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REVIEW

Rezpegaldesleukin and Regulatory T Cell Restoration in Immune-Mediated Skin Diseases

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ABSTRACT

Inflammatory skin diseases such as atopic dermatitis (AD), psoriasis, and alopecia areata (AA) are characterized by immune dysregulation involving impaired regulatory T cell (T_{reg}) function and persistent activation of effector inflammatory pathways. Current targeted therapies largely suppress downstream inflammatory signaling rather than correcting upstream regulatory abnormalities. Rezpegaldesleukin (REZPEG; NKTR-358) is a first-in-class, T_{reg}-selective interleukin-2 (IL-2) receptor agonist engineered to preferentially expand cluster of differentiation 4 positive ($CD4^+$) $FOXP3^+$ T_{reg}s while minimizing activation of conventional effector T cells and natural killer (NK) cells. This review summarizes the biological rationale, mechanism of action, and emerging clinical evidence supporting REZPEG across dermatologic indications, particularly AD and AA. In phase 1 and phase 1b studies, REZPEG induced selective and durable T_{reg} expansion, attenuation of inflammatory biomarkers, and clinical improvements in AD and psoriasis, including prolonged off-treatment responses. In the phase 2b REZOLVE-AD trial, all active dosing regimens significantly improved Eczema Area and Severity Index outcomes versus placebo, with responses maintained or further deepened through week 52 with monthly or quarterly maintenance dosing. In severe AA, the phase 2b REZOLVE-AA trial did not meet its primary endpoint: mean Severity of Alopecia Tool (SALT) reductions at week 36 were 28.2% and 30.3% with REZPEG 24 and 18 µg/kg, respectively, versus 11.2% with placebo (p = 0.186 and p = 0.121). A supportive sensitivity analysis excluding four participants with major eligibility violations reached statistical significance, while hypothesis-generating extension data suggested further hair regrowth through week 52. Across completed studies, REZPEG has demonstrated a favorable tolerability profile, predominantly characterized by mild injection-site reactions, without major safety signals. Collectively, these findings support selective T_{reg} expansion as a mechanistically novel therapeutic strategy in

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immune-mediated skin disease, while further controlled studies are needed to define REZPEG's long-term efficacy and therapeutic positioning.

Keywords: Alopecia areata; Atopic dermatitis; IL-2 pathway; Regulatory T cells; Rezpegaldesleukin

Key Summary Points
Rezpegaldesleukin (REZPEG) is a first-in-class interleukin-2 (IL-2) pathway agonist that selectively expands regulatory T cells (T_{reg}s), offering a novel immune-restorative mechanism of action distinct from currently approved targeted therapies in dermatology.
In the phase 2b REZOLVE-AD study, rezpegaldesleukin met its primary endpoint and all key secondary endpoints at week 16 in patients with moderate-to-severe atopic dermatitis, with response deepening and durability maintained through week 52 under both monthly and quarterly dosing regimens.
In the phase 2b REZOLVE-AA study in severe-to-very-severe alopecia areata, the primary endpoint did not reach statistical significance in the primary analysis, although numerical improvements favored rezpegaldesleukin; supportive sensitivity and exploratory extension analyses showed greater hair regrowth with active treatment and informed continued clinical development.
The safety profile of rezpegaldesleukin was consistent across studies, with injection-site reactions as the most common adverse event.
Rezpegaldesleukin represents a promising first-in-class therapeutic candidate with potential applicability across multiple immune-mediated dermatological conditions, with phase 3 development ongoing in both atopic dermatitis and alopecia areata.

INTRODUCTION

Inflammatory and autoimmune skin diseases, including atopic dermatitis (AD), psoriasis, and alopecia areata (AA), are characterized by immune dysregulation driven in part by impaired regulatory T cell (T_{reg}) function and pathologic activation of effector T cell subsets. Together, these conditions affect tens of millions of individuals worldwide and impose substantial burden on quality of life, psychological well-being, and healthcare use [1, 2].

Targeted therapies have substantially improved clinical outcomes in these disease states, including biologic agents directed against the interleukin (IL)-4/IL-13/IL-31 and IL-17/IL-23 pathways, as well as Janus kinase inhibitors (JAKi) [2–4]. Despite these advances, all currently approved therapies primarily act downstream to inhibit terminal effector pathways of inflammation rather than addressing the upstream regulatory defects resulting in an imbalance of immune activation versus resolution [4]. In addition, JAKi specifically carry US Food and Drug Administration (FDA) boxed warnings regarding serious infections, malignancy, major adverse cardiovascular events (MACE), and thrombosis, which limit broad and long-term use in various patient populations for AD and AA [3, 5].

T_{reg}s are cluster of differentiation 4 positive ($CD4^+$) $FOXP3^+$ lymphocytes that play a central role in maintaining peripheral immune homeostasis through suppression of autoreactive effector T cells and preservation of self-tolerance. T_{reg} dysfunction or insufficiency is increasingly recognized as a shared pathogenic mechanism across AD, psoriasis, and AA, resulting in unchecked activation and perpetuation of inflammation [6–8]. Rezpegaldesleukin (REZPEG; NKTR-358) is the first agent in dermatology specifically designed to therapeutically expand and activate T_{reg}s rather than directly inhibit downstream inflammatory mediators [9]. This review summarizes the preclinical rationale, clinical pharmacology, and emerging clinical evidence supporting REZPEG across dermatological indications, with particular emphasis on efficacy outcomes, safety data, and

its potential positioning within the evolving therapeutic landscape.

This narrative review was informed by a targeted search of PubMed/Medical Literature Analysis and Retrieval System Online (MEDLINE) and Google Scholar for English-language publications relevant to rezpegaldesleukin, regulatory T cell biology, IL-2 pathway modulation, and immune-mediated dermatologic diseases. Reference lists of relevant articles were also reviewed to identify additional mechanistic and clinical studies. Priority was given to primary peer-reviewed publications and pivotal clinical trial reports. Where full peer-reviewed data were not yet available, conference abstracts, congress presentations, clinical trial registry information, and sponsor communications were considered to capture the most recent results from the ongoing clinical development programs.

MECHANISM OF ACTION AND BIOLOGICAL RATIONALE

IL-2 regulates T cell proliferation, survival, and function through receptors with differing binding affinities. The high-affinity trimeric receptor (IL-2Rαβγ; CD25/CD122/CD132) is constitutively expressed on T_{reg}s, whereas conventional effector T cells (T_{con}s) and natural killer (NK) cells primarily depend on the lower-affinity dimeric receptor (IL-2Rβγ) [9–11]. This receptor asymmetry creates a therapeutic opportunity whereby molecules with preferential affinity for the trimeric receptor can selectively expand T_{reg}s while largely sparing effector immune cells (Fig. 1).

T_{reg} insufficiency has been documented across the major dermatological indications targeted by REZPEG. In AD, a meta-analysis of eight studies demonstrated significantly reduced peripheral blood T_{reg} levels, with the degree of depletion correlating with disease severity [6]. In psoriasis, T_{reg}s exhibit impaired suppressive function and, under a dominant T_h1/T_h17 inflammatory milieu, may acquire T_h17-like pathogenic features rather than maintain immune regulation [7, 8]. This functional instability may contribute to persistent inflammation and further highlights the importance of addressing the upstream regulatory defect rather than exclusively blocking downstream cytokines. In AA, T_{reg} insufficiency contributes to the collapse of immune privilege surrounding the anagen hair follicle [12, 13].

Native recombinant IL-2 (aldesleukin) is poorly suited for therapeutic T_{reg} expansion because of its short 13-min half-life, narrow therapeutic window, and dose-dependent toxicity resulting from concomitant effector immune-cell activation [9]. REZPEG, a polyethylene glycol (PEG)-conjugated recombinant human IL-2, was identified through in vivo screening of 23 distinct PEG-IL-2 conjugates in murine models evaluating T_{reg} expansion, off-target effector T cell activation, and pharmacokinetic properties simultaneously [4]. Compared with native IL-2, REZPEG demonstrates reduced affinity for both IL-2Rα and IL-2Rβ. However, because T_{reg}s constitutively express all three IL-2 receptor subunits, signaling through the high-affinity trimeric receptor is preserved, whereas T_{con}s are substantially less responsive because they primarily depend on dimeric IL-2 receptor signaling. This selectivity results in 12–17-fold T_{reg} expansion with minimal T_{con} or NK cell activation. In addition, PEGylation prolongs the plasma half-life to 7.4–12.9 days, enabling biweekly (q2w), monthly (q4w), or quarterly (q12w) subcutaneous dosing [4, 9].

In cynomolgus monkeys, a single dose of REZPEG produced a > 15-fold increase in T_{reg}s that persisted through day 14, compared with only a 3-fold increase following five consecutive daily doses of native recombinant human IL-2 (rhIL-2). Repeated dosing over 6 months resulted in cyclical and sustained T_{reg} expansion without evidence of diminished pharmacologic activity [4]. In a delayed-type hypersensitivity model, REZPEG-induced immune tolerance persisted for at least 1 month after treatment discontinuation, supporting the biological plausibility of the prolonged off-treatment responses subsequently observed in human studies [4].

Beyond T_{reg} expansion, REZPEG also modulates NK cell populations, a finding of potential therapeutic relevance given that

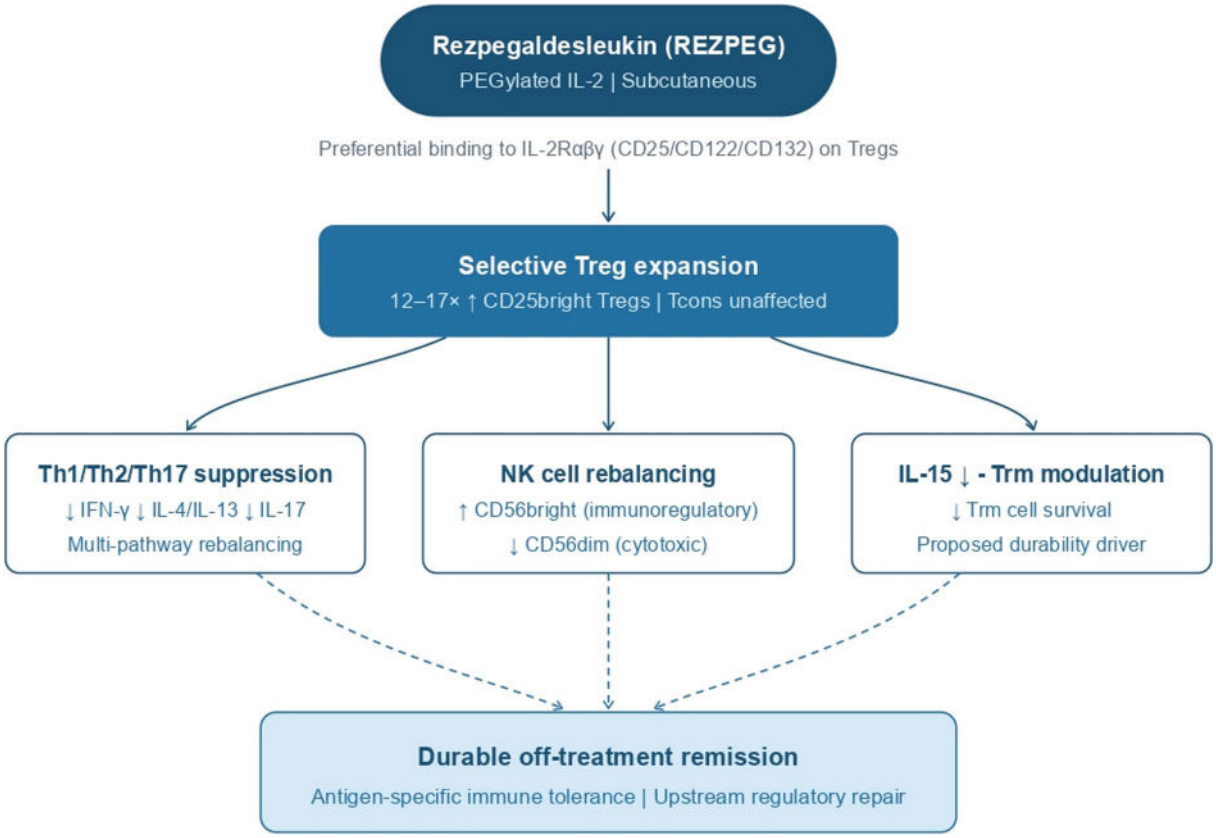


Fig. 1 Proposed mechanism of action of rezpegaldesleukin in immune-mediated skin diseases. *CD* cluster of differentiation, *IFN* interferon, *IL* interleukin, *IL-2R* interleukin-2 receptor, *NK* natural killer, *PEG* polyethylene glycol, *REZPEG* rezpegaldesleukin, *SC* subcutaneous, T_{con} conventional T cell, T_h T helper cell, T_{reg} regulatory T cell, T_{rm} tissue-resident memory T cell

NK cell dysfunction is a recognized feature of both AD and psoriasis [14, 15]. At higher doses, REZPEG expanded total NK cell numbers while simultaneously reducing the $CD56^{dim}$ subset and increasing the $CD56^{bright}$ subset. This shift is of particular interest, as $CD56^{bright}$ NK cells exert an important immunoregulatory function through the elimination of highly proliferative autoreactive $CD4^+$ conventional T cells that have escaped T_{reg}-mediated suppression [15, 16]. These observations suggest that the immunoregulatory effects of REZPEG may extend beyond direct T_{reg} expansion and involve coordinated rebalancing of multiple innate and adaptive immune compartments.

CLINICAL EVIDENCE

The key clinical studies evaluating rezpegaldesleukin in dermatologic indications are summarized in Table 1.

Phase 1 Program

The first-in-human development program included a single ascending dose (SAD) study in healthy volunteers (NCT04133116; 0.3–28.0 µg/kg; n = 100) and a multiple ascending dose (MAD) study in patients with systemic lupus erythematosus (SLE) (NCT03556007; 3–24 µg/kg q2w; n = 48) [9]. Both studies demonstrated

Table 1 Key clinical trials of rezpegaldesleukin in dermatological conditions

Condition	Phase/NCT	*n*	Regimen	Primary endpoint	Key efficacy results
Moderate-to-severe AD	Phase 1b NCT04081350 completed	44	REZPEG 10–12 or 24 μg/kg SC q2w × 12 weeks; 36-week off-drug follow-up	Safety, PK, T_{reg} expansion (exploratory EASI)	24 μg/kg: mean EASI improvement 83% at week 12; treatment difference versus placebo −35.8 percentage points (95% CI −57.78 to −13.76; $p = 0.002$; EASI-75 maintained in 71% and vIGA-AD response in 80% of week-12 responders at week 36 posttreatment; sustained $CD25^{bright}$ T_{reg} expansion; attenuation of T_h1, T_h2, T_h17 markers; IL-15 reduction postulated to underlie off-drug durability [1]
Chronic plaque psoriasis	Phase 1b NCT04119557 completed	30	REZPEG 24 μg/kg SC q2w × 12 weeks; 36-week follow-up	Safety, PK, T_{reg} expansion (exploratory PASI)	Dose-dependent PASI improvements versus placebo; sustained $CD25^{bright}$ T_{reg} expansion; broad $T_h1/T_h17/T_h2$ immune signature attenuation; consistent safety profile [1]

Table 1 continued

Condition	Phase/NCT	*n*	Regimen	Primary endpoint	Key efficacy results
Moderate-to-severe AD (biologic/JAKi naïve)	Phase 2b NCT06136741 (REZOLVE-AD) completed	393	3:3:3:2 ratio—24 µg/kg q2w/18 µg/kg q2w/24 µg/kg q4w/placebo × 16 weeks; EASI-50 responders re-randomized 1:1 to q4w or q12w maintenance to week 52	Mean percentage EASI change from baseline at week 16	Primary endpoint met across all active arms: mean EASI improvement 61%, 58%, and 53% versus 31% with placebo; treatment differences −30 percentage points (95% CI −41.3 to −18.0), −27 (95% CI −38.5 to −15.7), and −22 (95% CI −33.3 to −10.3), respectively; EASI-75: 42%, 46%, and 34% versus 17%; vIGA-AD 0/1: 20%, 26%, and 19% versus 8%; EASI-90: 25% (high dose, $p < 0.05$); Itch NRS ≥ 4 points: 42%, 35%, and 23% versus 16%; BSA: 54%, 48%, and 43% versus 17%; EASI-50: 66%, 66%, and 55% versus 34%; consistent across vIGA-AD 3 and 4 [17]

Table 1 continued

Condition	Phase/NCT	*n*	Regimen	Primary endpoint	Key efficacy results
Severe-to-very-severe AA (JAKi naïve)	Phase 2b NCT06340360 (REZOLVE-AA) completed	92	3:3:2 ratio—24 µg/kg/18 µg/kg/placebo SC q2w × 36 weeks; 16-week blinded extension to week 52 for SALT > 20 with hair growth	Mean percentage SALT reduction at week 36	Mean SALT reduction: 28–30% (active) versus 11% (placebo) at week 36; 16-week extension up to week 52: 26–28% of subjects who had achieved $SALT_{30}$ but not SALT score ≤ 20 at week 36 achieved SALT score ≤ 20 versus 0% placebo; eyebrow/eyelash regrowth documented

AD atopic dermatitis, *AA* alopecia areata, *EASI* Eczema Area and Severity Index, *EASI-50* 50% improvement from baseline Eczema Area and Severity Index score, *EASI-75* 75% improvement from baseline Eczema Area and Severity Index score, *EASI-90* 90% improvement from baseline Eczema Area and Severity Index score, *JAKi* JAK inhibitor, *NCT* National Clinical Trial identifier, *PASI* Psoriasis Area and Severity Index, *PK* pharmacokinetics, *q2w* every 2 weeks, *q4w* every 4 weeks, *q12w* every 12 weeks, *SALT* Severity of Alopecia Tool, *SC* subcutaneous, *vIGA-AD* validated Investigator Global Assessment for Atopic Dermatitis, *CI* confidence interval, *BSA* body surface area, *Itch NRS* Itch Numeric Ranking Scale

dose-proportional pharmacokinetics together with selective and sustained expansion of $CD4^+FOXP3^+CD25^{bright}$ T_{reg}s, reaching up to 17-fold above baseline and persisting for 20–30 days at the highest dose level [9]. No clinically meaningful changes in T_{con} cells were observed. Adverse events (AEs) were limited primarily to mild, self-limiting injection-site reactions (ISRs), with no dose-limiting toxicities, serious AEs, or deaths reported. Collectively, these findings established the pharmacokinetic–pharmacodynamic relationship of REZPEG and supported the development of an intermittent subcutaneous dosing strategy [9].

Phase 1b Trials in Atopic Dermatitis and Psoriasis

Two multicenter, randomized, double-blind, placebo-controlled phase 1b trials were conducted in parallel: one in moderate-to-severe AD (NCT04081350; n = 44) and the other in chronic plaque psoriasis (NCT04119557; n = 30) [1]. Patients received subcutaneous REZPEG at doses of 10–12 µg/kg or 24 µg/kg q2w for 12 weeks, followed by a 36-week off-treatment follow-up period.

In the 24 µg/kg AD cohort, mean Eczema Area and Severity Index (EASI) improvement reached 83% at week 12, corresponding to a treatment difference versus placebo of −35.8 percentage points (95% CI −57.78 to −13.76; p = 0.002), with statistically significant improvements also observed in body surface area (BSA), Dermatology Life Quality Index (DLQI), and itch scores. Among week-12 responders, 75% improvement from baseline EASI score (EASI-75) responses were maintained in 71% of patients and validated Investigator Global Assessment for AD (vIGA-AD) responses maintained in 80% at week 36, corresponding to approximately 6 months after the final dose [1]. The durability of these off-treatment responses is notable and contrasts with the more limited persistence typically observed following discontinuation of currently approved biologic therapies for AD. Mechanistic serum proteomic analyses demonstrated simultaneous attenuation of T_h1-, T_h2-, and T_h17-associated inflammatory

signatures. In addition, marked reductions in serum IL-15, a cytokine implicated in maintenance of tissue-resident memory T cells, were proposed as a potential contributor to the observed off-treatment durability [1].

In the psoriasis cohort, REZPEG 24 µg/kg produced dose-dependent PASI improvements versus placebo during the 12-week treatment period and subsequent 36-week follow-up. Although the study was exploratory and not powered for formal hypothesis testing, treatment was associated with sustained $CD25^{bright}$ T_{reg} expansion together with broad attenuation of T_h1- and T_h17-associated inflammatory markers, consistent with findings observed in AD [1].

Proteomic analyses of serial serum samples further demonstrated modulation of multiple immunoregulatory pathways beyond T_{reg} expansion. Treatment was associated with reductions in OX40 receptor, CCL22, CX3CL1, and IL-19, proteins implicated in AD pathobiology, as well as CXCL16, a chemokine involved in the recruitment of pathogenic $CD8^+$ T cells to psoriatic skin lesions. The observation that both a predominantly T_h17-driven disease (psoriasis) and a T_h2-dominant disease (AD) demonstrated overlapping pharmacodynamic responses supports the concept that upstream T_{reg} restoration may modulate multiple effector immune pathways simultaneously rather than targeting a single cytokine axis. Collectively, these findings provide mechanistic support for the crossindication clinical development strategy of REZPEG [1, 8].

Phase 2b Trials

REZOLVE-AD (Atopic Dermatitis)

The global phase 2b REZOLVE-AD trial (NCT06136741) enrolled 393 biologic- and JAKi-naïve adults with moderate-to-severe AD across 107 sites in ten countries [17, 18]. Patients were randomized in a 3:3:3:2 ratio to receive subcutaneous REZPEG at doses of 24 µg/kg q2w, 18 µg/kg q2w, 24 µg/kg q4w, or placebo, with stratification according to baseline vIGA-AD score and geographic region. The primary endpoint was mean percentage change in EASI from baseline at week 16 [17, 18].

All three active treatment arms met the primary endpoint, with mean EASI improvements of 61%, 58%, and 53% with REZPEG 24 µg/kg q2w, 18 µg/kg q2w, and 24 µg/kg q4w, respectively, compared with 31% for placebo. The corresponding treatment differences versus placebo were −30 percentage points (95% CI −41.3 to −18.0; $p < 0.0001$), −27 percentage points (95% CI −38.5 to −15.7; $p < 0.0001$), and −22 percentage points (95% CI −33.3 to −10.3; $p = 0.0002$), respectively [17]. Statistically significant improvements in EASI-75, 50% improvement from baseline EASI score (EASI-50), and BSA were observed across all active arms. The q2w regimens additionally achieved significance for vIGA-AD 0/1 and ≥ 4-point improvement in Itch Numeric Rating Scale (NRS), while the high-dose q2w arm also achieved significance for 90% improvement from baseline EASI score (EASI-90).

Two findings are of particular interest. First, EASI-75 and EASI-90 responses were generally comparable between patients with moderate (baseline vIGA-AD 3) and severe disease (baseline vIGA-AD 4), suggesting relative consistency of treatment effect across severity strata [17, 19]. Second, translational pharmacodynamic analyses demonstrated dose-dependent T_{reg} expansion, reaching up to sixfold in the high-dose arm, together with correlated reductions in T_h2-associated biomarkers, providing evidence of on-target biologic activity in phase 2b patients [17, 20].

Longer-term maintenance results through week 52 have, at the time of this review, been reported through sponsor communications and conference presentations but have not yet undergone full peer review. Following induction, patients who achieved an EASI-50 response at week 16 were re-randomized 1:1 to receive maintenance treatment on either a q4w or q12w schedule through week 52 [20]. Maintenance analyses demonstrated sustained efficacy across both dosing regimens. Among re-randomized patients receiving 24 µg/kg induction therapy, EASI-75 responses were maintained in 71% (q4w) and 83% (q12w), while EASI-90 responses were maintained in 80% and 78%, respectively

[20]. Similarly, vIGA-AD 0/1 responses were maintained in 85% and 63% of patients.

Clinical outcomes continued to improve during maintenance treatment, with additional patients achieving EASI-75, EASI-90, and vIGA-AD 0/1 responses between weeks 16 and 52. Rates of complete skin clearance (100% improvement from baseline EASI score [EASI-100]) increased substantially over time. Among all re-randomized maintenance patients, EASI-100 responses increased from 4% to 22% with q4w dosing and from 9% to 18% with q12w dosing. In the more selected subgroup of patients who had already achieved EASI-75 and/or vIGA-AD responses at the start of maintenance, corresponding EASI-100 rates increased from 6% to 30% and from 14% to 27%, respectively [20].

Based on the overall REZOLVE-AD findings, initiation of the phase 3 ZENITH-AD program was announced [19].

REZOLVE-AA (Alopecia Areata)

At the time of this review, detailed results from the phase 2b REZOLVE-AA trial (NCT06340360) have been reported primarily through sponsor communications and conference presentations, and full peer-reviewed publication of the efficacy dataset is awaited. The trial enrolled 92 with JAKi-naïve adults with severe-to-very-severe AA (Severity of Alopecia Tool [SALT] score ≥ 50) across approximately 30 sites worldwide [21, 22]. Enrollment of patients with very severe disease (baseline SALT score ≥ 95) was capped at 25%, and thus, there were 25 such patients. Mean baseline SALT scores were 78.5 in the active treatment arms and 76.6 in the placebo arm, while median disease duration was 6.9 and 6.1 years, respectively. Patients were randomized in a 3:3:2 ratio to receive REZPEG 24 µg/kg, REZPEG 18 µg/kg, or placebo q2w for 36 weeks.

The primary endpoint, a mean percentage reduction in SALT score at week 36, was 28.2% in the 24 µg/kg arm (p = 0.186) and 30.3% in the 18 µg/kg arm (p = 0.121), compared with 11.2% in the placebo group [22]. Following identification of four patients with major eligibility violations after randomization, a sensitivity analysis excluding these individuals demonstrated statistically significant reductions in SALT score in both treatment arms: 29.6% with 24 µg/kg (p = 0.049) and 30.4% with 18 µg/kg (p = 0.042) versus 5.7% with placebo [22]. Given its supportive nature and the absence of clear public documentation regarding whether this analysis was prespecified, these findings should be considered hypothesis generating.

Improvements across secondary efficacy endpoints were also observed. $SALT_{30}$ (at least 30% improvement from baseline SALT score) responses were achieved in 48.9% and 45.7% of patients receiving REZPEG 24 µg/kg and 18 µg/kg, respectively, compared with 19.1% for placebo [22]. Corresponding rates for a SALT score ≤ 30 were 29.0% and 21.9% versus 8.4%, while a SALT score ≤ 20 was achieved in 15.6% and 14.8% versus 6.7%, respectively [22]. Clinically meaningful eyebrow and eyelash regrowth was also reported.

In a hypothesis-generating extension analysis, patients with a SALT score > 20 at week 36 who demonstrated evidence of hair regrowth entered a blinded 16-week extension through week 52. A total of 31 patients were enrolled (27 REZPEG treated and 4 placebo treated), of whom 94% completed the extension phase [23]. Between weeks 36 and 52, additional patients achieved clinically meaningful hair regrowth, with SALT score ≤ 20 responses observed in 29% (n = 4) of patients receiving 18 µg/kg and 31% (n = 4) receiving 24 µg/kg, compared with 0% in the placebo arm [23].

Week 52 SALT score ≤ 20 response rates incorporate both patients who had already achieved this threshold at week 36 (whose data were carried forward; as per protocol, these patients did not continue into the extension) and those achieving new responses during the extension period. These rates therefore do not represent outcomes among a continuously treated, unselected week-52 randomized population. Combining these groups, SALT score ≤ 20 responses were achieved in 25.8% and 27.6% of patients receiving REZPEG 18 µg/kg and 24 µg/kg, respectively, compared with 6.7% for placebo [23]. Corresponding rates for a SALT score ≤ 30 were 30.2% and 35.0% versus 8.4% (p = 0.023), while $SALT_{50}$ (50% improvement from baseline SALT score) responses were

achieved in 37.7% and 38.8% of REZPEG-treated patients compared with 13.6% for placebo [23]. Overall, these exploratory findings suggest continued response deepening during extended treatment.

SAFETY AND TOLERABILITY

Safety data are now available from a pooled analysis of 746 participants enrolled across nine completed phase 1 and 2 studies, including healthy volunteers and patients with AD, psoriasis, SLE, and ulcerative colitis. Overall, REZPEG demonstrated a consistent safety profile across indications. Unless otherwise specified, percentages reported from this analysis refer to the pooled study population; trial-specific rates are subsequently identified by study. Although treatment-emergent adverse events (TEAEs) were more frequent with REZPEG than placebo, severe AEs were uncommon (3.2% versus 4.5% with placebo), and ISRs were the most common TEAE (26.4%), with severe reactions occurring in only 0.7% of participants [24].

Across completed clinical studies, the safety and tolerability profile remained favorable [17, 20, 23]. The most common AEs were ISRs, typically consisting of localized erythema that resolved spontaneously within approximately 5 days [20]. In REZOLVE-AD, ISRs were reported in 69.7% of all REZPEG-treated patients during the 16-week induction period, with 30.1% experiencing mild reactions, 13.8% moderate, and only 0.2% severe [17]. During the subsequent maintenance period, ISR frequency and severity declined further, with nearly all reactions graded as mild [20], while adverse-event-related discontinuation rates remained low (3.5% in REZOLVE-AD maintenance and 1.4% in REZOLVE-AA) [17, 22].

Beyond ISRs, AEs observed in REZOLVE-AD were generally mild and included eosinophilia (7.8% versus 2.7%), pyrexia (6.3% versus 2.7%), headache (6.3% versus 4.1%), and arthralgia (5.0% versus 1.4%) [17]. Notably, the overall rate of TEAEs excluding ISRs was comparable between REZPEG and placebo (60.3% versus 57.5%) [17]. Safety findings in REZOLVE-AA remained consistent through week 52, with no new safety signals identified during the extension phase [23].

Across studies, no increased rates of MACE, thrombosis, serious or opportunistic infections, malignancy, acne, oral herpes, or conjunctivitis have been identified [17, 20, 22, 23]. Overall, the available data support a favorable tolerability profile across dermatologic indications studied to date.

DISCUSSION

The emerging clinical evidence for REZPEG supports a novel therapeutic paradigm in dermatology based on restoration of immune regulation rather than direct blockade of individual inflammatory cytokines or signaling pathways. Current biologic therapies for AD, psoriasis, and AA primarily target downstream effector mechanisms, including the IL-4/IL-13 and IL-23/IL-17 axes, while JAKis more broadly suppress intracellular cytokine signaling [2, 3, 5]. Although highly effective, these approaches do not directly address the upstream regulatory abnormalities that contribute to persistent immune dysregulation.

REZPEG differs mechanistically by selectively expanding T_{reg}s, thereby targeting a shared immunologic defect implicated across multiple inflammatory and autoimmune skin diseases. This mechanism may help explain the clinical activity observed across AD, psoriasis, and AA despite the distinct inflammatory pathways underlying these conditions [1, 7, 8, 12, 25]. Collectively, the available data support the concept that restoration of T_{reg} function may modulate multiple downstream effector pathways simultaneously, rather than targeting a single cytokine axis, and suggest that T_{reg}-directed therapies may represent a broadly applicable therapeutic strategy across immune-mediated skin diseases [25]. This concept is further supported by the broad proteomic changes observed in early clinical studies, including modulation of biomarkers implicated in multiple inflammatory pathways [1]. Whether this translates into a broadly

applicable therapeutic strategy across immune-mediated skin diseases remains to be established in larger, indication-specific studies.

The clinical efficacy of REZPEG should also be interpreted in the context of established therapies, while recognizing that cross-trial comparisons are limited by differences in populations, endpoints, trial duration, concomitant treatment, and statistical methodology. In pivotal AD trials, dupilumab produced EASI-75 responses of approximately 44–51% at week 16, while upadacitinib achieved rates of approximately 60–80%, depending on dose and study [26, 27]. In severe AA, SALT ≤ 20 responses have been reported in approximately 19–39% of patients receiving baricitinib at week 36, 14–31% across effective ritlecitinib regimens at week 24, and approximately 30–42% with deuruxolitinib at week 24 [28, 29]. These figures cannot be directly compared with REZPEG outcomes, particularly given differences in study design and assessment time points, and should therefore be regarded only as contextual benchmarks. At present, the available evidence does not establish superiority or equivalence of REZPEG to approved therapies. Its eventual therapeutic positioning will depend not only on efficacy but also on safety, treatment burden, and durability, and on whether T_{reg}-directed immune modulation provides clinically meaningful advantages over continuous downstream pathway inhibition.

The durability of clinical responses observed with REZPEG is particularly noteworthy. The 36-week off-drug remission reported in the phase 1b study [1], the progressive deepening of responses with quarterly maintenance dosing in REZOLVE-AD [17], and the continued increase in SALT score ≤ 20 responders in the REZOLVE-AA extension study [19] collectively suggest that the therapeutic effects of REZPEG may extend beyond the period of active drug administration. These observations raise the possibility that selective T_{reg} expansion may induce sustained immunologic changes that persist after treatment discontinuation. Such an effect would be biologically plausible, given the central role of T_{reg}s in maintaining immune homeostasis and peripheral tolerance. However, the available studies were not designed to establish disease modification, and longer-term controlled data are required to determine whether the observed durability reflects sustained immune reprogramming, pharmacodynamic persistence, or other mechanisms. Accordingly, the current findings should be considered hypothesis generating rather than evidence of disease modification.

A potential mechanistic explanation for the observed durability warrants consideration. REZPEG induced dose-dependent reductions in serum IL-15, a cytokine that plays a key role in the maintenance and survival of tissue-resident memory T cells (T_{rm} cells) [30, 31]. Given the emerging role of T_{rm} cells in disease persistence and relapse across chronic inflammatory skin diseases [32, 33], attenuation of IL-15-dependent T_{rm} survival may contribute to the prolonged off-treatment responses observed in clinical studies. Although this hypothesis remains to be formally validated, it provides a biologically plausible link between T_{reg} expansion and the sustained clinical benefit observed after treatment discontinuation. Further studies evaluating the relationship between T_{reg} expansion, IL-15 modulation, T_{rm} cell dynamics, and long-term clinical outcomes will be important to clarify this potential mechanism.

Another notable finding was the relative consistency of REZPEG efficacy across baseline disease severity strata in AD. While patients with more severe disease often exhibit attenuated responses to therapies targeting individual inflammatory pathways, REZPEG appeared to maintain clinical activity across severity categories. Although this observation requires confirmation in larger studies and should not be overinterpreted, it is consistent with the hypothesis that restoration of immune regulation may remain effective even in the setting of complex, multifaceted inflammation. From a clinical perspective, such a characteristic would be particularly valuable in patients with severe disease, who often represent the subgroup with the highest unmet therapeutic need.

In AA, efficacy findings require cautious interpretation. REZOLVE-AA did not meet its primary endpoint in the primary analysis, despite numerically greater reductions in SALT score with both REZPEG doses compared with

placebo. Statistical significance was observed in a sensitivity analysis excluding four patients with major eligibility violations; however, this analysis should be regarded as supportive rather than definitive. Interpretation of the week 52 findings is further limited by the enriched extension design, as only patients with a SALT score > 20 at week 36 who had demonstrated evidence of hair regrowth were eligible to continue treatment, while data from patients who had already achieved SALT ≤ 20 were carried forward. Accordingly, the observed increases in SALT response rates through week 52 are encouraging but exploratory and require confirmation in adequately powered phase 3 trials.

Importantly, treatment selection in AA is influenced not only by efficacy but also by safety and tolerability. To date, there is not a non-JAKi treatment option in AA. Indeed, REZPEG could occupy a distinct position within the evolving AA treatment landscape, combining clinically meaningful efficacy with a distinct mechanism of action.

The clinical activity of REZPEG across AD, psoriasis, and AA further supports the concept that T_{reg} restoration may represent a broadly applicable therapeutic strategy in immune-mediated skin diseases characterized by impaired immune regulation.

T_{reg} dysfunction has also been implicated in other immune-mediated dermatologic diseases, including vitiligo and cutaneous lupus erythematosus (CLE), providing a biological rationale for exploring T_{reg}-directed approaches beyond AD, psoriasis, and AA [34, 35]. In CLE, exploratory clinical activity with REZPEG has been reported in early-phase studies, including reductions in Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity (CLASI-A) scores [9, 34]. In vitiligo, alterations in T_{reg} number, function, and tissue localization have been described, supporting interest in therapeutic strategies aimed at restoring immune tolerance [35]. Clinical experience with T_{reg}-directed IL-2 pathway modulation in vitiligo remains limited and has not involved REZPEG. In a randomized phase 2a study of 169 adults with nonsegmental vitiligo (NCT06113328), the T_{reg}-preferring IL-2 receptor agonist MK-6194 did not meet the primary endpoint of percentage change in Facial Vitiligo Area Scoring Index (F-VASI) at week 24, although numerical improvements in facial and total-body VASI outcomes were observed with active treatment [36]. Development of MK-6194 was subsequently discontinued following review of the phase 2a and other clinical data, which did not demonstrate sufficient clinical benefit. These findings underscore that a compelling biological rationale for T_{reg} modulation does not necessarily translate into clinically meaningful efficacy.

The safety findings observed to date are also of interest. Across studies conducted to date, no major safety signals, laboratory abnormalities requiring routine monitoring, or AEs typically associated with cytokine-directed or broader immunosuppressive therapies have been identified. In AD, the apparent absence of conjunctivitis and herpes infections is of particular interest, given their recognized association with currently available therapies [37, 38]. However, the available safety database remains limited compared with approved biologics and JAKi, and rare AEs cannot yet be excluded. Although longer-term data remain necessary, these observations are consistent with the underlying biology of T_{reg} expansion, which may attenuate pathological inflammation while preserving protective immune responses.

An important limitation of the current evidence base is its variable degree of publication maturity. Final 16-week induction results from REZOLVE-AD are now available as a peer-reviewed publication; however, the week 52 REZOLVE-AD maintenance findings and much of the REZOLVE-AA efficacy and extension dataset remain available primarily through conference presentations and sponsor communications at the time of this review. Such sources provide less methodological detail than full peer-reviewed reports and may limit independent assessment of statistical analyses, subgroup definitions, missing-data handling, and outcome precision. Accordingly, longer-term and AA findings should be regarded as provisional until full peer-reviewed datasets become available.

Nevertheless, these findings are consistent with the overall body of evidence generated across the clinical development program.

Taken together, the available evidence suggests that REZPEG may represent the first dermatologic therapy specifically designed to restore immune regulation through selective T_{reg} expansion. While definitive conclusions regarding long-term disease modification cannot yet be drawn, the consistency of efficacy across indications, durability of response, and favorable safety profile support continued clinical development of this therapeutic strategy.

CONCLUSIONS

REZPEG is a first-in-class T_{reg}-selective IL-2 receptor agonist with emerging evidence across multiple immune-mediated skin diseases. Across phase 1, phase 1b, and phase 2b studies in AD, psoriasis, and AA, REZPEG has demonstrated clinically meaningful efficacy associated with selective T_{reg} expansion, attenuation of inflammatory biomarkers, and durable clinical responses.

While long-term data in larger patient populations are needed to fully characterize the safety profile, to date, REZPEG has shown a favorable tolerability profile, with notable mild-to-moderate ISRs reported in a large proportion of patients and no major safety signals identified.

Collectively, the available findings support continued investigation of selective T_{reg} expansion as a therapeutic strategy in dermatology. REZPEG represents a mechanistically distinct approach aimed at modulating upstream immune regulation rather than directly inhibiting individual downstream inflammatory pathways. Ongoing phase 3 studies and longer-term follow-up will be essential to define its efficacy, durability, safety, and eventual positioning relative to established therapies.

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Declarations

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