nature portfolio

Corresponding author(s): Jonathan Zalevsky

Last updated by author(s): Aug 16, 2024

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	BD FACSDiva Flow Cytometry Software was used for acquisition.
Data analysis	Statistical analyses were performed with SAS version 9.4 using PROC MIXED procedure,. Serum protein biomarker analyses were performed using OlinkAnalyze v3.5.1 package, ImerTest v3.1-3 package, emmeans v1.8.7 package, and ggplot2 v3.4.2 package in R version 4.3.1. Pathway enrichment analysis performed using the reactome knowledgebase. For flow cytometry data processing, De Novo FCS Express Flow Clinical Edition was used.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

All source data are provided with this paper.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	Sex used to describe the biological attribute was self-reported. Sex-based analyses were not performed due to insufficient sample sizes to determine sex-based differences in this Phase 1 study.
Population characteristics	Race and ethnicity was self-reported based on available groups.
Recruitment	Key eligibility for PsO patients included males and females of ages 27 through 65 with a diagnosis of chronic plaque PsO based on an investigator-confirmed diagnosis of chronic PsO vulgaris for at least 6 months prior to baseline. Eligible patients were also required to meet the following criteria: Plaque PsO involving ≥ 10% of body surface area in the affected skin other than the face and scalp at screening and baseline; static Physician's Global Assessment (sPGA) score of ≥ 3 at screening at baseline; PASI score of ≥ 12 at screening and baseline; candidate for systemic therapy or phototherapy; and at least 2 similar and evaluable lesions that represent overall disease severity, located in 2 different body regions, preferably not exposed to sun, have at least a lesion size of 12 cm2 at baseline, with 1 lesion with a target lesion Total Sign Score (TSS) of ≥ 5, and the second lesion with a target lesion TSS of ≥ 6. Patients who were excluded included those with a clinically significant flare of PsO during the 12 weeks before baseline, history of drug-induced PsO or para-PsO, unstable forms of PsO, and history of any non-PsO disease that required treatment with oral or parenteral corticosteroids for more than 2 weeks within the 24 weeks prior to signing the ICF. The full inclusion and exclusion criteria are provided in the PsO study protocol, included within the Supplementary Information. Key eligibility for AD patients included males and females of ages 18 through 70 with a diagnosis of moderate-to-severe AD according to the American Academy of Dermatology Consensus Criteria for 12 months or more before the screening visit. Eligible patients must have met the following criteria: an Eczema Area and Severity Index (EASI) score of 16 or higher, a validated Investigator's Global Assessment scale for AD (vIGA-AD) score of 3 or higher, body surface area (BSA) involvement of 10% or greater at baseline, and a history of inadequate response or intolerance to treatment with topical medications. Patients experiencing or having a history of other concomitant skin conditions that would interfere with evaluations of the effect of study drug on AD were excluded. The full inclusion and exclusion criteria are provided in the AD study protocol, included within the Supplementary Information.
Ethics oversight	Study protocols were approved by institutional review boards at each study center.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The sample size for this trial was empirically selected based on the typical numbers for Phase 1 studies to evaluate safety, pharmacokinetics, and PD, and was not powered on the basis of statistical hypothesis testing.
Data exclusions	Data were excluded from one GCP non-compliant study site (PsO, n=1; AD, n=4).
Replication	Initial Phase 1 study results are reported in this manuscript. A Phase 2 trial for REZPEG in AD patients has been initiated (NCT06136741).
Randomization	Assignment to treatment groups was determined by a computer-generated random sequence using an interactive web-response system (IWRS).
Blinding	The investigator was blinded to block sizes.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

Antibodies used for pharmacokinetics:
Mouse anti-human IL-2 (Eli Lilly, custom)
Mouse anti-huamn IL-2 (MabTech, #3445-5-1000)
Rabbit biotin anti-PEG (Abcam, #ab53449)

Antibodies used in the Treg panel (Tregs, CD4+ T cells, CD8+ T cells, CD56bright NK cells, CD56dim NK cells):
BB515 Mouse Anti-Human CD25 (BD Biosciences, #564467)
PE Mouse Anti-Human CD8 (BD Biosciences, #555367)
PerCP-Cy5.5 Mouse Anti-Human CD3 (BD Biosciences, #340949)
PE-Cy7 Mouse Anti-Human CD56 (BD Biosciences, #335791)
AF647 Mouse Anti-Human FoxP3 (BD Biosciences, #560045)
APC-H7 Mouse Anti-Human CD45 (BD Biosciences, #560178)
BV421 Mouse Anti-Human Ki67 (BD Biosciences, #562899)
BV510 Mouse Anti-Human CD4 (BD Biosciences, #562970)

Antibodies used in TBNK panel (CD3-CD56+ NK cells):
PE Mouse Anti-Human CD8 (BD Biosciences, #555367)
PerCP-Cy5.5 Mouse Anti-Human CD3 (BD Biosciences, #340949)
PE-Cy7 Mouse Anti-Human CD56 (BD Biosciences, #335791)
AF647 Mouse Anti-Human FoxP3 (BD Biosciences, #560045)
APC-H7 Mouse Anti-Human CD45 (BD Biosciences, #560178)
BV421 Mouse Anti-Human Ki67 (BD Biosciences, #562899)
BV510 Mouse Anti-Human CD4 (BD Biosciences, #562970)

Validation

BB515 Mouse Anti-Human CD25 (BD Biosciences #564467), Manufacturer's validation: CD25 staining was demonstrated on peripheral blood lymphocytes from human whole blood compared to negative staining using mouse IgG1, K isotype control.

PE Mouse Anti-Human CD8 (BD Biosciences, #555367), Manufacturer's validation: CD8 staining was demonstrated on peripheral blood lymphocytes from human whole blood compared to negative staining using mouse IgG1 K isotype control.

PerCP-Cy5.5 Mouse Anti-Human CD3 (BD Biosciences, #340949), Manufacturer's validation: CD3 staining was demonstrated on lymphocytes from human whole blood.

PE-Cy7 Mouse Anti-Human CD56 (BD Biosciences, #335791), Manufacturer's validation: CD56 staining was demonstrated on lymphocytes from human peripheral blood.

AF647 Mouse Anti-Human FoxP3 (BD Biosciences, #560045), Manufacturer's validation: FOXP3 staining was demonstrated on human PBMC.

APC-H7 Mouse Anti-Human CD45 (BD Biosciences, #560178), Manufacturer's validation: CD45 staining was demonstrated on lymphocytes from human whole blood compared to negative staining using mouse IgG1, K isotype control.

Antibody BV421 Mouse Anti-Human Ki67 (BD Biosciences, #562899), Manufacturer's validation: Ki67 staining was demonstrated on human PBMC.

BV510 Mouse Anti-Human CD4 (BD Biosciences, #562970), Manufacturer's validation: CD4 staining was demonstrated on peripheral blood lymphocytes from human whole blood compared to negative staining using mouse IgG1, K isotype control.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	Female BALB/c mice (Taconic Biosciences, 6–8 weeks old, 18–25 gm) were divided into eight groups based on their body weight. Animals were maintained on sterile (autoclaved/irradiated) rodent chow and sterile water, both ad libitum. In addition to ear thickness measurements, body weight and clinical signs such as lethargy, piloerection, diarrhea, emaciation, and alopecia were noted on daily basis for the entire study period.
Wild animals	*Provide details on animals observed in or captured in the field; report species and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.*
Reporting on sex	Female mice were used for these studies due to practicalities in animal husbandry; in all REZPEG nonclinical studies, there were no significant sex-based differences reported in toxicology, toxicokinetics, pharmacokinetics, or pharmacodynamics.
Field-collected samples	*For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.*
Ethics oversight	All animal studies were conducted in compliance with the OECD guidance document No. 19, Guide for the care and use of animals (NRC, 2013), Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA, 2005), Government of India and the recommendations of association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) and reviewed and approved by the Institutional Animal Ethics Committee (IAEC)

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJEguidelines for publication of clinical research and a completedCONSORT checklist must be included with all submissions.

Clinical trial registration	NCT04081350 and NCT04119557.
Study protocol	Redacted protocols for both studies are included.
Data collection	The PsO study was conducted across 12 study sites in the US during the period between November 26, 2019 and July 21, 2021 . The AD study was conducted across 20 study sites in the US between November 18, 2019 and June 16, 2022.
Outcomes	The primary objective were to evaluate the safety and tolerability of multiple SC doses of REZPEG administered to patients with chronic plaque PsO or moderate-to-severe AD. The secondary objectives were to characterize the pharmacokinetics (PK) of REZPEG, with additional exploratory objectives assessing injection site reactions and the effects of REZPEG on pharmacodynamics (PD) and measures of physician-assessed and patient-reported disease outcomes. Safety and tolerability were assessed by monitoring adverse events (AEs), treatment-emergent AEs (TEAEs), serious AEs, vital signs, physical examination, electrocardiograms, serum chemistry, hematology, and urinalysis evaluations. AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs were defined as AEs occurring on or after receiving the first dose of study drug. Exploratory physician-reported and patient-reported efficacy outcomes are detailed in the methods.

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Whole blood samples were collected in sodium heparin BD Vacutainer tubes (Treg panel) or CytoChex tubes (TBNK panel). Red blood cells were lysed using BD FACS Lysing solution and incubating for 15 minutes at room temperature before freezing at -70C. For cell labeling, samples were labeled with surface staining antibodies for 20 minutes in the dark, at room temperature. For the Treg panel, after stain buffer addition and centrifugation, samples were incubated with permeabilization solution in the dark for 30 minutes at room temperature. After centrifugation, samples were labeled with intracellular antibodies (FoxP3, Ki67) and incubated at room temperature in the dark for 30 minutes. Samples then were washed with Stain Buffer and kept on ice in the dark until ready for acquisition. Immediately prior to acquisition, AccuCheck

	Counting Beads were added to sample tubes. All sample testing done at PRA Health Sciences, according to validated methods.
Instrument	Samples were analyzed with a FACSCanto II flow cytometer. Stable performance of the flow cytometer was ensured by applying setup beads with stable fluorescence intensity through time. Each day a validation run was performed, setup beads were measured. BD Cytometer Setup and Tracking (CS&T) beads were used with BD FACSDiva acquisition software.
Software	BD FACSDiva Flow Cytometry Software was used for acquisition. For data processing, De Novo FCS Express Flow Clinical Edition was used.
Cell population abundance	Determination of absolute cell counts was done with AccuCheck Counting Beads (Thermo Fisher, #PCB100)
Gating strategy	Cytometer settings and compensation were performed as per PRA's internal procedures. Compensation settings were determined with BD FACSComp beads. Compensation settings (percentages) were acquired before each day of acquisition. For tandem dyes (e.g. PE-Cy7 or APC-Cy7), compensation controls were acquired before each day of acquisition. The gating strategy used to identify different populations is reported in Supplementary Figure 10.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.