Safety Profile of Rezpegaldesleukin, a Selective Regulatory T-Cell-Inducing Interleukin-2 Conjugate, versus Placebo Based on an Aggregate Safety Evaluation of 746 Subjects Enrolled Across 9 Studies

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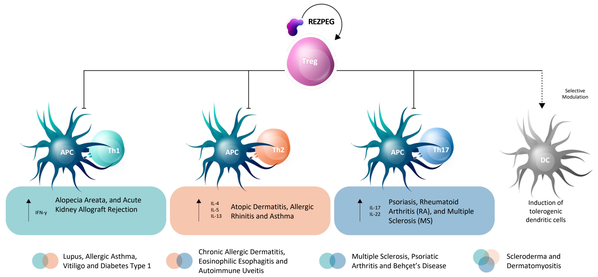
BACKGROUND

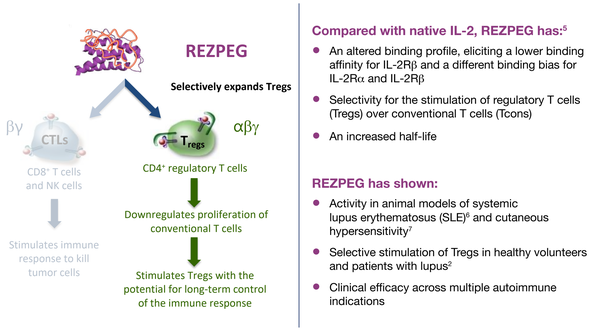
- Dysfunction of regulatory T cells (Treg) plays a key role in various immunological disorders.[1]
- Rezpegaldesleukin (REZPEG) is an IL-2 receptor (IL-2R) pathway agonist designed to stimulate the expansion and function of Tregs, while having minimal effect on conventional T cells (Tcons).[2]
- Targeting the Treg pathway is a novel therapeutic approach for patients with chronic inflammation and/or autoimmune disorders.[3]
- REZPEG has demonstrated preliminary clinical efficacy in patients with atopic dermatitis (AD), psoriasis (PsO), and systemic lupus erythematous (SLE).
- Phase 2b clinical trials are currently ongoing for moderate-to-severe AD (NCT06136741) and severe alopecia areata (NCT06340360).
- This report presents a pooled safety analysis from 9 completed Phase 1 and 2 studies evaluating REZPEG in healthy volunteers and subjects with chronic inflammatory diseases (i.e., AD, PsO, SLE, and ulcerative colitis [UC]).

Figure 1: Role of Regulatory T Cells in Autoimmune Disease



Regulatory T cells (Tregs) are indispensable for immune homoeostasis and for the prevention of autoimmune diseases.[4]

Figure 2: REZPEG: IL-2 Pathway Agonist that Selectively Induces Tregs and their Suppressive Activity



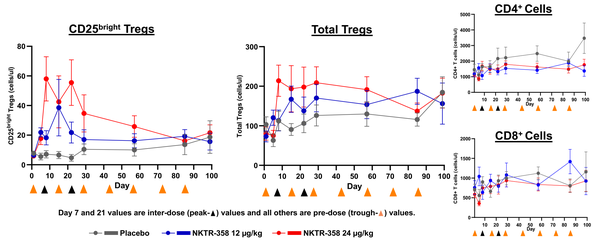
Compared with native IL-2, REZPEG has:[5]

- An altered binding profile, eliciting a lower binding affinity for IL-2Rβ and a different binding bias for IL-2Rα and IL-2Rβ
- Selectivity for the stimulation of regulatory T cells (Tregs) over conventional T cells (Tcons)
- An increased half-life

REZPEG has shown:

- Activity in animal models of systemic lupus erythematosus (SLE)[6] and cutaneous hypersensitivity[7]
- Selective stimulation of Tregs in healthy volunteers and patients with lupus[2]
- Clinical efficacy across multiple autoimmune indications

Figure 3: REZPEG Pharmacodynamics from Phase 1b Study in Atopic Dermatitis



The peak increase in CD25^{bright} Treg number was 10-fold above baseline after the first and second doses in the 24 µg/kg group.

Table 1: Completed Phase 1 and 2 Clinical Studies Evaluating REZPEG

Study	Phase	Title	REZPEG Dose(s) Evaluated	Planned Treatment/ Follow-up Duration	REZPEG Exposed (n)	Placebo (n)	Total Treated (n)
NCT03556007	1	A Phase 1, Double-blind, Randomized, Placebo-controlled, Ascending Multiple-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Subcutaneous Rezpegaldesleukin in Patients With Systemic Lupus Erythematosus	3 µg/kg; 6 µg/kg; 12 µg/kg; 24 µg/kg	11.3 Weeks	36	12	48
NCT04081350	1	A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Subcutaneous Rezpegaldesleukin in Patients With Atopic Dermatitis	10 µg/kg; 12 µg/kg; 24 µg/kg	48 Weeks	37	11	48*
NCT04119557	1	A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Subcutaneous Rezpegaldesleukin in Patients With Psoriasis	10 µg/kg; 24 µg/kg	48 Weeks	25	5	30**
NCT04133116	1	A Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Rezpegaldesleukin in Japanese and Caucasian Healthy Subjects	450 µg; 900 µg; 1800 µg	7 Weeks	30	6	36
NCT04380324	1	A Phase 1, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Ascending Subcutaneous Dose of Rezpegaldesleukin in Healthy Volunteers	0.3 µg/kg; 1 µg/kg; 3 µg/kg; 6 µg/kg; 9 µg/kg; 13.5 µg/kg; 20 µg/kg; 28 µg/kg	7.1 Weeks	76	24	100
NCT04433585	2	A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of Rezpegaldesleukin in Adults With Systemic Lupus Erythematosus	300 µg; 900 µg; 1800 µg	30 Weeks	217	74	291
NCT04677179	2	An Adaptive Phase 2, Randomized, Double Blind, Placebo Controlled Study of Rezpegaldesleukin in Patients With Moderately to Severely Active Ulcerative Colitis	900 µg; 1800 µg	58 Weeks	67	14	81
NCT04998487	1	A Phase 1, Randomized, Open-Label, Single-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Subcutaneous Rezpegaldesleukin in Healthy Participants	1800 µg; 3000 µg	8 Weeks	69	2	71
NCT05565729	1	A Phase 1, Randomized, Placebo-controlled, Participant- and Investigator-blind, Single-dose Study of the Pharmacokinetics of Rezpegaldesleukin Following Subcutaneous Dosing of Rezpegaldesleukin in Healthy Participants	1800 µg	8 Weeks	35	6	41

*Includes 1 REZPEG exposed subject excluded from analysis due to study site GCP noncompliance; **Includes 3 REZPEG exposed and 1 placebo subject excluded from analysis due to study site GCP noncompliance.

RESULTS

Table 2: Treatment Emergent Adverse Events (TEAEs) Reported in >2% of REZPEG Exposed Subjects

System Organ Class Preferred Term	REZPEG Exposed (N = 592) Mild	Moderate	Severe	Any	Placebo (N = 154) Mild	Moderate	Severe	Any
Patients with at least one TEAE	242 (40.9%)	130 (22.0%)	19 (3.2%)	391 (66.0%)	36 (23.4%)	32 (20.8%)	7 (4.5%)	75 (48.7%)
General disorders and administration site conditions	149 (25.2%)	39 (6.6%)	6 (1.0%)	194 (32.8%)	3 (1.9%)	4 (2.6%)	0 (0.0%)	7 (4.5%)
Injection site erythema	78 (13.2%)	6 (1.0%)	0 (0.0%)	84 (14.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Injection site pain	46 (7.8%)	2 (0.3%)	0 (0.0%)	48 (8.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Injection site reaction	30 (5.1%)	15 (2.5%)	2 (0.3%)	47 (7.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Injection site pruritus	38 (6.4%)	3 (0.5%)	0 (0.0%)	41 (6.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pyrexia	28 (4.7%)	8 (1.4%)	0 (0.0%)	36 (6.1%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.6%)
Injection site swelling	20 (3.4%)	2 (0.3%)	0 (0.0%)	22 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fatigue	10 (1.7%)	4 (0.7%)	1 (0.2%)	15 (2.5%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Infections and infestations	98 (16.6%)	44 (7.4%)	2 (0.3%)	144 (24.3%)	14 (9.1%)	16 (10.4%)	4 (2.6%)	34 (22.1%)
COVID-19	24 (4.1%)	5 (0.8%)	1 (0.2%)	30 (5.1%)	4 (2.6%)	6 (3.9%)	0 (0.0%)	10 (6.5%)
Urinary tract infection	12 (2.0%)	6 (1.0%)	0 (0.0%)	18 (3.0%)	3 (1.9%)	3 (1.9%)	1 (0.6%)	7 (4.5%)
Upper respiratory tract infection	12 (2.0%)	5 (0.8%)	0 (0.0%)	17 (2.9%)	3 (1.9%)	0 (0.0%)	0 (0.0%)	3 (1.9%)
Nasopharyngitis	15 (2.5%)	1 (0.2%)	0 (0.0%)	16 (2.7%)	3 (1.9%)	1 (0.6%)	0 (0.0%)	4 (2.6%)
Gastrointestinal disorders	53 (9.0%)	9 (1.5%)	1 (0.2%)	63 (10.6%)	10 (6.5%)	7 (4.5%)	0 (0.0%)	17 (11.0%)
Nausea	13 (2.2%)	1 (0.2%)	0 (0.0%)	14 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	33 (5.6%)	20 (3.4%)	2 (0.3%)	55 (9.3%)	9 (5.8%)	7 (4.5%)	2 (1.3%)	18 (11.7%)
Arthralgia	10 (1.7%)	5 (0.8%)	0 (0.0%)	15 (2.5%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Nervous system disorders	41 (6.9%)	10 (1.7%)	1 (0.2%)	52 (8.8%)	11 (7.1%)	5 (3.2%)	0 (0.0%)	16 (10.4%)
Headache	29 (4.9%)	3 (0.5%)	0 (0.0%)	32 (5.4%)	7 (4.5%)	2 (1.3%)	0 (0.0%)	9 (5.8%)
Skin and subcutaneous tissue disorders	33 (5.6%)	15 (2.5%)	2 (0.3%)	50 (8.4%)	6 (3.9%)	1 (0.6%)	1 (0.6%)	8 (5.2%)
Erythema	10 (1.7%)	2 (0.3%)	0 (0.0%)	12 (2.0%)	2 (1.3%)	0 (0.0%)	0 (0.0%)	2 (1.3%)
Blood and lymphatic system disorders	32 (5.4%)	10 (1.7%)	0 (0.0%)	42 (7.1%)	2 (1.3%)	3 (1.9%)	0 (0.0%)	5 (3.2%)
Eosinophilia	11 (1.9%)	2 (0.3%)	0 (0.0%)	13 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anaemia	9 (1.5%)	3 (0.5%)	0 (0.0%)	12 (2.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Investigations	26 (4.4%)	12 (2.0%)	1 (0.2%)	39 (6.6%)	5 (3.2%)	3 (1.9%)	1 (0.6%)	9 (5.8%)
Injury, poisoning and procedural complications	14 (2.4%)	16 (2.7%)	0 (0.0%)	30 (5.1%)	2 (1.3%)	3 (1.9%)	0 (0.0%)	5 (3.2%)
Respiratory, thoracic and mediastinal disorders	24 (4.1%)	2 (0.3%)	0 (0.0%)	26 (4.4%)	7 (4.5%)	1 (0.6%)	0 (0.0%)	8 (5.2%)

The Most Common Grouped TRAE in REZPEG Exposed Subjects Is ISR (26.4%), Severe in 0.7% of Subjects.

Table 3: Serious Treatment Related Adverse Events (all)

System Organ Class Preferred Term, n (%)	REZPEG Exposed (N = 592)	Placebo (N = 154)
Patients with at least one Serious TEAE Related to IP	2 (0.3%)	3 (1.9%)
Cardiac disorders*	1 (0.2%)	0
Acute myocardial infarction*	1 (0.2%)	0
General disorders and administration site conditions	1 (0.2%)	0
Injection site reaction	1 (0.2%)	0
Pyrexia	1 (0.2%)	0
Infections and infestations	0	3 (1.9%)
Cellulitis	0	1 (0.6%)
Pneumonia	0	1 (0.6%)
Urinary tract infection	0	1 (0.6%)
Musculoskeletal and connective tissue disorders	0	1 (0.6%
Tenosynovitis	0	1 (0.6%)

*Observed in a 53 y/o male with PMH significant for SLE, lymphopenia, transaminases increased, and hepatic steatosis, an independent risk factor for myocardial infarction. Angiography demonstrated severe atherosclerosis, and the subject had received a COVID-19 vaccine 9-days before the SAE. Subject's concomitant medications included: hydroxychloroquine, meprednisone, and omeprazole. Event was assessed to be unrelated by study sponsor (Eli Lilly & Co.).

Serious TEAEs Were Observed in 2.7% of REZPEG Exposed Subjects and 4.5% of Placebo Exposed Subjects.

CONCLUSIONS

- REZPEG is a novel regulatory T-cell stimulating therapy and the pooled safety analysis of the 9 completed Phase 1 & 2 studies demonstrates a consistent and potentially favorable safety profile.

% Subject with:	REZPEG Exposed (N = 592)	Placebo (N = 154)
Any TEAE	66.0%	48.7%
Severe TEAE	3.2%	4.5%
Serious TEAE	2.7%	4.5%
Serious TRAE	0.3%	1.9%

- ISRs are the most common grouped TRAE observed in 26.4% of REZPEG exposed subjects, and severe in 0.7% of the subjects.
- No increased risk of infections in REZPEG exposed subjects compared to placebo.
- Two Phase 2b, double-blind studies are currently ongoing, evaluating REZPEG in subjects with moderate-to-severe AD (NCT06136741) and severe alopecia areata (NCT06340360).
  - Preliminary safety and efficacy data from the Phase 2b moderate-to-severe AD trial is expected in 2Q2025.[8]
  - Preliminary safety and efficacy data from the Phase 2b severe alopecia areata trial is expected in 2H2025.[8]

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ABBREVIATIONS
Regulatory T cells (Treg); Rezpegaldesleukin (REZPEG); IL-2 receptor (IL-2R); conventional T cells (Tcons); atopic dermatitis (AD); psoriasis (PsO); systemic lupus erythematous (SLE); moderate-to-severe AD (NCT06136741); severe alopecia areata (NCT06340360)

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AUTHOR DISCLOSURE INFORMATION
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