

Safety Profile of Repegaldesleukin, 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
- Repegaldesleukin (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 erythematosus (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

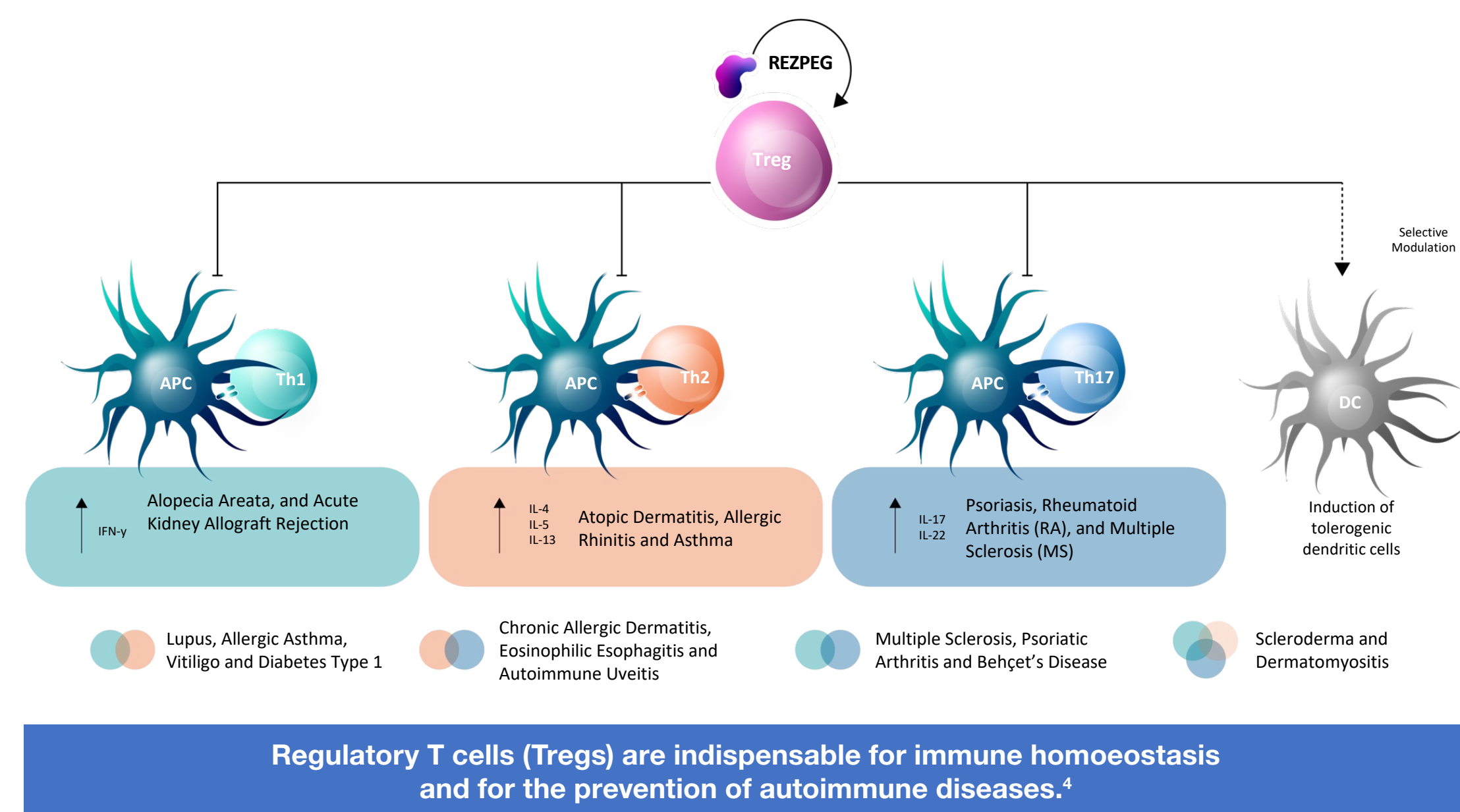


Figure 2: REZPEG: IL-2 Pathway Agonist that Selectively Induces Tregs and their Suppressive Activity

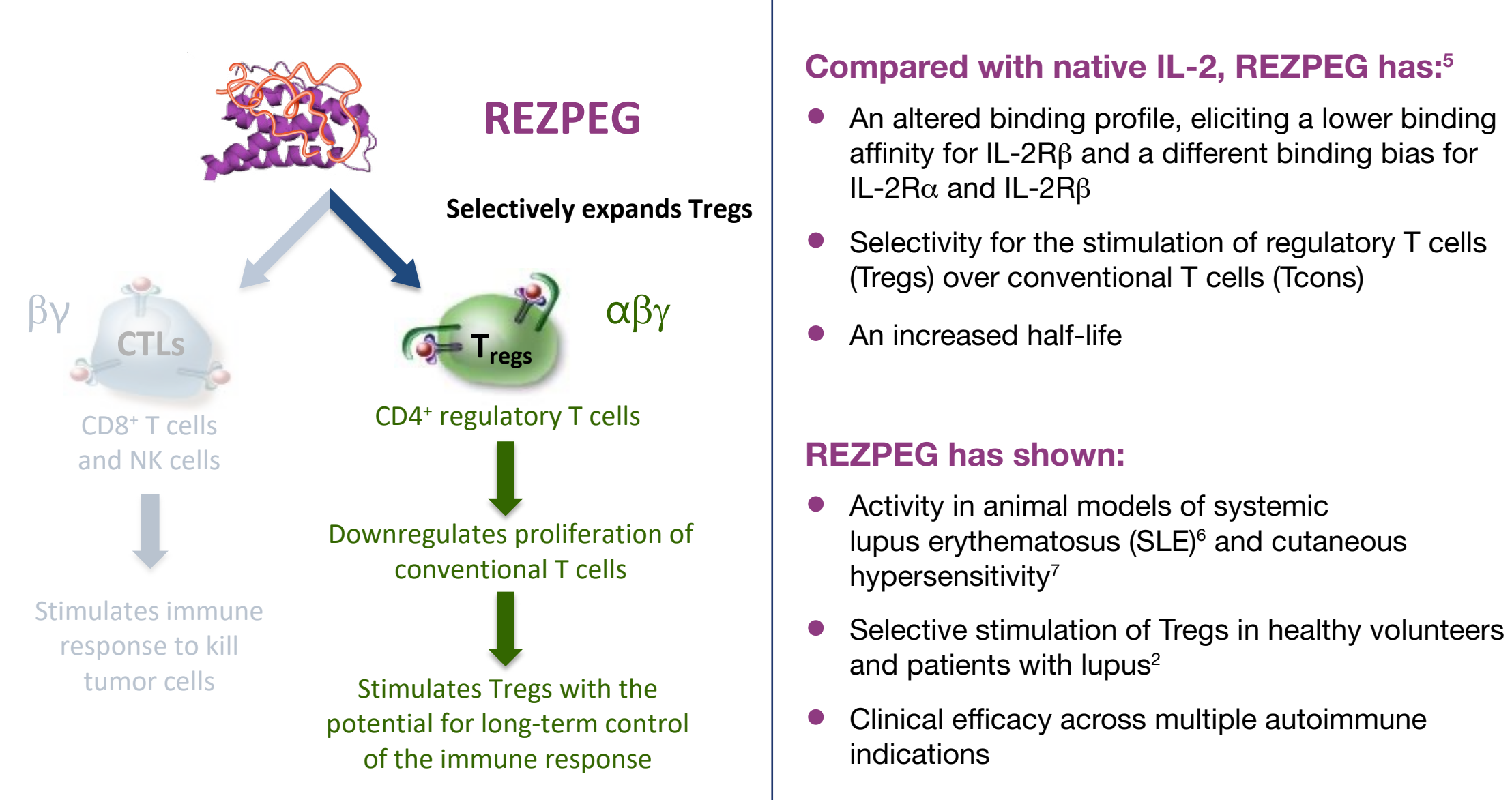
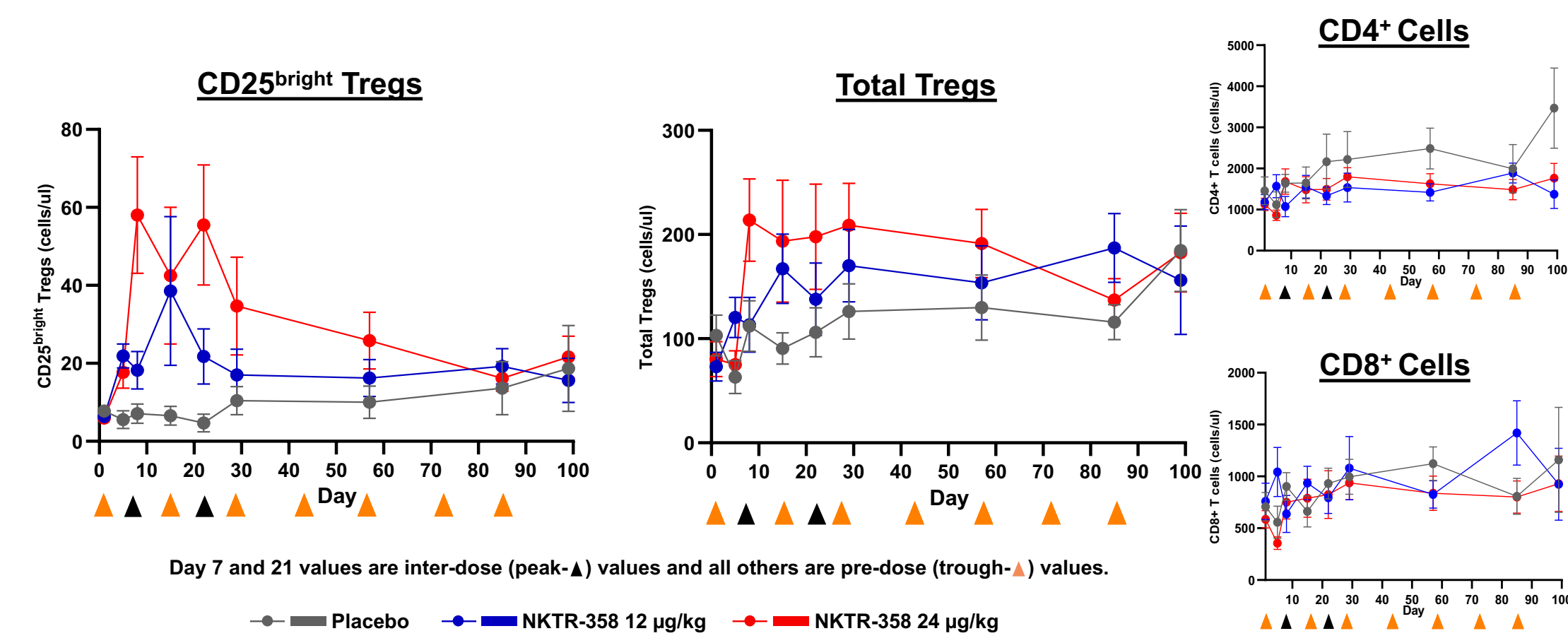


Figure 3: REZPEG Pharmacodynamics from Phase 1b Study in Atopic Dermatitis



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 Repegaldesleukin 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 Repegaldesleukin 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 Repegaldesleukin 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 Repegaldesleukin 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 Repegaldesleukin 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 Repegaldesleukin 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 Repegaldesleukin 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 Repegaldesleukin 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 Repegaldesleukin Following Subcutaneous Dosing of Repegaldesleukin 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)				Placebo (N = 154)			
	Mild	Moderate	Severe	Any	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%)	1 (0.6%)	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	32 (4.9%)	3 (0.5%)	0 (0.0%)	32 (5.4%)	2 (1.3%)	0 (0.0%)	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 yo male with PMI 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, prednisolone, 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.

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ABBREVIATIONS

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

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AUTHOR DISCLOSURE INFORMATION

JS has served as a speaker, advisory board member, consultant and/or received institutional grants from AbbVie, Alamar, Aldena, Amgen, ADOImune, Arcutis, Arena, Asana, Aslan, BioMx, Biosion, Bodewell, Boehringer-Ingelheim, Bristol-Myers Squibb, Cara, Castle Biosciences, Celgene, Connect Biopharma, Corevitas, Dermavant, Dermtech, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Leo Pharma, Nektar, Novartis, Optum, Pfizer, RAPT, Reclux, Regenex, Sanofi-Genzyme, Shaperon, TARGET-RWE, Union, UpToDate.

MJG has served as a speaker, advisory board member, consultant, investigator, and/or received institutional grants from AbbVie, Amgen, AnaptyBio, Arcutis Biotherapeutics, Arista Therapeutics, ASLAN Pharmaceuticals, Bauhaus Health, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Celgene Corporation, Dermavant Sciences, Dermira, Eli Lilly and Company, Galderma Laboratories, LP, Immagine Biopharmaceuticals, Inc. Leo Pharma Inc, Leo Pharma Inc., MedImmune, Meiji Seika Pharma Co., Ltd. Moonlake, Nektar, Nimbus Therapeutics, Novartis Pharmaceuticals Corp., Pfizer Inc., Regenex, Reistone Biopharma, Sanofi Genzyme, Sanofi/Regeneron, Sun Pharmaceutical Industries Ltd., Takeda Pharmaceuticals USA Inc, Tarsus, UCB, Vertex Biosciences.

AR has served as an investigator or participated in advisory boards for AbbVie, Almiral, AltrBio, Amgen, AnaptyBio, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltron, Dermira, Galderma, Infliximab, Janssen, Kiniksa, Kyamb, LEO Pharma, Nektar, Novartis, Pierre Fabre, Pfizer, Trevi Therapeutics, and UCB, and has received honoraria from Boehringer Ingelheim, Chema Rzeszow, Eli Lilly, LEO Pharma, Novartis, Sandoz, and Takeda.

SG has served as a consultant, speaker, or investigator for AbbVie, Celgene, Eli Lilly, Janssen, Leo Pharma, Nektar, Novartis, Pfizer, Sanofi, BMS, DICE and UCB.

SC, ZL, DY, YL, MT, JZ: Employee and stockholder at Nektar Therapeutics.

DR has consulted, spoken for, or conducted trials for the following companies: AbbVie, Abcurio, Almiral, AltrBio, Amgen, Arena, Astria, Boehringer-Ingelheim, Bristol Myers Squibb, Celgene, Concert, CSL Behring, Dermavant, Dermira, Duilio, EMD Serono, Galderma, Incyte, Janssen, Kymera, Kyowa Kirin, Lilly, Merck, Nektar, Novartis, Pfizer, RAPT, Regenex, Reclux, Revivo Biotechnologies, Sanofi, Sun Pharmaceuticals, UCB, Vialbio, Zura Bio.

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 2H2025.⁹

