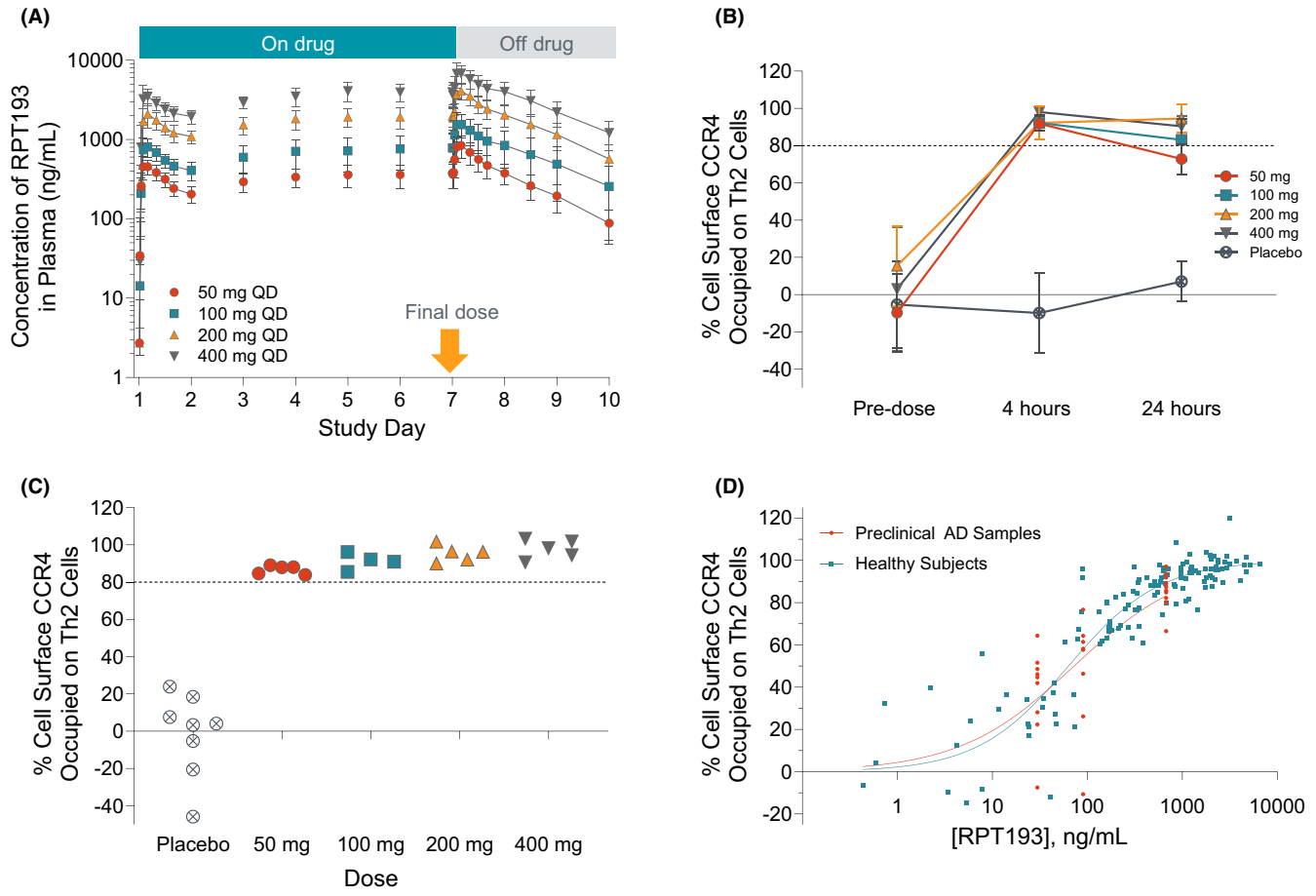


FIGURE 2 PK/PD data from healthy subjects in the SAD and MAD cohorts. (A) PK of RPT193 in the MAD cohort. Dose-proportional exposure was observed in the plasma with once-daily oral dosing of RPT193 over 7 days in healthy subjects in the MAD cohort; the mean terminal half-life of RPT193 was ~25 h across all dose levels; (B) Surface RO (sRO) in healthy volunteers in the SAD cohort. Dotted line represents 80% sRO, the target sRO for this assay. Black circle data points represent placebos; (C) sRO in healthy volunteers in the MAD cohort at Day 8 (24-h after the final RPT193 dose). CCR4 inhibition was achieved with repeated daily RPT193 dosing (50, 100, 200, or 400 mg) across all dose levels at Day 8. All subjects in the MAD cohort* showed ≥80% sRO (83%–103%); (D) sRO correlates with RPT193 plasma concentration (data from the SAD and MAD cohorts). The preclinical curve (red line) was previously determined by pre-incubating whole blood from subjects with AD with various concentrations of RPT193. *six dosed/two placebo subjects per dose group; analysis for some subjects did not pass QC, resulting in fewer than expected points per dose group.

3.6 | Effect of RPT193 on skin biomarkers

Subjects who received RPT193 showed a statistically significant improvement ($p < .001$) versus the placebo group in the expression of the meta-analysis derived AD (MADAD) transcriptome[38] (Figure 4A), a well-established, robust AD gene signature, with modules that track with AD disease severity. With RPT193 treatment, there was a 52% mean improvement in the MADAD transcriptome towards non-lesional skin at Day 29 ($p < .001$ vs. placebo; Figure 4A), whereas placebo-treated subjects showed a 4.8% worsening of lesional skin at Day 29, bringing it even further away from non-lesional skin. The overall expression of up and down dysregulated genes in baseline lesional AD skin approached that of non-lesional levels in RPT193-treated subjects at Day 29 (as shown by the shift toward the solid line marking non-lesional skin in Figure 4A), while minimal changes were observed in subjects receiving placebo. Additionally, Gene Set Variation Analysis (GSVA) showed significant improvements following RPT193 treatment (but not placebo) in MADAD (Figure 4B) and validated gene signatures associated with key immune pathways relevant in AD,[20,39,40] such as Th2, Th17/Th22, and Th1 (Figure 4B), at Day 29.

The expression of a panel of immune and barrier related genes, including key genes for AD, was also quantified using quantitative real-time PCR (qRT-PCR) (Appendix Figure 7). At Day 29, RPT193-treated subjects demonstrated a significant downregulation of the expression of CCR4 in the lesional skin, while no changes were seen in the placebo group. Many Th17/22-related markers (IL-19, CCL20, CXCL1 PI3/Elafin, DEFB4), were significantly downregulated in the RPT193-treated subjects, but not in the placebo group; many of them are known to contribute to skin hyperplasia (such as keratin 16, KRT16) and skin lichenification (such as IL-36G, S1008/9/12). Other markers that were significantly downregulated in the RPT193 group are related to innate immunity (IL-8), general inflammation (MMP12), T cell/NK cell activation and

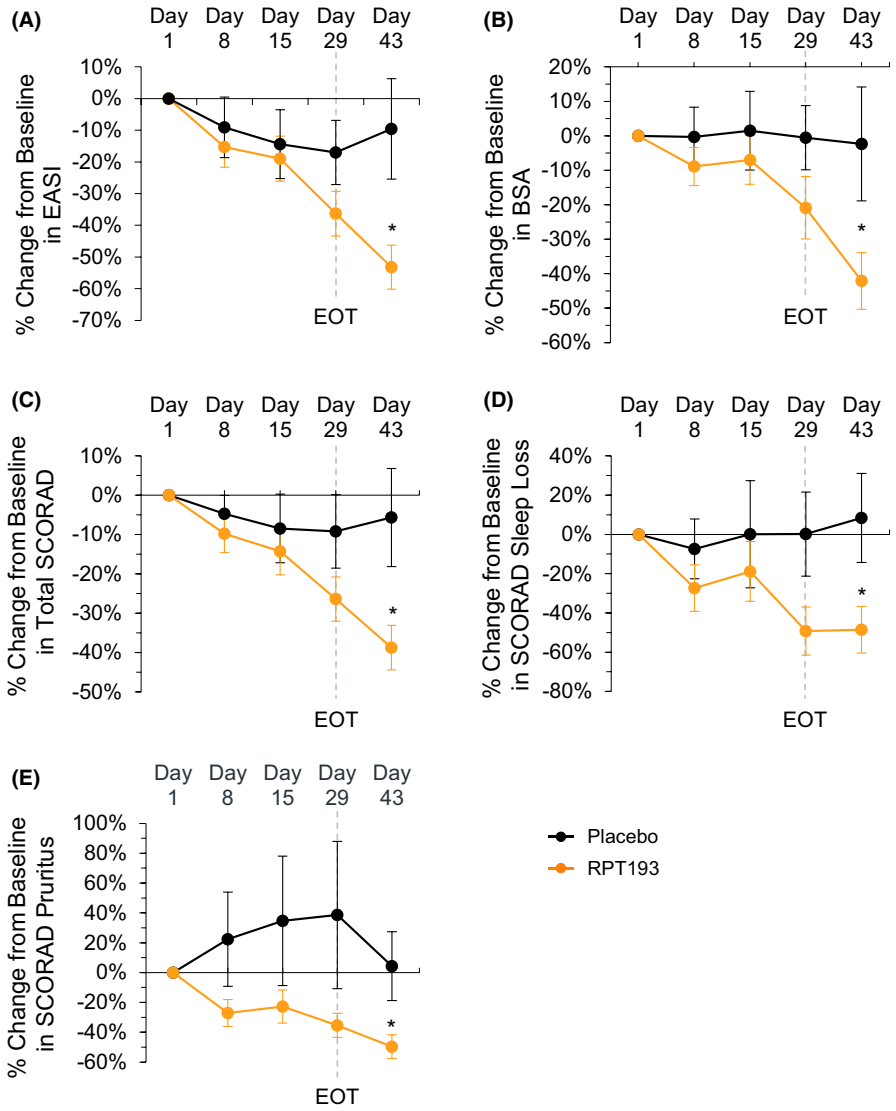


FIGURE 3 Improvements in key exploratory efficacy endpoints in subjects with AD (mITT analysis set) following treatment with RPT193 400 mg QD versus placebo at end of treatment (Day 29) and 2 weeks after the end of treatment (Day 43). Graphs show mean values, and error bars represent standard error of the mean. *$p < .05$ (post-hoc analysis). BSA, body surface area; EASI, Eczema Area and Severity Index; EOT, end of treatment; SCORAD, SCORing Atopic Dermatitis.

migration (CCL19, CCR7), Th1 (CCL2), Th9 (IL-9), and regulatory (CTLA-4) markers.

Changes in inflammatory AD-related biomarkers showed significant correlations with disease improvement as measured by changes in EASI and SCORAD at Day 29 (Spearman correlations, $p < .1$, $R > 0.37$ or $R < -0.37$, Appendix Table 8). Among them, several Th22 markers involved in skin hyperplasia, such as S100A7/9, correlated with changes in EASI, while T cell activation-markers (CD8A, LCK, CD3D) demonstrated correlations with SCORAD. Th1- (CXCR3, CCR2, CXCL10), Th2- (OX40 receptor) dendritic cell-related markers (CCR7) also demonstrated moderate to strong correlations with clinical improvement (EASI and/or SCORAD), while attenuation of SCORAD or EASI was associated with increases in barrier markers (e.g. CERS5, CLDN1/8, GJB3, CDH20).

4 | DISCUSSION

This is the first clinical study with an oral, small molecule CCR4 antagonist to show clinical improvement in an inflammatory skin disease. In subjects with moderate-to-severe AD, numerically greater improvements in EASI, BSA, vIGA, and SCORAD were observed versus placebo, which suggests the efficacy and clinical potential of blocking CCR4 with RPT193. Although the study was not designed/powered to detect statistical significance for any given endpoint, statistically significant improvement, compared to Day 29 and placebo, was observed 2 weeks after the end of treatment (Day 43) on multiple clinical efficacy endpoints ($p < .05$). CCR4 inhibition with once-daily, oral RPT193 treatment was generally well tolerated in healthy subjects and subjects with moderate-to-severe AD, with no SAEs reported and all TEAEs reported as mild/moderate. Moreover, skin biomarker data of Day 29 showed improvement in the expression of the MADAD transcriptome and a change towards a non-lesional phenotype of the AD skin in the RPT193-treated subjects but not in the placebo-treated subjects. RPT193 treatment decreased the mRNA expression of CCR4 in the AD lesions of RPT193-treated subjects and downregulated key pathogenic pathways and molecules involved in AD. Downregulated transcripts included Th2, Th1, Th17, and Th22-related products. These changes are consistent with inhibitory effects on the Th2 pathway, as other

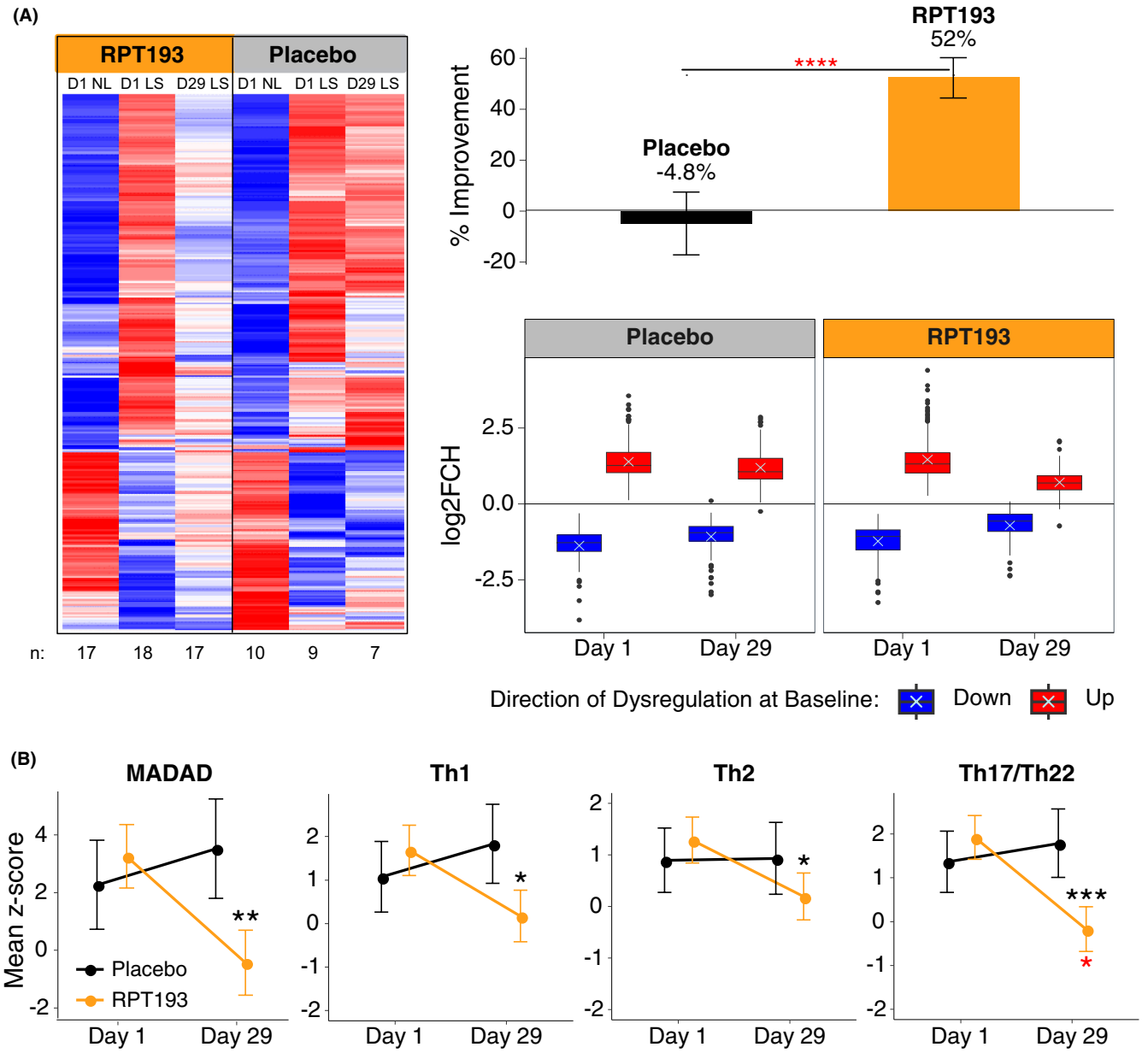


FIGURE 4 (A) RPT193 treatment led to an improvement in the MADAD transcriptome expression and to a shift towards a non-lesional transcriptional profile at Day 29. (B) RPT193 treatment resulted in improvements in MADAD and gene signatures associated with pathways relevant in AD, such as Th1, Th2, and Th17/Th22. ****($p = 2.5e\text{-}13$), ***($p < .001$), **($p < .01$), *($p < .05$). Red symbol denotes significance versus placebo; black symbol denotes significance relative to baseline (Day 1) of the same treatment group. The heatmap in Panel A depicts averaged expression. LS, lesional; NS, non-lesional.

Th2-targeting agents such as dupilumab also reduce Th17 and Th22 gene signatures.[20]

The continued clinical benefits of RPT193 observed after dosing cessation are intriguing and could be related to its mechanism of action. This could be due to the decrease in CCR4 cell surface expression observed with RPT193 treatment, as well as RPT193's upstream mechanism of action of reducing Th2 cell accumulation in the skin which could decrease the production of pro-inflammatory cytokines and subsequently induce clinical improvement. This could also relate to its effects on memory T-cell formation, and regulatory markers.[41] The exact mechanisms of this improvement off-drug have not yet been investigated. However, similar extended clinical benefit after cessation of dosing has also been observed with T-cell targeting approaches. Rocatinlimab, which depletes OX40-expressing cells, has been studied in patients with moderate-to-severe AD following both short- and long-term treatment with evidence of extended benefit beyond the treatment period as well as the half-life of rocatinlimab.[42,43] Future clinical studies with RPT193 could explore the mechanism of action with a series of skin tissue sampling to further assess changes in gene expression and inflammatory cell accumulation in the skin during treatment and during a longer follow up period, after cessation of the drug.

RPT193 treatment modulated the mRNA expression of key pathogenic pathways and molecules involved in AD in the AD skin lesions of RPT193-treated subjects, including a reduction in Treg markers CTLA4 and FOXP3 and an increase in Th2 cytokine IL-13 (but not IL-4). As RPT193 inhibits CCR4-mediated chemotaxis of Tregs as observed in vitro (data not shown), a reduction in Treg markers would not be surprising. Tregs in patients with AD (and asthma) have been suggested to become "non-functional" as immune suppressors and even produce inflammatory cytokines.[44] Decreases in skin Treg markers have been observed with dupilumab and the ANS002 Jak inhibitor, with both drugs demonstrating efficacy in patients with AD.[20,45] Moreover, as CCR4 promotes the migration of activated Th2 cells to the skin, decreases in both IL-4 and IL-13 expression would be expected with CCR4 inhibition. While the detailed mechanism for the observed significant increase in IL-13, but not IL-4, remains to be studied, it may reflect a transient, paradoxical increase in primary Th2 cytokines that would decrease with additional treatment, similar to findings in the 4-week[46] and 16-week[20] mechanistic studies with the IL-4R alpha inhibitor dupilumab. In the 4-week study, both IL-4 and IL-13 were observed to increase, though not significantly, with dupilumab 150 mg after 4 weeks.[46] In the follow-up study with a 16-week observation period, IL-4 increased, though not significantly, relative to baseline while IL-13 was significantly downregulated by Week 16,[20] also showing a dissociation in treatment effect with these cytokines. The small sample size of the study may also have contributed.

The statistically significant decrease in CCR4 cell surface expression observed with RPT193 treatment in healthy subjects, along with the statistically significant increase in circulating MDC/CCL22 in the plasma (and no significant changes in circulating TARC/CCL17) provides additional insights into the mechanism of action of RPT193. Previous work has demonstrated that antagonists targeting chemokine receptors may result in increases in the circulating levels of the ligands for those receptors.[47–50] Circulating levels of TARC/CCL17 and MDC/CCL22 have been associated with severity of disease, response to treatment, or both.[51] In healthy subjects, a strong correlation was established between the concentration of RPT193 and the inhibition of CCL22 binding on human Th2 cells as assessed via the CCR4 sRO assay. The mechanism of action of RPT193, which includes blockade of CCL17 and CCL22 binding to CCR4 and reductions of surface CCR4, may obscure any disease-related reductions by inhibiting receptor-mediated clearance of these ligands. In addition, the observed difference between CCL17 and CCL22 could be due to alternative normal clearance rates and alternative clearance pathways for the two ligands.

The PK/PD and CCR4 sRO profiles differentiate RPT193 from previous CCR4 antagonists such as GSK2239633[52] and AZD2098,[53] which did not proceed in clinical development due to low exposure and target engagement. In vitro assessments showed that RPT193 inhibited CCL22- and CCL17-induced CCR4-mediated Th2 chemotaxis by over 90% in full serum (IC_{50} ~ 370 nM), accounting for the protein binding of the compound and affirming the potency of RPT193 against Th2 chemotaxis compared with previous CCR4 antagonists (GSK2239633 and AZD2098: IC_{50} ~ 3 μM; data not shown). In healthy subjects in the Phase 1 study, dose-proportional exposure was observed in the plasma with once-daily oral dosing of RPT193, with the mean terminal half-life of ~25 h across all dose levels. Furthermore, data from the SAD and MAD cohorts demonstrated that RPT193 at the dose of 50 mg was sufficient to achieve the targeted CCR4 sRO of 80%, which corresponds to the drug level required to obtain 90% inhibition in the in vitro chemotaxis assay. This high level of Th2 chemotaxis inhibition is thought to be required for near maximal efficacy targeting the CCR4 pathway. The continued clinical benefits of RPT193 observed after dosing cessation in the AD cohort, which utilized a RPT193 dose of 400 mg, could be due to a prolonged efficacy signal resulting from CCR4 sRO that is well above the 80% target sRO and/or due to an extended biological effect from the disruption of Th2 trafficking.

Peripheral blood eosinophil counts and total immunoglobulin E levels have been shown to correlate with AD disease severity.[54] No differences in eosinophil counts and total immunoglobulin E levels were observed between placebo and RPT193-dosed subjects, and there were no RPT193-dependent changes during the 28-day treatment period and the 15-day safety follow-up visit. While increased eosinophils correlate with AD disease severity, data from dupilumab trials suggest that a decrease in eosinophils is not needed to decrease disease severity.[46] Nonetheless, the relationship between RPT193-mediated efficacy and levels of eosinophil and immunoglobulin E will be further explored in the follow-up investigation with larger sample sizes, longer observation periods of at least 16 weeks, and/or with proteomic validation in the ongoing Phase 2 studies in subjects with AD (NCT05399368) and asthma (NCT05935332).

This study has several limitations including its small sample size and short, 28-day, treatment duration. In addition, the 2-week follow-up time of the current study was too short to assess the long-term benefits of RPT193 after treatment cessation, and to fully evaluate the potential of maintenance and deepening of response without treatment that can potentially raise the idea of disease modification as with the OX40-targeting antibody.[43] Additionally, long-term safety of RPT193 remains to be studied, and longer treatment is probably required to achieve maximal efficacy. In the biomarker analyses, normal skin sample controls from healthy subjects were not included, which would allow for more in-depth insights into the effects of RPT193 on a pathomechanistic level.

CCR4 antagonism with RPT193 has the potential to provide a unique mechanism of action and therapeutic option compared to other current and potential AD therapies. By limiting the ability of Th2 cells to access inflamed skin and decrease local production of Type 2 cytokines, RPT193 has the potential to improve both the symptoms and signs of AD similar to injectable biologics targeting the IL-4R alpha and/or IL-13. Compared to systemic JAK inhibitors, RPT193 has the potential to more specifically target allergic inflammatory pathways, thereby diminishing risks of immunosuppression and other serious side effects. Finally, similar to T-cell targeting therapies focused on OX40 or OX40L, a 28-day course of RPT193

has shown evidence of extended clinical benefit after completion of the treatment period. A dose-ranging Phase 2 trial (RPT193-02; NCT05399368) is currently underway to further investigate RPT193's efficacy and safety in subjects with AD.

In addition to AD, Th2 cells are involved in the pathogenesis of many other inflammatory and allergic disorders including asthma, urticaria, allergic rhinosinusitis, eosinophilic esophagitis, systemic lupus erythematosus, and systemic sclerosis. The effects of blocking CCR4 in other atopic diseases, that are driven by Th2 T-cells deserve to be studied, as targeting CCR4 may be valuable to the entire atopic spectrum and beyond. A Phase 2 trial in asthma is currently underway (NCT05935332). The Phase 2 studies with RPT193 in AD and asthma will help in furthering our understanding of RPT193 as a therapeutic option in a broad swath of diseases associated with dysregulated allergic inflammation.

In conclusion, these data showed that the oral CCR4 antagonist RPT193 was well tolerated and induced clinical improvement and renormalization of the skin transcriptome in subjects with moderate to severe AD. CCR4 antagonists merit further investigation in AD and other diseases where the Th2 axis plays a key role.

AUTHOR CONTRIBUTIONS

All authors contributed to the acquisition, analysis, or interpretation of data; critically reviewed and revised the manuscript for important intellectual content; approved the final draft for publication; and are accountable for their contributions and the integrity of the work.

ACKNOWLEDGEMENTS

The authors wish to thank Ana Pavel for her contributions during manuscript development; and Lisa Marshall and Svetlana Miakicheva for their contributions to the Th2 chemotaxis assay data and sRO assay development data, respectively. This study was sponsored by RAPT Therapeutics, Inc. The Sponsor would like to thank contributors to the program at RAPT Therapeutics, Inc., study investigators, site staff, and the study participants for their support of and contributions to the trial. Medical writing and editorial support, under the direction of the authors, was provided by Grace Jeong, PhD of Alphabet Health and was funded by RAPT Therapeutics, Inc. This manuscript was developed in accordance with Good Publication Practice Guidelines (https://www.ismpp.org/gpp-2022). Authors had full control of the content and made the final decision on all aspects of this publication.

CONFLICT OF INTEREST STATEMENT

Robert Bissonnette is an Advisory Board Member, Consultant, Speaker and/or Investigator for and receives honoraria and/or grant from AbbVie, Arcutis, Arena Pharma, Aristea, Asana BioSciences, Bellus Health, Bluefin Biomedicine, Boehringer-Ingelheim, CARA, Dermavant, Eli Lilly, EMD Serono, Evidera, Galderma, GSK, Inmagene Bio, Incyte, Kiniksa, Kyowa Kirin, LEO Pharma, Novan, Pfizer, Ralexar, RAPT, Regeneron, Respivant, Sanofi-Genzyme, Sienna and Target RWE. He is also an employee and shareholder of Innovaderm Research. Janet DuBois is an investigator for AbbVie, Acrotech Biopharma Inc., AiViva BioPharma, Allergan, Almirall, AnaptysBio, Arcutis Biotherapeutics, Bausch Health, Biofrontera, Bristol-Myers Squibb, Caliway Biopharmaceuticals, Cara Therapeutics, Croma-Pharma GmbH Austria, Dermata Therapeutics, DermBiont, Dr Reddy, Endo Pharmaceuticals, Evommune, Galderma USA, Incyte Corporation, LEO Pharma, Merck, Moberg Pharma, Nielsen BioSciences Inc., Palvella Therapeutics, Q32 Bio Inc., RAPT Therapeutics, Scarless Laboratories Inc., Therapeutics Inc., and Veradermics Inc. Paola Facheris, Ester Del Duca, Madeline Kim, Joel Correa Da Rosa, Swaroop Bose, and Angel D. Pagan declare no conflict of interest. Damian L. Trujillo, David Wustrow, Dirk G. Brockstedt, Brian Wong, Paul D. Kassner, William Ho, and Laurence E. Cheng are employees and stockholders of RAPT Therapeutics, Inc. Jasmina Jankicevic has received honoraria as a Consultant from Amryt Pharma, Arena Pharma, ConcertoBio, Cutera, Curology, DeepSense, Dermalique, Dermaxon, Foamix, Kamari Pharma, QuantifiCare, Patagonia Pharmaceuticals, Pomega, RAPT Therapeutics, and Reistone. She is also a part-time employee of Innovaderm Research. Emma Guttman-Yassky has received honoraria for consultant services from AbbVie, Almirall, Amgen, Asana Biosciences, Boehringer Ingelheim, Cara Therapeutics, Celgene, Concert, DBV, Dermira, DS Biopharma, Lilly, EMD Serono, Escalier, Galderma, Glenmark, Kyowa Kirin, LEO Pharma, Mitsubishi Tanabe, Pfizer, RAPT Therapeutics, Regeneron, Sanofi, Sienna Biopharma, and Union Therapeutics and received research grants for investigator services from AbbVie, Almirall, Amgen, AnaptysBio, Asana Biosciences, Boehringer Ingelheim, Celgene, Concert, Dermavant, Dermira, DS Biopharma, Lilly, Glenmark, Galderma, Innovaderm, Janssen, Kiniska, Kyowa Kirin, LEO Pharma, Novan, Pfizer, Ralexar, Regeneron, Sienna Biopharma, UCB, and Union Therapeutics.

DATA AVAILABILITY STATEMENT

RAPT Therapeutics will provide access to individual de-identified participant data from RAPT-sponsored interventional clinical studies after a medicine has received regulatory approval in the United States or European Union, or after a program has been terminated. Requests for data from RAPT trials by qualified researchers may be made 24 months after study completion by contacting data.request@rapt.com. To gain access, data requestors must enter into a data access agreement with RAPT.

ORCID

Paola Facheris https://orcid.org/0000-0002-5171-9854
Madeline Kim https://orcid.org/0000-0002-8108-3631
Angel D. Pagan https://orcid.org/0000-0002-4913-6705
Paul D. Kassner https://orcid.org/0000-0002-1471-1191
Emma Guttman-Yassky https://orcid.org/0000-0002-9363-324X

REFERENCES

1. Hadi HA, Tarmizi AI, Khalid KA, Gajdács M, Aslam A, Jamshed S. The epidemiology and global burden of atopic dermatitis: a narrative review. *Life*. 2021;11(9):936.
2. Ständer S. Atopic dermatitis. *N Engl J Med*. 2021;384(12):1136-1143.

3. Drucker AM, Wang AR, Li W-Q, Sevetson E, Block JK, Qureshi AA. The burden of atopic dermatitis: summary of a report for the National Eczema Association. *J Invest Dermatol*. 2017;137(1):26-30.
4. Ali F, Vyas J, Finlay AY. Counting the burden: atopic dermatitis and health-related quality of life. *Acta Derm Venereol*. 2020;100(12):adv00161.
5. Silverberg JI, Gelfand JM, Margolis DJ, et al. Patient burden and quality of life in atopic dermatitis in US adults: a population-based cross-sectional study. *Ann Allergy Asthma Immunol*. 2018;121(3):340-347.
6. Silverberg JI. Public health burden and epidemiology of atopic dermatitis. *Dermatol Clin*. 2017;35(3):283-289.
7. Ismail N, Bray N. Atopic dermatitis: economic burden and strategies for high-quality care. *Br J Dermatol*. 2020;182(5):1087-1088.
8. Adamson AS. The economics burden of atopic dermatitis. In: Fortson EA, Feldman SR, Strowd LC, eds. *Management of Atopic Dermatitis: Methods and Challenges*. Springer International Publishing; 2017:79-92.
9. Ortsäter G, Geale K, Dun AR, et al. Clinical and economic burden of pediatric mild-to-moderate atopic dermatitis: a population-based nested case–control study in Sweden. *Dermatol Ther*. 2021;11(1):161-172.
10. Toron F, Neary MP, Smith TW, et al. Clinical and economic burden of mild-to-moderate atopic dermatitis in the UK: a propensity-score-matched case–control study. *Dermatol Ther*. 2021;11(3):907-928.
11. Moyle M, Cevikbas F, Harden JL, Guttman-Yassky E. Understanding the immune landscape in atopic dermatitis: the era of biologics and emerging therapeutic approaches. *Exp Dermatol*. 2019;28(7):756-768.
12. Dubin C, Del Duca E, Guttman-Yassky E. The IL-4, IL-13 and IL-31 pathways in atopic dermatitis. *Expert Rev Clin Immunol*. 2021;17(8):835-852.
13. Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *J Allergy Clin Immunol*. 2017;139(4s):S65-s76.
14. Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. *J Allergy Clin Immunol*. 2019;143(1):1-11.
15. Guttman-Yassky E, Waldman A, Ahluwalia J, Ong PY, Eichenfield LF. Atopic dermatitis: pathogenesis. *Semin Cutan Med Surg*. 2017;36(3):100-103.
16. Kim J, Kim BE, Leung DYM. Pathophysiology of atopic dermatitis: clinical implications. *Allergy Asthma Proc*. 2019;40(2):84-92.
17. Leung DY, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. *J Allergy Clin Immunol*. 2014;134(4):769-779.
18. Guttman-Yassky E, Krueger JG, Lebwohl MG. Systemic immune mechanisms in atopic dermatitis and psoriasis with implications for treatment. *Exp Dermatol*. 2018;27(4):409-417.
19. Suárez-Fariñas M, Tintle SJ, Shemer A, et al. Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities. *J Allergy Clin Immunol*. 2011;127(4):954-964.
20. Guttman-Yassky E, Bissonnette R, Ungar B, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2019;143(1):155-172.
21. Suárez-Fariñas M, Ungar B, Correa da Rosa J, et al. RNA sequencing atopic dermatitis transcriptome profiling provides insights into novel disease mechanisms with potential therapeutic implications. *J Allergy Clin Immunol*. 2015;135(5):1218-1227.
22. Zhou L, Leonard A, Pavel AB, et al. Age-specific changes in the molecular phenotype of patients with moderate-to-severe atopic dermatitis. *J Allergy Clin Immunol*. 2019;144(1):144-156.
23. Brunner PM, Suárez-Fariñas M, He H, et al. The atopic dermatitis blood signature is characterized by increases in inflammatory and cardiovascular risk proteins. *Sci Rep*. 2017;7(1):8707.
24. Brunner PM, He H, Pavel AB, et al. The blood proteomic signature of early-onset pediatric atopic dermatitis shows systemic inflammation and is distinct from adult long-standing disease. *J Am Acad Dermatol*. 2019;81(2):510-519.
25. Glickman JW, Dubin C, Renert-Yuval Y, et al. Cross-sectional study of blood biomarkers of patients with moderate to severe alopecia areata reveals systemic immune and cardiovascular biomarker dysregulation. *J Am Acad Dermatol*. 2021;84(2):370-380.
26. Zlotnik A, Yoshie O. Chemokines: a new classification system and their role in immunity. *Immunity*. 2000;12(2):121-127.
27. Horikawa T, Nakayama T, Hikita I, et al. IFN-gamma-inducible expression of thymus and activation-regulated chemokine/CCL17 and macrophage-derived chemokine/CCL22 in epidermal keratinocytes and their roles in atopic dermatitis. *Int Immunol*. 2002;14(7):767-773.
28. Kataoka Y. Thymus and activation-regulated chemokine as a clinical biomarker in atopic dermatitis. *J Dermatol*. 2014;41(3):221-229.
29. Reinhardt RL, Bullard DC, Weaver CT, Jenkins MK. Preferential accumulation of antigen-specific effector CD4 T cells at an antigen injection site involves CD62E-dependent migration but not local proliferation. *J Exp Med*. 2003;197(6):751-762.
30. Campbell JJ, O'Connell DJ, Wurbel MA. Cutting edge: chemokine receptor CCR4 is necessary for antigen-driven cutaneous accumulation of CD4 T cells under physiological conditions. *J Immunol*. 2007;178(6):3358-3362.
31. Oyoshi MK, Elkhal A, Scott JE, et al. Epicutaneous challenge of orally immunized mice redirects antigen-specific gut-homing T cells to the skin. *J Clin Invest*. 2011;121(6):2210-2220.
32. Zibinsky M, Robles O, Wustrow D, et al. Discovery of a selective oral CCR4 antagonist RPT193 for treatment of atopic dermatiris and other allergic disorders. 2022 *Presented at the XXVII EFMC International Symposium on Medicinal Chemistry; Nice, France; Sept 4–8, 2022*.
33. Matsuo K, Hatanaka S, Kimura Y, et al. A CCR4 antagonist ameliorates atopic dermatitis-like skin lesions induced by dibutyl phthalate and a hydrogel patch containing ovalbumin. *Biomed Pharmacother*. 2019;109:1437-1444.
34. Simpson E, Bissonnette R, Eichenfield LF, et al. The validated investigator global assessment for atopic dermatitis (vIGA-AD): the development and reliability testing of a novel clinical outcome measurement instrument for the severity of atopic dermatitis. *J Am Acad Dermatol*. 2020;83(3):839-846.
35. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol*. 2001;10(1):11-18.
36. ETFAD. Severity scoring of atopic dermatitis: the SCORAD index. Consensus report of the European task force on atopic dermatitis. *Dermatology*. 1993;186(1):23-31.
37. Yosipovitch G, Reaney M, Mastey V, et al. Peak pruritus numerical rating scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. *Br J Dermatol*. 2019;181(4):761-769.
38. Ewald DA, Malajian D, Krueger JG, et al. Meta-analysis derived atopic dermatitis (MADAD) transcriptome defines a robust AD signature highlighting the involvement of atherosclerosis and lipid metabolism pathways. *BMC Med Genomics*. 2015;8(1):60.
39. Glickman JW, Dubin C, Han J, et al. Comparing cutaneous molecular improvement with different treatments in atopic dermatitis patients. *J Allergy Clin Immunol*. 2020;145(4):1285-1288.
40. Brunner PM, Pavel AB, Khattri S, et al. Baseline IL-22 expression in patients with atopic dermatitis stratifies tissue responses to fezakinumab. *J Allergy Clin Immunol*. 2019;143(1):142-154.

41. Nakatani T, Kaburagi Y, Shimada Y, et al. CCR4 memory CD4+ T lymphocytes are increased in peripheral blood and lesional skin from patients with atopic dermatitis. *J Allergy Clin Immunol*. 2001;107(2):353-358.
42. Nakagawa H, Iizuka H, Nemoto O, et al. Safety, tolerability and efficacy of repeated intravenous infusions of KHK4083, a fully human anti-OX40 monoclonal antibody, in Japanese patients with moderate to severe atopic dermatitis. *J Dermatol Sci*. 2020;99(2):82-89.
43. Guttman-Yassky E, Simpson EL, Reich K, et al. An anti-OX40 antibody to treat moderate-to-severe atopic dermatitis: a multicentre, double-blind, placebo-controlled phase 2b study. *Lancet*. 2023;401:204-214.
44. Agrawal R, Wisniewski JA, Woodfolk JA. The role of regulatory T cells in atopic dermatitis. *Curr Probl Dermatol*. 2011;41:112-124.
45. Pavel AB, Song T, Kim HJ, et al. Oral Janus kinase/SYK inhibition (ASN002) suppresses inflammation and improves epidermal barrier markers in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2019;144(4):1011-1024.
46. Hamilton JD, Suárez-Fariñas M, Dhingra N, et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(6):1293-1300.
47. Ward ST, Li KK, Hepburn E, et al. The effects of CCR5 inhibition on regulatory T-cell recruitment to colorectal cancer. *Br J Cancer*. 2015;112(2):319-328.
48. Miao S, Tang B, Liu H, et al. CXCR3 blockade combined with cyclosporine a alleviates acute graft-versus-host disease by inhibiting alloreactive donor T cell responses in a murine model. *Mol Immunol*. 2018;94:82-90.
49. Jurcevic S, Humfrey C, Uddin M, Warrington S, Larsson B, Keen C. The effect of a selective CXCR2 antagonist (AZD5069) on human blood neutrophil count and innate immune functions. *Br J Clin Pharmacol*. 2015;80(6):1324-1336.
50. Moss RB, Mistry SJ, Konstan MW, et al. Safety and early treatment effects of the CXCR2 antagonist SB-656933 in patients with cystic fibrosis. *J Cyst Fibros*. 2013;12(3):241-248.
51. Renert-Yuval Y, Thyssen JP, Bissonnette R, et al. Biomarkers in atopic dermatitis-a review on behalf of the international eczema council. *J Allergy Clin Immunol*. 2021;147(4):1174-1190.e1171.
52. Cahn A, Hodgson S, Wilson R, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics of GSK2239633, a CC-chemokine receptor 4 antagonist, in healthy male subjects: results from an open-label and from a randomised study. *BMC Pharmacol Toxicol*. 2013;14:14.
53. Kindon N, Andrews G, Baxter A, et al. Discovery of AZD-2098 and AZD-1678, two potent and bioavailable CCR4 receptor antagonists. *ACS Med Chem Lett*. 2017;8(9):981-986.
54. Hu Y, Liu S, Liu P, Mu Z, Zhang J. Clinical relevance of eosinophils, basophils, serum total IgE level, allergen-specific IgE, and clinical features in atopic dermatitis. *J Clin Lab Anal*. 2020;34(6):e23214.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bissonnette R, DuBois J, Facheris P, et al. Clinical and molecular effects of oral CCR4 antagonist RPT193 in atopic dermatitis: A Phase 1 study. *Allergy*. 2023;00:1-13. doi:10.1111/all.15949