TREATMENT OF ATOPIC DERMATITIS

REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Application No. 63/516,535, filed on July 31, 2023, the entire contents of which is incorporated herein by reference.

BACKGROUND

[0002] Interleukin-7 (IL-7) is a member of the common γ chain (γc) family of cytokines that also includes IL-2, IL-4, IL-9, IL-15, and IL-21. Like other members, IL-7 signals via a ternary complex formed with its unique α-receptor, IL-7Rα (CD127), and the common γ receptor (γc, CD132). IL-7 regulates T-cell homeostasis by enhancing survival and proliferation of naïve and memory T cells; however, it appears to be dispensable for B cell development in humans. IL-7Rα is expressed on T cells including most mature T cells, on dendritic cells (DCs) and activated monocytes.

[0003] IL-7 / IL-7R interaction stimulates the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) proteins with subsequent activation of the phosphoinositol 3-kinase (PI3K)/Akt, or Src pathways to facilitate target gene transcription. IL-7 Rα is also used by thymic stromal-derived lymphopoietin (TSLP) as part of a complex that contains a second receptor chain, TSLPR.

[0004] The TSLPR complex contains CD127 and TSLPR (CRLF2), and is expressed on several types of immune cells, including B cells, T cells, monocytes and DCs. TSLP has been shown to be a potent activator of antigen presenting cells such as DCs to induce TH2-mediated immune responses. For example, TSLP-stimulated DCs increase OX40L expression and production of TH2 chemokines, such as CCL17 and CCL21, leading to the priming of TH2 cell development.

[0005] IL-7 plays a critical role in the development of a normal immune system, as it is essential for the thymic development, peripheral maintenance, and survival of lymphocytes. Thymic T cell precursors require IL-7 for proliferation, differentiation, and survival. In the periphery, IL-7 regulates T cell hemostasis by enhancing the survival and proliferation of naive and memory T cells.

[0006] IL-7 is a tissue-derived cytokine and is primarily produced from stromal and epithelial cells in various tissues. For instance, in the small and large intestines, IL-7 is produced by the intestinal goblet epithelial cells and has been described as being essential for

the persistence of chronic colitis in animal models. IL-7 has also been shown to interfere with the immunosuppressive capabilities of regulatory T cells (T_{reg}s). Thus, agents that can modulate the activity of IL-7 *in vivo* and thereby decrease the survival/function of pathogenic T cells and/or increase the induction of regulatory T cells are highly desirable for the treatment of inflammatory diseases, such as inflammatory bowel disease.

[0007] Atopic dermatitis (synonymous with Atopic eczema) is the most common chronic inflammatory skin disease. Approximately 80% of cases start in infancy or childhood, with the remaining developing during adulthood (Silverberg *et al* 2021, Nutten 2015, Barbarot *et al* 2018). Historically, the main therapeutic approaches have included avoidance of triggers, paired with the use of agents that are intended to exert local control of skin lesions and/or itch, and broad-spectrum immunosuppressive agents for more severe or high surface area disease. Many of these commonly used treatments have limited efficacy and/or harbor substantial long-term toxicity concerns. Lastly, most of these treatments are not designed to target specific pathways underlying disease biology.

[0008] Beyond the conventional therapeutics alluded to above, the approval of systemic, targeted, immunomodulating biologics as part of an alternative therapeutic strategy has revolutionized treatment of AD. The anti-IL-4Rα antibody dupilumab (United States [US] approval in 2016/European Union [EU] approval in 2017) was the first systemic biologic to become available for the treatment of AD patients. More recently the approvals of the small-molecule Janus kinase inhibitor baricitinib (EU 2020), upadicitinib and abrocitinib (US 2021) and the anti-IL-13 antibody tralokinumab (US 2021) have been catalysts to this evolving therapeutic approach. Nonetheless, the current therapeutic options remain limited and disease management still generally follows a narrow "one-size-fits-all" approach, without consistent regard to the clinical, and likely biologic heterogeneity characteristic of the disease (Bieber *et al* 2021).

[0009] Recent literature (Patrizi *et al* 2021) highlights the multidimensional and inter-related challenges of AD treatment, with particular emphasis on the importance of establishing treat to target approaches, and the difficulty with patient adherence. The clinical heterogeneity of the disease paired with the limited number of approved targeted, systemic therapeutics also complicates the creation and implementation of treatment algorithms. There exists several validated instruments from which endpoints used in clinical trials are derived, all of which assess disease activity (*e.g.*, validated investigator global assessment [vIGA], eczema area and severity index [EASI], scoring atopic dermatitis [SCORAD]). Although differing slightly in their stringency, these instruments are essentially based on the same

parameters and stratify patients by disease severity (Leshem *et al.*, 2015, Chopra *et al.*, 2017, Bożek and Reich, 2017).

[0010] However, the use of these instruments "at the bedside" remains limited. Recently, validated instruments addressing long-term disease control have been introduced (recap of atopic eczema [RECAP] and atopic dermatitis control tool [ADCT]) and an important challenge will be in correlating short and long-term clinical trial results based on improvements in these validated instruments, with more practical and pragmatic bedside assessments that can be reliably performed by a range of care providers.

[0011] Thus, there is a need to develop effective treatment for atopic dermatitis.

SUMMARY

[0012] Provided herein is a method of treating atopic dermatitis (AD) in a subject in need thereof, the method comprising administering an effective amount of a composition comprising an antibody for IL-7Rα, wherein the antibody comprises: (a) a heavy chain variable region (HCVR) that comprises a VH CDR1 comprising the sequence of SEQ ID NO: 1 (DHAMH, such as any one of SEQ ID NOs: 7-22), a VH CDR2 sequence of SEQ ID NO: 2 (GISWNSRGIGYADSVKG), and a VH CDR3 sequence of SEQ ID NO: 3 (DEYSRGYYVLDV); and (b) a light chain variable region (LCVR) that comprises a VL CDR1 sequence of SEQ ID NO: 4 (RASQGISSALA), a VL CDR2 sequence of SEQ ID NO: 5 (DASSLES), and a VL CDR3 sequence of SEQ ID NO: 6 (QQFNSYPLWIT), and wherein the composition comprising the antibody is administered to the subject to maintain serum concentration of the antibody at $\geq$5 μg/mL throughout dosing, such that atopic dermatitis is treated in the subject.

[0013] Also provided herein is a composition for use in treating atopic dermatitis (AD) in a subject in need thereof, the composition comprising an antibody for IL-7Rα, wherein the antibody comprises: (a) a heavy chain variable region (HCVR) that comprises a VH CDR1 comprising the sequence of SEQ ID NO: 1 (DHAMH, such as any one of SEQ ID NOs: 7-22), a VH CDR2 sequence of SEQ ID NO: 2 (GISWNSRGIGYADSVKG), and a VH CDR3 sequence of SEQ ID NO: 3 (DEYSRGYYVLDV); and (b) a light chain variable region (LCVR) that comprises a VL CDR1 sequence of SEQ ID NO: 4 (RASQGISSALA), a VL CDR2 sequence of SEQ ID NO: 5 (DASSLES), and a VL CDR3 sequence of SEQ ID NO: 6 (QQFNSYPLWIT), and wherein the composition comprising the antibody is administered to the subject to maintain serum concentration of the antibody at $\geq$5 μg/mL throughout dosing, such that atopic dermatitis is treated in the subject.

[0014] Also provided is a method of treating atopic dermatitis (AD) in a subject (*e.g.*, a human) in need thereof, the method comprising administering an effective amount of a composition comprising an antibody for IL-7Rα, wherein the antibody comprises: (a) a heavy chain variable region (HCVR) that comprises a VH CDR1 comprising the sequence of SEQ ID NO: 1 (DHAMH, such as any one of SEQ ID NOs: 7-22), a VH CDR2 sequence of SEQ ID NO: 2 (GISWNSRGIGYADSVKG), and a VH CDR3 sequence of SEQ ID NO: 3 (DEYSRGYYVLDV); and (b) a light chain variable region (LCVR) that comprises a VL CDR1 sequence of SEQ ID NO: 4 (RASQGISSALA), a VL CDR2 sequence of SEQ ID NO: 5 (DASSLES), and a VL CDR3 sequence of SEQ ID NO: 6 (QQFNSYPLWIT), wherein the antibody comprises an effectorless IgG1 Fc, wherein 200 mg of the antibody is administered subcutaneously every 2 weeks, such that atopic dermatitis is treated in the subject.

[0015] Additionally provided is a composition for use in treating atopic dermatitis (AD) in a subject (*e.g.*, a human) in need thereof, the composition comprising an antibody for IL-7Rα, wherein the antibody comprises: (a) a heavy chain variable region (HCVR) that comprises a VH CDR1 comprising the sequence of SEQ ID NO: 1 (DHAMH, such as any one of SEQ ID NOs: 7-22), a VH CDR2 sequence of SEQ ID NO: 2 (GISWNSRGIGYADSVKG), and a VH CDR3 sequence of SEQ ID NO: 3 (DEYSRGYYVLDV); and (b) a light chain variable region (LCVR) that comprises a VL CDR1 sequence of SEQ ID NO: 4 (RASQGISSALA), a VL CDR2 sequence of SEQ ID NO: 5 (DASSLES), and a VL CDR3 sequence of SEQ ID NO: 6 (QQFNSYPLWIT), wherein the antibody comprises an effectorless IgG1 Fc, wherein the composition is administered to the subject subcutaneously at a dose of 200 mg every 2 weeks, such that atopic dermatitis is treated in the subject

[0016] Further provided herein is a pharmaceutical composition comprising an antibody having two heavy chains and two light chains, wherein each said heavy chain has the amino acid sequence of SEQ ID NO: 23, and each said light chain has the amino acid sequence of SEQ ID NO: 24; and wherein the antibody is formulated in a pharmaceutically acceptable solution comprising about 50-200 mg/mL (*e.g.*, about 100 mg/mL) of the antibody in about 15-25 mM (*e.g.*, about 20 mM) histidine, 200-300 mM (*e.g.*, about 260 mM) sucrose, and about 0.03-0.07% (w/v) (*e.g.*, about 0.05% (w/v)) polysorbate 80 at pH 6.0.

[0017] Additionally provided herein is a container (*e.g.* a polycarbonate bottle) containing about 2 mL of extractable volume of a pharmaceutical composition described herein.

[0018] It should be understood that any embodiment described herein, including those described only in the examples, can be combined with any one or more other embodiments, unless such combination is expressly disclaimed or is improper. Thus, the term "embodiment", as used herein, is not to be considered as excluding features recited in other embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] FIG. 1 is a schema for the Phase 2 clinical trial described in Example 1. The abbreviations used include: EOS = end of study; LPI = last patient in; RP2D = recommended Phase 2 dose; Q2W = every 2 weeks; SRC = Safety Review Committee. In Cohorts 1 and 2, n = 6; 4 treated with COMPOUND A and 2 placebo. An additional cohort may be opened (Cohort 3) where COMPOUND A is administered SC Q2W for a total of 7 doses, at an intermediate or lower weight-based dose with respect to Cohorts 1 and 2, or at a fixed dose with predicted exposures ≤ those at 3 mg/kg.

[0020] FIGs. 2A-2C show effects of prophylactic treatment with COMPOUND A (Comp. A) and a comparator IL-7Rα antibody (A3312F) in the Hu-NSG mouse model of GvHD on body weight loss (FIG. 2A), plasma cytokine levels (ELISA) (FIG. 2B) and percent human T cells (CD45+ CD3+) in blood as measured by flow cytometry (FIG. 2C). Measurements were determined 21 days post PBMC transfer. Abbreviations: CCL1: antimicrobial protein with bactericidal activity; CD: cluster differentiation; GvHD: graft-versus host disease; Hu-NSG: humanized nod/SCID/IL2rγnull; IFN: interferon; IL-7Rα: interleukin-7 receptor alpha; IP: intraperitoneal; PBMC: peripheral blood mononuclear cells; TNF: tumor necrosis factor.

[0021] FIGs. 3A-3B show target engagement and inhibition of pSTAT5 levels on human T cells in blood (FIG. 3A) and spleens (FIG. 3B) of Hu-NSG mice after treatment with (Comp. A) (18B1), a comparator IL-7Rα antibody (A3312F) or vehicle (PBS). Antibodies were administered in vivo at concentrations of 0.2, 1, and 5 mg/kg. IL-7–induced pSTAT5 was evaluated in an ex vivo assay and included a non-targeting IL-7 negative control sample (CTL Unstim). Abbreviations: CTL: control; Hu-NSG: Hu-NSG: humanized nod/SCID/IL2rγnull; IL-7Rα: interleukin-7 receptor alpha; MFI: mean fluorescence intensity; PBS: phosphate buffered saline; pSTAT5: phosphorylated signal transducer and activator of transcription 5.

[0022] FIGs. 4A and 4B show data after administration of single ascending dose (SAD; 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 2 mg/kg and 4 mg/kg) and multiple doses (MAD; 1 mg/kg) in phase 1 clinical data in human (see Example 8). FIG. 4A shows percentage of IL-7

receptor occupancy (RO) in CD3+ T cells, and FIG. 4B shows percentage of inhibition of IL-7 signaling via phosphorylated STAT5 (pSTAT5) in T cells.

[0023] FIG. 5A shows data (Mean ± SD) on serum concentration profile in patients with topic dermatitis (AD) after subcutaneous administration of COMPOUND A at doses of 2 or 3 mg/kg every 2 weeks. SD: standard deviation. 5 μg/mL represents the concentration with predicted maximum receptor occupancy in skin.

[0024] FIG. 5B shows preliminary data (mean ± SD) on IL-7Rα receptor occupancy (RO) on circulating CD3+ T cells in patients with atopic dermatitis (AD) after subcutaneous administration of COMPOUND A at doses of 2 or 3 mg/kg every 2 weeks. RO: receptor occupancy; SD: standard deviation. Dashed vertical lines represent the dosing days.

DETAILED DESCRIPTION

[0025] Provided is a method of treating atopic dermatitis (AD) in a subject (*e.g.*, human) in need thereof, the method comprising administering an effective amount of a composition comprising an antibody for IL-7Rα, wherein the antibody comprises: (a) a heavy chain variable region (HCVR) that comprises a VH CDR1 comprising the sequence of SEQ ID NO: 1 (DHAMH, such as any one of SEQ ID NOs: 7-22), a VH CDR2 sequence of SEQ ID NO: 2 (GISWNSRGIGYADSVKG), and a VH CDR3 sequence of SEQ ID NO: 3 (DEYSRGYYVLDV); and (b) a light chain variable region (LCVR) that comprises a VL CDR1 sequence of SEQ ID NO: 4 (RASQGISSALA), a VL CDR2 sequence of SEQ ID NO: 5 (DASSLES), and a VL CDR3 sequence of SEQ ID NO: 6 (QQFNSYPLWIT), and wherein the composition comprising the antibody is administered to the subject to maintain serum concentration of the antibody at ≥5 μg/mL throughout dosing, such that atopic dermatitis is treated in the subject (*e.g.*, human).

[0026] Also provided herein is a composition for use in treating atopic dermatitis (AD) in a subject (*e.g.*, human) in need thereof, the composition comprising an antibody for IL-7Rα, wherein the antibody comprises: (a) a heavy chain variable region (HCVR) that comprises a VH CDR1 comprising the sequence of SEQ ID NO: 1 (DHAMH, such as any one of SEQ ID NOs: 7-22), a VH CDR2 sequence of SEQ ID NO: 2 (GISWNSRGIGYADSVKG), and a VH CDR3 sequence of SEQ ID NO: 3 (DEYSRGYYVLDV); and (b) a light chain variable region (LCVR) that comprises a VL CDR1 sequence of SEQ ID NO: 4 (RASQGISSALA), a VL CDR2 sequence of SEQ ID NO: 5 (DASSLES), and a VL CDR3 sequence of SEQ ID NO: 6 (QQFNSYPLWIT), and wherein the composition comprising the antibody is administered to the subject to maintain serum concentration of the antibody at ≥5 μg/mL

throughout dosing, such that atopic dermatitis is treated in the subject (*e.g.*, human).

[0027] In some embodiments, the antibody has a heavy chain sequence of SEQ ID NO: 23 and a light chain sequence of SEQ ID NO: 24.

[0028] In some embodiments, the subject has moderate to severe AD (*e.g.*, chronic AD having a disease duration of ≥3 years, as diagnosed by the Eichenfield revised criteria of Hanifin and Rajka). See Eichenfield *et al.*, Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol.* 70(2):338-351, Epub Nov. 27, 2013 (incorporated herein by reference).

[0029] The diagnosis of atopic dermatitis is made clinically and is based on historical features, morphology and distribution of skin lesions, and associated clinical signs. One of the earliest and most recognized sets of diagnostic criteria is the 1980 Hanifin and Rajka criteria, which requires that three of four major criteria and three of twenty-three minor criteria be met. While comprehensive and often utilized in clinical trials, such a large number of criteria are unwieldy for use in clinical practice. The current criteria for AD diagnosis is widely based on the Eichenfield revised criteria of Hanifin and Rajka as described in Eichenfield *et al.* (*J Am Acad Dermatol.* 70(2):338-351, Epub Nov. 27, 2013). Specifically, the recommended criteria for the diagnosis of atopic dermatitis are shown in Table II of Eichenfield *et al.*, and the strength of the recommendation is displayed in Table VI of Eichenfield *et al.* (both incorporated herein by reference).

[0030] According to Table II of Eichenfield, patients with presumed atopic dermatitis should have their diagnosis based on the criteria summarized in Box 1 (copied below). On occasion, skin biopsy or other tests (such as serum IgE, potassium hydroxide (KOH) preparation, patch testing, and/or genetic testing) may be helpful to rule out other or associated skin conditions.

Box 1

- **ESSENTIAL FEATURES**; must be present:
  - Pruritus
  - Eczema (acute, subacute, chronic):
    - Typical morphology and age-specific patterns*
    - Chronic or relapsing history

  Patterns include:
  1) facial, neck, and extensor involvement in infants and children;
  2) current or prior flexural lesions in any age group;
  3) sparing of groin and axillary regions.

- **IMPORTANT FEATURES**; seen in most cases, adding support to the diagnosis:
  - Early age of onset
  - Atopy
    - Personal and/or family history
    - IgE reactivity
  - Xerosis

- **ASSOCIATED FEATURES** ; these clinical associations help to suggest the diagnosis of AD but are too non-specific to be used for defining or detecting AD for research and epidemiologic studies:
  - Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
  - Keratosis pilaris / pityriasis alba / hyperlinear palms / ichthyosis
  - Ocular / periorbital changes
  - Other regional findings (e.g., perioral changes / periauricular lesions)
  - Perifollicular accentuation / lichenification / prurigo lesions

- **EXCLUSIONARY CONDITIONS;** it should be noted that a diagnosis of AD depends on excluding conditions such as:
    - scabies
    - seborrheic dermatitis
    - contact dermatitis (irritant or allergic)
    - ichthyoses
    - cutaneous T-cell lymphoma
    - psoriasis
    - photosensitivity dermatoses
    - immune deficiency diseases
    - erythroderma of other causes

[0031] In some embodiments, the antibody is administered to the subject subcutaneously (*s.c.*).

[0032] In some embodiments, the antibody is administered once a week (Q1W), once every two weeks (Q2W), once every three weeks (Q3W), once every four weeks (Q4W), once every eight weeks (Q8W), once every twelve weeks (Q12W), or any intermittent PRN (*pro re nata*).

[0033] In some embodiments, each administration, starting from the second dose, is separated from the immediate prior administration by the same number of days, preferably

around the same time of the day of the administration.

[0034] In some embodiments, the antibody is administered once every two weeks, preferably, each administration starting from the second dose is separated by 14 days from the immediate prior administration, preferably around the same time of the day of the administration.

[0035] In some embodiments, the antibody is administered for 5-10 (*e.g.*, 5, 6, 7, 8, 9, or 10) consecutive doses. In some embodiments, the antibody is administered for 5 consecutive doses. In some embodiments, the antibody is administered for 6 consecutive doses. In some embodiments, the antibody is administered for 7 consecutive doses. In some embodiments, the antibody is administered for 8 consecutive doses. In some embodiments, the antibody is administered for 9 consecutive doses. In some embodiments, the antibody is administered for 10 consecutive doses.

[0036] In some embodiments, the antibody is administered for a period of up to 10 weeks, 13 weeks, 26 weeks, 52 weeks, 2 years, 3 years, 5 years, 10 years, or lifetime / permanently. In some embodiments, the antibody is administered as needed when there is AD symptom.

[0037] In some embodiments, efficacy of treatment is measured by mean difference in percentage reduction from baseline level (just prior to commencement of treatment) of Eczema Area and Severity Index (EASI) score, at 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 14 weeks, 16 weeks, and/or 24 weeks after the first dose at Week 0, for treatment vs. placebo / untreated control. As used herein, "just prior to" refers to within one day, 12 hrs, 6 hours, or 1 hour prior to the commencement of treatment, *e.g.*, first dose at Week 0.

[0038] In some embodiments, ≥50% , ≥75%, or ≥90% mean difference in percentage reduction from baseline level of EASI score is achieved at 4 weeks (Week 4), 8 weeks (Week 8), 12 weeks (Week 12), 16 weeks (Week 16), and/or 24 weeks (Week 24) after the first dose at Week 0, in the treated subject compared to placebo / untreated control.

[0039] In some embodiments, efficacy of treatment is measured by mean percentage change from baseline level (just prior to commencement of treatment) in Scoring Atopic Dermatitis (SCORAD) score, at 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 14 weeks, 16 weeks, and/or 24 weeks after the first dose at Week 0, for treatment vs. placebo / untreated control. As used herein, "just prior to" refers to within one day, 12 hrs, 6 hours, or 1 hour prior to the commencement of treatment, *e.g.*, first dose at Week 0.

[0040] In some embodiments, ≥50% , ≥75%, or ≥90% mean percentage change from

baseline level in SCORAD score is achieved at 4 weeks (Week 4), 8 weeks (Week 8), 12 weeks (Week 12), 16 weeks (Week 16), and/or 24 weeks (Week 24) after the first dose at Week 0 in the treated subject compared to placebo / untreated control.

[0041] In some embodiments, ≥50% , ≥75%, or ≥90% of all treated subject achieve EASI 50, EASI 75 and/or EASI 90 at Week 4, 8, 12, 14, 16, and/or 24.

[0042] In some embodiments, ≥50% , ≥75%, or ≥90% of all treated subject achieve Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score of 0 or 1 with at least 2 grades of reduction from Baseline at Week 4, 8, 12, 14, 16, and/or 24.

[0043] In some embodiments, the antibody is formulated as 100 mg/mL solution in 20 mM histidine, 260 mM sucrose, and 0.05% (w/v) polysorbate 80 at pH 6.0, with an optional 0.05 mM pentetic acid.

[0044] In some embodiments, the antibody is administered to the subject based on a weight-based dosing regimen.

[0045] In some embodiments, the antibody is administered to the subject at about 0.1 mg/kg – about 10 mg/kg per dose, about 0.2 mg/kg – about 8 mg/kg per dose, about 0.5 mg/kg – about 5 mg/kg per dose, about 1 mg/kg – about 4 mg/kg per dose, or about 2 mg/kg – about 3 mg/kg per dose.

[0046] In some embodiments, the antibody is administered to the subject at about 0.2 mg/kg per dose, about 0.5 mg/kg per dose, about 1 mg/kg per dose, about 2 mg/kg per dose, about 3 mg/kg per dose, about 4 mg/kg per dose, about 5 mg/kg per dose, about 6 mg/kg per dose, about 7 mg/kg per dose, about 8 mg/kg per dose, about 9 mg/kg per dose, or about 10 mg/kg per dose.

[0047] In some embodiments, the antibody is administered to the subject based on a body surface area (BSA)-based dosing regimen. For example, the dose for an adult male patient of any weight (in kg) and height (in cm) can be calculated / converted, based on a BSA Base Dose used for a standard male weight of 91 kg and height of 175 cm, to reach a dose of about 10 mg – about 800 mg per dose, about 20 mg – about 500 mg per dose, about 50 mg – about 300 mg per dose, about 100 mg – about 250 mg per dose.

[0048] In some embodiments, the dose for an adult male patient of any weight (in kg) and height (in cm) can be calculated / converted, based on a BSA Base Dose used for a standard male weight of 91 kg and height of 175 cm, to reach a dose of about 25 mg per dose, about 50 mg per dose, about 100 mg per dose, about 150 mg per dose, about 200 mg per dose, about 250 mg per dose, about 300 mg per dose, or about 350 mg per dose.

[0049] In some embodiments, the dose for an adult female patient of any weight (in kg)

and height (in cm) can be calculated / converted, based on a BSA Base Dose used for a standard female weight of 77.5 kg and height of 160 cm, to reach a dose of about 10 mg – about 800 mg per dose, about 20 mg – about 500 mg per dose, about 50 mg – about 300 mg per dose, or about 100 mg – about 250 mg per dose.

[0050] In some embodiments, the dose for an adult female patient of any weight (in kg) and height (in cm) can be calculated / converted, based on a BSA Base Dose used for a standard female weight of 77.5 kg and height of 160 cm, to reach a dose of about 25 mg per dose, about 50 mg per dose, about 100 mg per dose, about 150 mg per dose, about 200 mg per dose, about 250 mg per dose, about 300 mg per dose, or about 350 mg per dose.

[0051] In some embodiments, the BSA dosing is based on Dubois Formula for BSA Dosing, in which Dose = BSA Based Dose × 0.007184 × Height (cm)$^{0.725}$ × Weight (kg)$^{0.425}$.

[0052] In some embodiments, the BSA dosing is based on Monteller Formula for BSA Dosing, in which Dose = BSA Based Dose × square root [(Height (cm) × Weight (kg)) / 3600].

[0053] In some embodiments, the antibody is administered to the subject based on a fixed / flat dosing regimen.

[0054] In some embodiments, the antibody is administered to the subject at about 10 mg – about 800 mg per dose, about 20 mg – about 500 mg per dose, about 50 mg – about 300 mg per dose, or about 100 mg – about 250 mg per dose.

[0055] In some embodiments, the antibody is administered to the subject at about 25 mg per dose, about 50 mg per dose, about 100 mg per dose, about 150 mg per dose, about 200 mg per dose, about 250 mg per dose, about 300 mg per dose, or about 350 mg per dose.

[0056] In some embodiments, the antibody is administered to the subject based on a weight-banded dosing regimen, in which patients within certain ranges of weights (weight-bands) are dosed a fixed amount for that specific weight band. In some embodiments, patients with a body weight of about 10-25 kg are grouped in the same body weight band and given the same fixed dose. In some embodiments, patients with a body weight of about 25-50 kg are grouped in the same body weight band and given the same fixed dose. In some embodiments, patients with a body weight of about 50-75 kg are grouped in the same body weight band and given the same fixed dose. In some embodiments, patients with a body weight of about 75-100 kg are grouped in the same body weight band and given the same fixed dose. In some embodiments, the fixed dose for each weight band is based on the average weight in the weight band (*e.g.*, all patients in the weight band of 50-75 kg are dosed a fixed dose based on the dose for the middle weight – *i.e.*, 62.5 kg for this weight band). In

some embodiments, the fixed dose for the weight band 50-75 kg is about 150 mg, about 200 mg, about 250 mg, about 300 mg, or about 350 mg. In some embodiments, the fixed dose for a weight band is proportional to the fixed dose for the 50-75 kg weight band (*e.g.*, the fixed dose for the weight band 10-25 kg is based on the middle weight of 17.5 kg, which is 17.5 / 62.5 = 28% of the fixed dose for the 50-75 kg weight band).

[0057] In some embodiments, the antibody is administered to the subject based on a dosing regimen comprising a loading dose or an accelerated initial dosing schedule, followed by a maintenance dose, wherein the maintenance dose is administered according to any of the preceding weight-based dosing regimens, body surface area (BSA)-based dosing regimens, or fixed dose dosing regimens. In some embodiments, the loading dose comprises twice the dose of the maintenance dose (*e.g.*, if the maintenance doses are administered once every two weeks (Q2W) as 200 mg fixed dose, the loading dose of 400 mg fixed dose may be administered once every two weeks (Q2W)). In some embodiments, an initial accelerated dosing schedule is used (*e.g.*, if the 200 mg maintenance doses are administered once every two weeks (Q2W), the initial accelerated dosing schedule includes administering 200 mg once a week (Q1W) for two weeks).

[0058] In some embodiments, the maintenance dose comprises infinite number of doses, which may be useful, for example, for management of a chronic condition such as atopic dermatitis. In some embodiments, the maintenance dose is administered intermittently (prn).

[0059] In some embodiments, the subject has impaired renal function (*e.g.*, mildly impaired renal function (such as a glomerular filtration rate <60 mL/min and/or the presence of albuminuria >30 mg/d), moderately impaired renal function (such as a glomerular filtration rate <45 mL/min), or severely impaired renal function (such as a glomerular filtration rate <30 mL/min). In other embodiments, the subject is normal, *e.g.*, normal with respect to renal function.

[0060] In some embodiments, the subject is an adult (*e.g.*, 18 years and older).

[0061] In some embodiments, the subject is not an adult, or is a pediatric patient or an adolescent patient (*e.g.*, a patient of under 18-year old, under 16-year old, under 14-year old, under 12-year old, under 10-year old, under 5-year old, under 3-year old, under 2-year old, under 1-year old, under 6-month old, or under 3-month old).

[0062] In some embodiments, the subject is a Caucasian. In some embodiments, the subject is Asian. In some embodiments, the subject is African. In some embodiments, the subject is native American. In some embodiments, the subject is of mixed race or ethnic

group. In some embodiments, the subject is biologic male. In some embodiments, the subject is biologic female.

[0063] In some embodiments, the subject is further being treated by or has been treated by a second therapeutic agent effective to treat atopic dermatitis. In some embodiments, the second therapeutic agent comprises a topical immunomodulator (*e.g.*, a calcineurin, PDE-4, and/or JAK inhibitor); a systemic steroid (corticosteroid); a topical corticosteroid; tacrolimus; pimecrolimus; phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]); allergen immunotherapy; a leukotriene inhibitor; or an oral chemical synthetic immunomodulator (*e.g.*, methotrexate, mycophenolate mofetil, interferon (IFN)-γ, azathioprine, cyclosporine, a systemic biologic (dupliumab, ustekinumab, tralokinumab, or nemolizumab), a systemic targeted synthetic JAK inhibitor (tofacitinib, ruxolitinib, upadacitinib, abrocitinib, and baricitinib), a topical synthetic JAK inhibitor (delgocitinib), or a PDE-4 inhibitor (crisaborole)).

[0064] In some embodiments, the antibody is administered to the subject at about 25, 50, 100, 150, 200, or 250 mg per dose; optionally, the doses of the antibody are administered to the subject once every two weeks, for a total of 10, 11, 12, 13, 14, or 15 doses.

[0065] In some embodiments, the method reduces the measurement of an AD-associated biomarker after treatment (compared to before treatment).

[0066] In some embodiments, the method further comprises detecting in the individual an AD-associated biomarker, either before or after treatment, or both.

[0067] In some embodiments, prior to administering the subject anti-IL-7Rα antibody, antigen binding fragment thereof, or a pharmaceutically acceptable salt thereof, to the individual, the method further comprises selecting the individual based on a level of an AD-associated biomarker.

[0068] In some embodiments, the administration of the subject anti-IL-7Rα antibody, antigen binding fragment thereof, or a pharmaceutically acceptable salt thereof, results in a change in a level of an AD- associated biomarker in the individual.

[0069] In some embodiments, the subject in need thereof satisfies one or more criteria in the inclusion criteria specified in Example 1. In some embodiments, the subject in need thereof satisfies all criteria in the inclusion criteria specified in Example 1.

[0070] In some embodiments, the subject in need thereof does not satisfy (*i.e.*, is not excluded by) any one criteria in the exclusion criteria specified in Example 1.

[0071] In some embodiments, the method comprises administering the antibody (*e.g.*, one with the heavy chain sequence of SEQ ID NO: 23 and the light chain sequence of SEQ ID

NO: 24) to the subject subcutaneously one dose every two weeks (Q2W), at about 200 mg per dose, for (at least) about 7 doses, (at least) about 8 doses, (at least) about 9 doses, (at least) about 10 doses, (at least) about 11 doses, (at least) about 12 doses, (at least) about 13 doses, or (at least) about 14 doses.

[0072] Also provided is a method of treating atopic dermatitis (AD) in a subject (*e.g.*, a human) in need thereof, the method comprising administering an effective amount of a composition comprising an antibody for IL-7Rα, wherein the antibody comprises: (a) a heavy chain variable region (HCVR) that comprises a VH CDR1 comprising the sequence of SEQ ID NO: 1 (DHAMH, such as any one of SEQ ID NOs: 7-22), a VH CDR2 sequence of SEQ ID NO: 2 (GISWNSRGIGYADSVKG), and a VH CDR3 sequence of SEQ ID NO: 3 (DEYSRGYYVLDV); and (b) a light chain variable region (LCVR) that comprises a VL CDR1 sequence of SEQ ID NO: 4 (RASQGISSALA), a VL CDR2 sequence of SEQ ID NO: 5 (DASSLES), and a VL CDR3 sequence of SEQ ID NO: 6 (QQFNSYPLWIT); wherein 200 mg of the antibody is administered subcutaneously every 2 weeks; wherein the antibody comprises an effectorless IgG1 Fc.

[0073] A related aspect provides a method of treating atopic dermatitis (AD) in a subject (*e.g.*, a human) in need thereof, the method comprising administering an effective amount of a composition comprising an antibody for IL-7Rα, wherein the antibody comprises: (a) a heavy chain variable region (HCVR) that comprises a VH CDR1 comprising the sequence of SEQ ID NO: 1 (DHAMH, such as any one of SEQ ID NOs: 7-22), a VH CDR2 sequence of SEQ ID NO: 2 (GISWNSRGIGYADSVKG), and a VH CDR3 sequence of SEQ ID NO: 3 (DEYSRGYYVLDV); and (b) a light chain variable region (LCVR) that comprises a VL CDR1 sequence of SEQ ID NO: 4 (RASQGISSALA), a VL CDR2 sequence of SEQ ID NO: 5 (DASSLES), and a VL CDR3 sequence of SEQ ID NO: 6 (QQFNSYPLWIT); wherein 200 mg of the antibody is administered subcutaneously every 2 weeks; wherein the antibody comprises an effectorless IgG1 Fc; and, wherein the subject: (1) has moderate to severe AD (*e.g.*, chronic AD having a disease duration of ≥3 years, as diagnosed by the Eichenfield revised criteria of Hanifin and Rajka); (2) has moderate to severe disease activity characterized by: a) BSA affected ≥10%, b) EASI Score ≥12, and/or c) Investigators Global Score (IGA) ≥3; and/or, (3) has inadequate response to treatment by: i) a (medium-potency) topical steroid or a topical immunomodulator (such as a calcineurin inhibitor, a PDE-4 inhibitor, or a JAK inhibitor), optinally, said inadequate response is observed after at least 4 weeks of treatment; ii) a systemic steroid or phototherapy; and/or, iii) an oral chemical synthetic immunomodulator (such as methotrexate (MTX), mycophenolate mofetil,

azathioprine, cyclosporine, a systemic biologic (*e.g.*, dupliumab, ustekinumab or tralokinumab)), or a systemic targeted synthetic JAK inhibitor (*e.g.*, upadacitinib or abrocitinib); such that atopic dermatitis is treated in the subject.

[0074] Another related aspect provides a composition for use in treating atopic dermatitis (AD) in a subject (*e.g.*, a human) in need thereof, the composition comprising an antibody for IL-7Rα, wherein the antibody comprises: (a) a heavy chain variable region (HCVR) that comprises a VH CDR1 comprising the sequence of SEQ ID NO: 1 (DHAMH, such as any one of SEQ ID NOs: 7-22), a VH CDR2 sequence of SEQ ID NO: 2 (GISWNSRGIGYADSVKG), and a VH CDR3 sequence of SEQ ID NO: 3 (DEYSRGYYVLDV); and (b) a light chain variable region (LCVR) that comprises a VL CDR1 sequence of SEQ ID NO: 4 (RASQGISSALA), a VL CDR2 sequence of SEQ ID NO: 5 (DASSLES), and a VL CDR3 sequence of SEQ ID NO: 6 (QQFNSYPLWIT); wherein 200 mg of the antibody is administered subcutaneously every 2 weeks; wherein the antibody comprises an effectorless IgG1 Fc; and, wherein the subject: (1) has moderate to severe AD (*e.g.*, chronic AD having a disease duration of ≥3 years, as diagnosed by the Eichenfield revised criteria of Hanifin and Rajka); (2) has moderate to severe disease activity characterized by: a) BSA affected ≥10%, b) EASI Score ≥12, and/or c) Investigators Global Score (IGA) ≥3; and/or, (3) has inadequate response to treatment by: i) a (medium-potency) topical steroid or a topical immunomodulator (such as a calcineurin inhibitor, a PDE-4 inhibitor, or a JAK inhibitor), optinally, said inadequate response is observed after at least 4 weeks of treatment; ii) a systemic steroid or phototherapy; and/or, iii) an oral chemical synthetic immunomodulator (such as methotrexate (MTX), mycophenolate mofetil, azathioprine, cyclosporine, a systemic biologic (*e.g.*, dupliumab, ustekinumab or tralokinumab)), or a systemic targeted synthetic JAK inhibitor (*e.g.*, upadacitinib or abrocitinib); such that atopic dermatitis is treated in the subject.

[0075] In some embodiments, the composition comprising the antibody is administered to the subject to maintain serum concentration of the antibody at ≥5 μg/mL throughout dosing.

[0076] Serum concentration of the antibody can be measured using any methods known in the art. For example, the level of the anti-IL-7Rα antibody in serum can be determined using a target capture approach. Specifically, the serum is flowed through a surface (*e.g.*, column) pre-coated with a capture agent specific for the anti-IL-7Rα antibody (*e.g.*, human IL-7R extracellular domain), and the antibody in the serum is captured onto the surface. After washing off unbound materials, a labeled secondary antibody that specifically binds to the anti-IL-7Rα antibody but does not compete for binding with the capture agent (*e.g.*, a labeled

secondary antibody which binds to the Fc region of the anti-IL-7Rα antibody) is added to detect the presence of the anti-IL-7Rα antibody captured by the pre-coated substrate. Signal intensity from the labeled secondary antibody is proportional to the concentration of the anti-IL-7Rα antibody in the serum, and serum concentration of the antibody is determined by comparing its measured signal to signals produced by standards with known concentrations of the antibody.

[0077] In a non-limiting example, serum concentration of the antibody can be measured using a Gyrolab® system which is a flow through immunoassay platform. In this fit-for-purpose assay, the antibody present in serum is captured on the columns in the Gyrolab® CD, which is pre-coated with biotinylated recombinant human IL-7R extracellular domain (target). The bound anti-IL-7Rα antibody is detected with AlexaFluor®-647 labeled Cyno anti-human IgG Fc mAb (Pur Clone 10C7). The immunofluorescence measured using the Gyrolab®'s laser-induced fluorescence (LIF) detector is proportional to the concentration of the anti-IL-7Rα antibody in samples, standards, and controls.

[0078] In another non-limiting example, serum concentration of the antibody can be measured using a Gyrolab® system, which is a flow through immunoassay platform. In this validated assay, the antibody present in serum is captured on the columns in the Gyrolab® CD which is pre-coated with biotinylated anti-idiotypic monoclonal antibody (mAb) that specifically bind to the anti-IL-7Rα antibody. The bound anti-IL-7Rα antibody is detected with AlexaFluor®-647 labeled mAb which is a non-competing clone but also binds to anti-IL-7Rα antibody. The immunofluorescence measured using the Gyrolab®'s LIF detector is proportional to the concentration of the anti-IL-7Rα antibody in samples, standards, and controls.

[0079] In some embodiments, the VH CDR1 comprises SEQ ID NO: 7 (GFTFDDHAMH).

[0080] In some embodiments, the composition comprises 100 mg/ml of the antibody in 20 mM histidine, 260 mM sucrose, and 0.05% (w/v) polysorbate 80 at pH 6.0, with an optional 0.05 mM pentetic acid.

[0081] In some embodiments, the subject has an absolute lymphocyte count (ALC) of ≥ 800 per microL.

[0082] In some embodiments, administration of the antibody is stopped when the subject's ALC is < 500 per microL.

[0083] In some embodiments, the antibody is administered to the subject at about 200 mg per dose.

[0084] In some embodiments, the antibody is administered once every two weeks (Q2W).

[0085] In some embodiments, the antibody is administered for at least about 7 doses.

[0086] In some embodiments, the antibody comprises an effectorless IgG1 Fc.

[0087] A related aspect provides a pharmaceutical composition comprising an antibody having two heavy chains and two light chains, wherein each said heavy chain has the amino acid sequence of SEQ ID NO: 23, and each said light chain has the amino acid sequence of SEQ ID NO: 24; and wherein the antibody is formulated in a pharmaceutically acceptable solution comprising about 50-200 mg/mL (*e.g.*, about 100 mg/mL) of the antibody in about 15-25 mM (*e.g.*, about 20 mM) histidine, 200-300 mM (*e.g.*, about 260 mM) sucrose, and about 0.03-0.07% (w/v) (*e.g.*, about 0.05% (w/v)) polysorbate 80 at pH 6.0.

[0088] In some embodiments, the solution further comprises about 0.01-0.10 mM (*e.g.*, about 0.05 mM) of pentetic acid.

[0089] In some embodiments, the pharmaceutical composition comprises, consists essentially of, or consists of the antibody formulated as 100 mg/mL of the antibody in 20 mM histidine, 260 mM sucrose, and 0.05% (w/v) polysorbate 80 at pH 6.0.

[0090] In some embodiments, the pharmaceutical composition comprises, consists essentially of, or consists of the antibody formulated as 100 mg/mL of the antibody in 20 mM histidine, 260 mM sucrose, 0.05 mM of pentetic acid, and 0.05% (w/v) polysorbate 80 at pH 6.0.

[0091] Yet another aspect provides a container (*e.g.*, a polycarbonate bottle) containing about 2 mL of extractable volume of a pharmaceutical composition described herein.

[0092] In some embodiments, the container comprises about 2.26 mL of a pharmaceutical composition of described herein.

[0093] The definitions and methods provided define the present disclosure and guide those of ordinary skill in the art in the practice of the present disclosure. Unless otherwise noted, terms are to be understood according to conventional usage by those of ordinary skill in the relevant art.

[0094] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about."

[0095] As used herein, the term "about" is construed to include all values less than a full increment and greater than a full decrement of the least significant digit claimed. In other

words, the term "about," as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean that range which would encompass the recited value and the range which would be included by rounding up or down to that figure as well, taking into account significant figures.

[0096] As used herein, "atopic dermatitis" or "AD" or "atopic eczema" is a chronic, pruritic inflammatory dermatosis that affects up to 25% of children and 2-3% of adults, especially including those diagnosed under the Eichenfield revised criteria of Hanifin and Rajka (Eichenfield *et al.*, Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol.* 70(2):338-351, Epub Nov. 27, 2013 (incorporated herein by reference).

[0097] As used herein, "Eczema Area and Severity Index (EASI)" is a standardized evaluation tool for evaluating severity of atopic dermatitis (AD) signs in clinical studies (see Tofte *et al.*, Eczema Area and Severity Index (EASI): a new tool to evaluate atopic dermatitis. *J Eur Acad Dermatol Venereol* 11, 1998, incorporated herein by reference). The EASI is the most widely utilized signs/severity scale in AD trials. Reference tables to aid in the steps and calculation of the EASI score are available for both adult and pediatric patient sets. In brief, the area of involvement must be visually estimated in each of the 4 body regions separately (head and neck, upper extremities, trunk, and lower extremities) and assigned an area score: 1 (1%–9%), 2 (10%–29%), 3 (30%–49%), 4 (50%–69%), 5 (70%–89%), and 6 (90%–100%). The feet and buttocks are included as part of the lower extremities, whereas the axilla and groin are counted as part of the trunk. Next, each region is assessed separately for 4 signs: erythema, edema/papulation, excoriation, and lichenification. Each sign is assigned an intensity score from 0 to 3, with 0 being absent; 1, mild; 2, moderate; and 3, severe. Half points may be used between points 1 and 3 (*e.g.*, 1.5 and 2.5 but not 0.5) as any sign present should be treated as at least mild. It is important to note that only inflamed areas should be included in the assessment. Xerosis, ichthyosis, keratosis pilaris, urticaria, and postinflammatory pigment changes should not be included unless underlying eczema is present. Regions that present with varying severity of a particular sign should be roughly averaged across involved areas only; half units may be useful in this scenario. Each region is assigned an adult (>8 years old) or pediatric multiplier that reflects the relative contribution of that region to the total body surface area (BSA). The region score is calculated separately for each region by multiplying the sum of the regional

intensity score by the regional area score and the region-specific multiplier. The final EASI score is the summation of the 4 regional scores, ranging from 0 to 72. A score of 0 indicates clear or no eczema, 0.1 to 1.0 indicates almost clear, 1.1 to 7 indicates mild disease, 7.1 to 21 indicates moderate disease, 21.1 to 50 indicates severe disease, and greater than 51 indicates very severe disease.

[0098] As used herein, "SCORAD" is a clinical tool used to assess the extent and severity of eczema (SCORing Atopic Dermatitis). Dermatologists may use this tool before and after treatment to determine whether the treatment has been effective. Briefly, to determine extent in the various body areas, the sites affected by eczema are shaded on a drawing of a body. The rule of 9 is used to calculate the affected area (A) as a percentage of the whole body (Head and neck 9%; Upper limbs 9% each; Lower limbs 18% each; Anterior trunk 18%; Back 18%; Genitals 1%). The score for each area is added up. The total area is "A," which has a possible maximum of 100%. Further, to determine the intensity of the affected areas, a representative area of eczema is selected. In this area, the intensity of each of the following signs is assessed as none (0), mild (1), moderate (2) or severe (3) – Redness, Swelling, Oozing/crusting, Scratch marks, Skin thickening (lichenification), and Dryness (this is assessed in an area where there is no inflammation). The intensity scores are added together to give "B" (maximum 18). Subjective symptoms (itch and sleeplessness), are each scored by the patient or relative using a visual analogue scale where 0 is no itch (or no sleeplessness) and 10 is the worst imaginable itch (or sleeplessness). These scores are added to give "C" (maximum 20). The total SCORAD score for that individual is A/5 + 7B/2 + C.

[0099] As used herein, the "Validated Investigator Global Assessment for Atopic Dermatitis" or "vIGA" is an assessment scale used in clinical studies to determine severity of AD and clinical response to treatment based on a 5-point scale ranging from 0 (clear) to 4 (severe). See Simpson *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.* 83(3):839-846, 2020 (incorporated herein by reference).

[0100] As used herein "Body Surface Area (BSA) Involvement of Atopic Dermatitis" is used herein for assessing body surface area affected by AD for each major section of the body (head, trunk, arms, and legs), and is reported as a percentage of all major body sections combined.

[0101] As used herein, "Peak Pruritis Numerical Rating Scale (NRS)" refers to an 11-point scale to evaluate itch intensity. Subjects are asked to rate the overall severity of their

itch in the past 24 hours using a scale described in Yosipovitch *et al.* (*Br J Dermatol.* 181(4):761-769, Epub 2019 May 1 2019, incorporated herein by reference).

[0102] As used herein, "Patient-Oriented Eczema Measure" (or POEM) is a self-assessed, repeatable measurement tool for measuring atopic dermatitis (AD) severity. Patients will answer questions about the frequency of seven symptoms: itch, sleep disturbance, skin bleeding, skin weeping/oozing, skin cracking, skin flaking, and skin dryness/roughness over the last week. The total score from this assessment reflects overall disease activity. The POEM utilizes a 5-point Likert scale for each question. POEM scores can range from 0 to 28 where lower total scores reflect lower disease activity and higher scores reflect higher disease activity (Charman *et al.*, *Arch Dermatol.* 140(12):1513-9, 2004, erratum in: *Arch Dermatol.* 141(3):3812004, 2005; Kido-Nakahara *et al.*, *Acta Derm Venereol.* 100(10):adv00159, 2020, both incorporated herein by reference).

[0103] As used herein, the "Dermatology Life Quality Index (DLQI)" refers to a self-administered questionnaire designed to measure the health-related quality of life of adult patients suffering from a skin disease. The DLQI consists of 10 questions concerning symptoms and feelings, daily activities, leisure, work, and school, personal relationships and treatment. Each question is answered by a tick box: "not at all", "a little", "a lot" or "very much". Each question is scored from 0 to 3 and the scores summed, giving a range from 0 (no impairment of life quality) to 30 (maximum impairment). All questions relate "to the last week." See Lewis and Finlay, 10 years experience of the Dermatology Life Quality Index (DLQI). *J Investig Dermatol Symp Proc.* 9(2):169-180, 2004, incorporated herein by reference).

[0104] As used herein, "Atopic Dermatitis Control Tool (ADCT)" is a brief patient self-administered instrument designed and validated to assess AD control; six AD symptoms and impacts are evaluated over the past week, including overall severity of symptoms, days with intense episodes of itching, intensity of bother, problem with sleep, impact on daily activities, and impact on mood or emotions. See Simpson *et al.* (Validation of the Atopic Dermatitis Control Tool (ADCT©) using a longitudinal survey of biologic-treated patients with atopic dermatitis. *BMC Dermatol.* 19(1):15, 2019, incorporated herein by reference).

[0105] As used herein, "PROMIS Sleep Disturbance (SD) and Sleep Related Impairment (SRI)" assesses perceptions of alertness, sleepiness, and tiredness during usual waking hours, and the perceived functional impairments during wakefulness associated with sleep problems or impaired alertness. These instruments were previously validated and found to strongly correlate with both objective and other PRO measures of sleep quality. See Li *et al.* (Sleep

Disturbance and Sleep-Related Impairment in Adults With Atopic Dermatitis: A Cross-sectional Study. *Dermatitis*. 29(5):270-277, 2018, incorporated herein by reference).

[0106] As used herein, the term "AD-associated biomarker" means any biological response, cell type, parameter, protein, polypeptide, enzyme, enzyme activity, metabolite, nucleic acid, carbohydrate, or other biomolecule which is present or detectable in an AD patient at a level or amount that is different from (*e.g.*, greater than or less than) the level or amount of the marker present or detectable in a non-AD patient. The term "AD-associated biomarker" also includes a gene or gene probe known in the art which is differentially expressed in a subject with AD as compared to a subject without AD. Alternatively, "AD-associated biomarker" also includes genes which are down regulated due to AD.

[0107] Exemplary AD-associated biomarkers include one or more of: total eosinophil count, total IgE (*e.g.*, high total serum IgE levels), CCL17 (Thymus and Activation-Regulated Chemokine (TARC)), CCL18 (PARC), LDH (lactate dehydrogenase), serum levels of CD30, Macrophage-Derived Chemoattractant (MDC), interleukins (IL)-12, IL-16, IL-18, IL-31, and *filaggrin* gene null mutations.

[0108] In some embodiments, AD-associated biomarkers include one or more of: total eosinophil count, total IgE, CCL17 (TARC), CCL18 (PARC), and/or LDH.

[0109] Another exemplary AD-associated biomarker include the SCORing Atopic Dermatitis (SCORAD) index and other severity scales known in the art.

[0110] In some embodiments, the biomarker comprises total eosinophil count. In some embodiments, the biomarker comprises total IgE. In some embodiments, the biomarker comprises CCL17. In some embodiments, the biomarker comprises CCL18. In some embodiments, the biomarker comprises LDH.

[0111] In some embodiments, the biomarker is assessed using histology. In some embodiments, the biomarker is assessed using RNAseq. In some embodiments, the biomarker is assessed using proteomic analysis. In some embodiments, the biomarker is assessed using enzyme-linked immunosorbent assay. In some embodiments, the biomarker is assessed using mass spectrometry. In some embodiments, the biomarker is assessed using a blood sample. In some embodiments, the biomarker will be assessed using a serum sample. In some embodiments, the biomarker will be assessed using a plasma sample. In some embodiments, the biomarker is assessed using a tissue sample. In some embodiments, the biomarker will be assessed using a punch biopsy.

[0112] In some embodiments, the biomarker is a gene expression signature.

[0113] Also provided are biomarkers for monitoring disease reversal with the administration of the subject antibody, or a pharmaceutically acceptable formulation thereof. Methods for detecting and/or quantifying such AD-associated biomarkers are known in the art; kits for measuring such AD-associated biomarkers are available from various commercial sources; and various commercial diagnostic laboratories offer services which provide measurements of such biomarkers as well.

[0114] As used herein, "TSLP" refers to a growth factor that closely resembles IL-7 and plays a role in the maturation and activation of myeloid cells (*e.g.*, monocytes and dendritic cells). TSLP is produced by various cell types, such as fibroblasts, epithelial cells, and stromal cells. Elevated levels of TSLP have been associated with diseases, such as asthma, atopic dermatitis, and inflammatory arthritis, which are also known to be associated with abnormal regulation of IL-7.

[0115] As used herein, the term "antibody" refers to a protein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region (abbreviated herein as CH). In certain antibodies, *e.g.*, naturally occurring IgG antibodies, the heavy chain constant region is comprised of a hinge and three domains, CH1, CH2 and CH3. In certain antibodies, *e.g.*, naturally occurring IgG antibodies, each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain (abbreviated herein as CL). The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies can mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (Clq) of the classical complement system. A heavy chain may have the C-terminal lysine or not. Unless specified otherwise herein, the amino acids in the variable regions are numbered using the Rabat numbering system and those in the constant regions are numbered using the EU system. "Antibody" includes, by way of example, both naturally occurring and non-naturally occurring antibodies; monoclonal and polyclonal antibodies;

chimeric and humanized antibodies; human and nonhuman antibodies and wholly synthetic antibodies.

[0116] An "IgG antibody", *e.g.*, a human IgG1, IgG2, IgG3 and IgG4 antibody, as used herein, has, in some embodiments, the structure of a naturally occurring IgG antibody, *i.e.*, it has the same number of heavy and light chains and disulfide bonds as a naturally occurring IgG antibody of the same subclass. For example, an anti-IL-7R IgGl, IgG2, IgG3 or IgG4 antibody consists of two heavy chains (HCs) and two light chains (LCs), wherein the two heavy chains and light chains are linked by the same number and location of disulfide bridges that occur in naturally occurring IgGl, IgG2, IgG3 and IgG4 antibodies, respectively (unless the antibody has been mutated to modify the disulfide bridges).

[0117] Antibodies typically bind specifically to their cognate antigen with high affinity, reflected by a dissociation constant (K_D) of 10^{-5} to 10^{-11} M or less. Any K_D greater than about 10^{-4} M is generally considered to indicate nonspecific binding.

[0118] In some embodiments, the anti-IL-7Rα antibody used or useful for the method described herein specifically binds to IL-7Rα, such as binding specifically with a K_D of 10^{-5} to 10^{-11} M or less (*e.g.*, 10^{-5} M or less, 10^{-6} M or less, 10^{-7} M or less, 10^{-8} M or less, 10^{-9} M or less, 10^{-10} M or less, or 10^{-11} M or less).

[0119] In some embodiments, the anti-IL-7Rα antibody used or useful for the method described herein binds specifically to IL-7Rα (such as human IL-7Rα) with a K_D of 10^{-7} M or less, 10^{-8} M or less, 5 x 10^{-9} M or less, or between 10^{-8} M and 10^{-10} M or less, but does not bind with high affinity to unrelated antigens.

[0120] An antigen is "substantially identical" to a given antigen if it exhibits a high degree of sequence identity to the given antigen, for example, if it exhibits at least 80%, at least 90%, at least 95%, at least 97%, or at least 99% sequence identity to the sequence of the given antigen. By way of example, an antibody that binds specifically to human IL-7Ra can, in some embodiments, also have cross-reactivity with IL-7Ra antigens from certain primate species (*e.g.*, cynomolgus IL-7Ra), but cannot cross-react with IL-7Ra antigens from other species or with an antigen other than IL-7Ra.

[0121] As used herein, "isotype" refers to the antibody class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgM, IgAl, IgA2, IgD, and IgE antibody) that is encoded by the heavy chain constant region genes. The IgG isotype is divided in subclasses in certain species: IgGl, IgG2, IgG3 and IgG4 in humans, and IgGl, IgG2a, IgG2b and IgG3 in mice. In some embodiments, the anti-IL-7R antibodies described herein are of the IgGl isotype. Immunoglobulins, *e.g.*, IgGl, exist in several allotypes, which differ from each other in at most a few amino acids.

[0122] As used herein, the term "allotype" refers to naturally occurring variants within a specific isotype group, wherein the variants differ in a few amino acids. Anti-IL-7R antibodies described herein can be of any allotype. As used herein, antibodies referred to as "IgGlf," "IgGl. If," or "IgG1.3f" isotype are IgGl, effectorless IgGl.l, and effectorless IgGl.3 antibodies, respectively, of the allotype "f," *i.e.*. having 214R, 356E and 358M according to the EU index as in Kabat, as shown, *e.g.*, in SEQ ID NO: 23.

[0123] The term "antigen-binding portion" of an antibody, as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (*e.g.*, human IL-7Ra). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody, *e.g.*, an anti-IL-7R antibody described herein, include (i) a Fab fragment (fragment from papain cleavage) or a similar monovalent fragment consisting of the VL, VH, LC and CH1 domains; (ii) a $F(ab')_2$ fragment (fragment from pepsin cleavage) or a similar bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a F_d fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment which consists of a VH domain; (vi) an isolated complementarity determining region (CDR) and (vii) a combination of two or more isolated CDRs which can optionally be joined by a synthetic linker. Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody.

[0124] These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies. Antigen-binding portions can be produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact immunoglobulins.

[0125] The term "monoclonal antibody," as used herein, refers to an antibody from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprised in the population are substantially similar and bind the same epitope(s) (*e.g.*, the antibodies display a single binding specificity and affinity), except for possible variants that may arise during production of the monoclonal antibody, such variants generally being present in minor amounts. The modifier "monoclonal" indicates the character of the antibody as being

obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method.

[0126] The term "human monoclonal antibody" refers to an antibody from a population of substantially homogeneous antibodies that display(s) a single binding specificity and which has variable and optional constant regions derived from human germline immunoglobulin sequences. In one embodiment, human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic non-human animal, *e.g.*, a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

[0127] The term "recombinant human antibody," as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, (b) antibodies isolated from a host cell transformed to express the antibody, *e.g.*, from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies comprise variable and constant regions that utilize particular human germline immunoglobulin sequences are encoded by the germline genes, but include subsequent rearrangements and mutations which occur, for example, during antibody maturation. As known in the art, the variable region contains the antigen binding domain, which is encoded by various genes that rearrange to form an antibody specific for a foreign antigen. In addition to rearrangement, the variable region can be further modified by multiple single amino acid changes (referred to as somatic mutation or hypermutation) to increase the affinity of the antibody to the foreign antigen. The constant region will change in further response to an antigen (*i.e.*, isotype switch). Therefore, the rearranged and somatically mutated nucleic acid molecules that encode the light chain and heavy chain immunoglobulin polypeptides in response to an antigen cannot have sequence identity with the original nucleic acid molecules, but instead will be substantially identical or similar (*i.e.*, have at least 80% identity).

[0128] A "human" antibody (HuMAb) refers to an antibody having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The anti-

IL-7R antibodies described herein can include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. The terms "human" antibodies and "fully human" antibodies are used synonymously.

[0129] A "humanized" antibody refers to an antibody in which some, most or all of the amino acids outside the CDR domains of a non-human antibody are replaced with corresponding amino acids derived from human immunoglobulins. In one embodiment of a humanized form of an antibody, some, most or all of the amino acids outside the CDR domains have been replaced with amino acids from human immunoglobulins, whereas some, most or all amino acids within one or more CDR regions are unchanged. Small additions, deletions, insertions, substitutions or modifications of amino acids are permissible as long as they do not abrogate the ability of the antibody to bind to a particular antigen. A "humanized" antibody retains an antigenic specificity similar to that of the original antibody.

[0130] A "chimeric antibody" refers to an antibody in which the variable regions are derived from one species and the constant regions are derived from another species, such as an antibody in which the variable regions are derived from a mouse antibody and the constant regions are derived from a human antibody.

[0131] The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen."

[0132] An "isolated antibody," as used herein, is intended to refer to an antibody which is substantially free of other proteins and cellular material.

[0133] As used herein, an antibody that "inhibits binding of IL-7 to IL-7Rα" is intended to refer to an antibody that inhibits the binding of IL-7Rα to its ligand, *e.g.*, interleukin-7 (IL-7), *e.g.*, in binding assays using T cells from whole blood that express IL-7Rα, with an EC50 of about 1 pg/mL or less, such as about 0.9 pg/mL or less, about 0.85 pg/mL or less, about 0.8 pg/mL or less, about 0.75 pg/mL or less, about 0.7 pg/mL or less, about 0.65 pg/mL or less, about 0.6 pg/mL or less, about 0.55 pg/mL or less, about 0.5 pg/mL or less, about 0.45 pg/mL or less, about 0.4 pg/mL or less, about 0.35 pg/mL or less, about 0.3 pg/mL or less, about 0.25 pg/mL or less, about 0.2 pg/mL or less, about 0.15 pg/mL or less, about 0.1 pg/mL

or less, or about 0.05 pg/mL or less, in art-recognized methods, *e.g.*, the FACS-based binding assays described herein.

[0134] An "effector function" refers to the interaction of an antibody Fc region with an Fc receptor or ligand, or a biochemical event that results therefrom. Exemplary "effector functions" include Clq binding, complement dependent cytotoxicity (CDC), Fc receptor binding, FcyR-mediated effector functions such as ADCC and antibody dependent cell-mediated phagocytosis (ADCP), and downregulation of a cell surface receptor (*e.g.*, the B cell receptor; BCR). Such effector functions generally require the Fc region to be combined with a binding domain (*e.g.*, an antibody variable domain).

[0135] An "Fc receptor" or "FcR" is a receptor that binds to the Fc region of an immunoglobulin. FcRs that bind to an IgG antibody comprise receptors of the FcγR family, including allelic variants and alternatively spliced forms of these receptors. The FcγR family consists of three activating (FcγRI, FcγRIII, and FcγRIV in mice; FcRIA, FcRIIA, and FcyRIIIA in humans) and one inhibitory (FcγRIIB) receptor. Various properties of human FcyRs are known in the art. The majority of innate effector cell types coexpress one or more activating FcγR and the inhibitory FcγRIIB, whereas natural killer (NK) cells selectively express one activating Fc receptor (FcγRIII in mice and FcγRIIIA in humans) but not the inhibitory FcγRIIB in mice and humans. Human IgGl binds to most human Fc receptors and is considered equivalent to murine IgG2a with respect to the types of activating Fc receptors that it binds to.

[0136] An "Fc region" (fragment crystallizable region) or "Fc domain" or "Fc" refers to the C-terminal region of the heavy chain of an antibody that mediates the binding of the immunoglobulin to host tissues or factors, including binding to Fc receptors located on various cells of the immune system (*e.g.*, effector cells) or to the first component (Clq) of the classical complement system. Thus, an Fc region comprises the constant region of an antibody excluding the first constant region immunoglobulin domain (*e.g.*, CHI or CF). In IgG, IgA and IgD antibody isotypes, the Fc region comprises two identical protein fragments, derived from the second (CH2) and third (CH3) constant domains of the antibody's two heavy chains; IgM and IgE Fc regions comprise three heavy chain constant domains (CH domains 2-4) in each polypeptide chain. For IgG, the Fc region comprises immunoglobulin domains CH2 and CH3 and the hinge between CH1 and CH2 domains. Although the definition of the boundaries of the Fc region of an immunoglobulin heavy chain might vary, as defined herein, the human IgG heavy chain Fc region is defined to stretch from an amino acid residue D221 for IgGl, V222 for IgG2, F221 for IgG3 and P224 for IgG4 to the carboxy-terminus of the

heavy chain, wherein the numbering is according to the EU index as in Kabat. The CH2 domain of a human IgG Fc region extends from amino acid 237 to amino acid 340, and the CH3 domain is positioned on C-terminal side of a CH2 domain in an Fc region, *i.e.*, it extends from amino acid 341 to amino acid 447 or 446 (if the C-terminal lysine residue is absent) or 445 (if the C-terminal glycine and lysine residues are absent) of an IgG. As used herein, the Fc region can be a native sequence Fc, including any allotypic variant, or a variant Fc (*e.g.*, a non-naturally occurring Fc). Fc can also refer to this region in isolation or in the context of an Fc-comprising protein polypeptide such as a "binding protein comprising an Fc region," also referred to as an "Fc fusion protein" (*e.g.*, an antibody or immunoadhesion).

[0137] A "native sequence Fc region" or "native sequence Fc" comprises an amino acid sequence that is identical to the amino acid sequence of an Fc region found in nature. Native sequence human Fc regions include a native sequence human IgGl Fc region; native sequence human IgG2 Fc region; native sequence human IgG3 Fc region; and native sequence human IgG4 Fc region as well as naturally occurring variants thereof. Native sequence Fc include the various allotypes of Fes.

[0138] The term "epitope" or "antigenic determinant" refers to a site on an antigen (*e.g.*, IF-7Rα) to which an immunoglobulin or antibody specifically binds, *e.g.*, as defined by the specific method used to identify it. Epitopes can be formed both from contiguous amino acids (usually a linear epitope) or noncontiguous amino acids juxtaposed by tertiary folding of a protein (usually a conformational epitope). Epitopes formed from contiguous amino acids are typically, but not always, retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids in a unique spatial conformation. Methods for determining what epitopes are bound by a given antibody (*i.e.*. epitope mapping) are well known in the art and include, for example, immunoblotting and immunoprecipitation assays, wherein overlapping or contiguous peptides from (*e.g.*, from IF-7Rα) are tested for reactivity with a given antibody (*e.g.*, anti-IF-7R antibody). Methods of determining spatial conformation of epitopes include techniques in the art and those described herein, for example, x-ray crystallography, antigen mutational analysis, 2-dimensional nuclear magnetic resonance and HDX-MS.

[0139] The term "k_{assoc}" or "k_a", as used herein, is intended to refer to the association rate of a particular antibody- antigen interaction, whereas the term "k_{dis}" or "k_d," as used herein, is intended to refer to the dissociation rate of a particular antibody-antigen interaction. The term "K_D", as used herein, is intended to refer to the dissociation constant, which is obtained from

the ratio of kd to ka (*i.e.*. kd/ka) and is expressed as a molar concentration (M). K_D values for antibodies can be determined using methods well established in the art. Available methods for determining the K_D of an antibody include surface plasmon resonance, a biosensor system such as a BIACORE® system or flow cytometry and Scatchard analysis.

[0140] As used herein, the term "high affinity" for an IgG antibody refers to an antibody having a K_D of 10^{-8} M or less, 10^{-9} M or less, or 10^{-10} M or less for a target antigen. However, "high affinity" binding can vary for other antibody isotypes. For example, "high affinity" binding for an IgM isotype refers to an antibody having a K_D of 10^{-10} M or less, or 10^{-8} M or less.

[0141] The term "EC50" in the context of an *in vitro* or *in vivo* assay using an antibody or antigen binding fragment thereof, refers to the concentration of an antibody or an antigen-binding portion thereof that induces a response that is 50% of the maximal response, *i.e.*, halfway between the maximal response and the baseline.

[0142] As used herein, the term "autoimmune disease" refers to a disease or disorder in which the immune system produces an immune response (*e.g.*, a B cell or a T cell response) against an antigen that is part of the normal host (*i.e.*, an autoantigen), with consequent injury to tissues. An autoantigen may be derived from a host cell, or may be derived from a commensal organism such as the micro-organisms (known as commensal organisms) that normally colonize mucosal surfaces.

[0143] The term "inflammation" or an "inflammatory process," as used herein, refers to a complex series of events, including dilatation of arterioles, capillaries and venules, with increased permeability and blood flow, exudation of fluids, including plasma proteins and leukocyte migration into the inflammatory focus. Inflammation may be measured by many methods well known in the art, such as the number of leukocytes, the number of polymorphonuclear neutrophils (PMN), a measure of the degree of PMN activation, such as luminal enhanced-chemiluminescence, or a measure of the amount of proinflammatory cytokines (*e.g.*, IL-6 or TNF-a) present.

[0144] As used herein, the term "regulatory T cells" (Tregs) refer to a population of T cells with the ability to reduce or suppress the induction and proliferation of effector T cells, and thereby, modulate an immune response. In some embodiments, Tregs can suppress an immune response by secreting anti-inflammatory cytokines, such as IL-10, TGF-b, and IL-35, which can interfere with the activation and differentiation of naive T cells into effector T cells. In some embodiments, Tregs can also produce cytolytic molecules, such as Granzyme B, which can induce the apoptosis of effector T cells. In some embodiments, the regulatory T

cells are natural regulatory T cells (nTregs) (*i.e.*. developed within the thymus). In some embodiments, the regulatory T cells are induced regulatory T cells (iTregs) (*i.e.*, naive T cells that differentiate into Tregs in the peripheral tissue upon exposure to certain stimuli). Methods for identifying Tregs are known in the art. For example, Tregs express certain phenotypic markers (*e.g.*, CD25, Foxp3, or CD39) that can be measured using flow cytometry. In some embodiments, the Tregs are CD45RA- CD39+ T cells.

[0145] As used herein, "administering" refers to the physical introduction of a composition comprising a therapeutic agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Different routes of administration for the anti-IL-7R antibodies described herein include intravenous, intraperitoneal, intramuscular, subcutaneous, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intraperitoneal, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrastemal injection and infusion, as well as *in vivo* electroporation. Alternatively, an antibody described herein can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally, sublingually or topically. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

[0146] As used herein, the terms "inhibits" or "blocks" (*e.g.*, referring to inhibition/blocking of binding of IL-7 to IL-7Ra on cells) are used interchangeably and encompass both partial and complete inhibition/blocking. In some embodiments, the anti-IL-7R antibody inhibits binding of IL-7 to IL-7Ra by at least about 50%, for example, about 60%, 70%, 80%, 90%, 95%, 99%, or 100%, determined, *e.g.*, as further described herein.

[0147] The terms "treat," "treating," and "treatment," as used herein, refer to any type of intervention or process performed on, or administering an active agent to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, or slowing down or preventing the progression, development, severity or recurrence of a symptom, complication, condition or biochemical indicia associated with a disease or enhancing overall survival. These terms do not include prophylatic intervention.

[0148] The term "prophylatic intervention" refers to treating a subject who does not yet have a disease for preventive purpose.

[0149] The term "effective dose" or "effective dosage" is defined as an amount sufficient to achieve or at least partially achieve a desired effect.

[0150] A "therapeutically effective amount" or "therapeutically effective dosage" of a drug or therapeutic agent (*e.g.*, the subject anti-IL-7Ra antibody) is any amount of the drug that, when used alone or in combination with another therapeutic agent, promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. A therapeutically effective amount or dosage of a drug includes a "prophylactically effective amount" or a "prophylactically effective dosage," which is any amount of the drug that, when administered alone or in combination with another therapeutic agent to a subject at risk of developing a disease or of suffering a recurrence of disease, inhibits the development or recurrence of the disease. The ability of a therapeutic agent to promote disease regression or inhibit the development or recurrence of the disease can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials (including the methods described in the examples), in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays.

[0151] The term "patient" includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment. In some embodiments, the patient is a human.

[0152] As used herein, the term "subject" includes any human or non-human animal. For example, the methods and compositions described herein can be used to treat a subject having cancer. The term "non-human animal" includes all vertebrates, *e.g.*, mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, reptiles, *etc.*

[0153] The term "weight-based" dose or dosing as referred to herein means that a dose that is administered to a patient is calculated based on the weight of the patient. For example, when a patient with 60 kg body weight requires 3 mg/kg of an anti-IL-7R antibody, one can calculate and use the appropriate amount of the anti-IL-7Ra antibody (*i.e.*, 180 mg) for administration.

[0154] Provided are methods for the treatment of atopic dermatitis (AD), the method comprising administering to a subject in need thereof an isolated antibody or antigen binding portion thereof, which specifically binds to an alpha-chain of a human IL-7 receptor ("anti-IL-7Rα antibody," or "anti-IL-7R antibody" for short), comprising a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3, respectively, wherein the antibody

(a) is capable of binding to T cells ($CD4^+CD45RA^+$, $CD4^+CD45RA^-$, $CD8^+CD45RA^+$, and/or $CD8^+CD45RA^-$) in whole blood with an EC_{50} of about 5 nM or less (*e.g.*, less than about 3 nM);

(b) is not capable of binding to non-T cells in whole blood;

(c) does not agonize IL-7 receptor signaling upon binding to the IL-7 receptor, *e.g.*, minimal pSTAT5 activation; or

(d) any combination thereof.

[0155] In some embodiments, the heavy chain CDR3 of the subject anti-IL-7Rα antibody (*e.g.*, disclosed herein) comprises the amino acid sequence set forth in SEQ ID NO: 3 (DEYSRGYYVLDV).

[0156] In some embodiments, the anti-IL-7Rα antibody has one or more properties selected from the group consisting of:

(a) is capable of selectively binding to an alpha-chain of a human and cynomolgus IL-7 receptor (IL-7R);

(b) is capable of binding to an alpha-chain of soluble and membrane bound IL-7R;

(c) is capable of blocking an expansion and/or survival of pathogenic T cells when administered to a subject in need thereof;

(d) is capable of restoring a T regulatory cell (Treg) function and/or promoting a Treg survival when administered to a subject in need thereof;

(e) is capable of maintaining a drug free remission longer than that by CTLA4-Ig (ORENCIA®);

(f) is capable of blocking inflammation and mucosal damage, *e.g.*, induced by pathogenic T cells, within an intestinal tissue of a subject in need thereof;

(g) is capable of decreasing a frequency of T effector cells in the mesenteric lymph nodes (MLN) and/or lamina propria (LP) in a subject in need thereof;

(h) is capable of reducing or inhibiting IL-7 mediated pSTAT activation in T cells (*e.g.*, $CD4^+CD45RA^+$);

(i) is capable of blocking expansion of IL-17 and/or IFN-gamma producing cells;

(j) is capable of treating a subject with an inflammatory disease (*e.g.*, inflammatory bowel disease); and

(k) any combination thereof.

[0157] In some embodiments, the subject anti-IL-7Rα antibody comprises a heavy chain CDR1, wherein the heavy chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 1 (DHAMH), such as any one of amino acid sequences set forth in SEQ ID NOs: 7 to 22. In some embodiments, an anti-IL-7Rα antibody comprises a heavy chain CDR2, wherein the heavy chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 2 (GISWNSRGIGYADSVKG). In some embodiments, an anti-IL-7Rα antibody comprises a heavy chain CDR3, wherein the heavy chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 3 (DEYSRGYYVLDV). In some embodiments, an anti-IL-7Rα antibody comprises a light chain CDR1, wherein the light chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 4 (RASQGISSALA). In some embodiments, an anti-IL-7Rα antibody comprises a light chain CDR2, wherein the light chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 5 (DASSLES). In some embodiments, an anti-IL-7Rα antibody comprises a light chain CDR3, wherein the light chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 6 (QQFNSYPLWIT).

[0158] In some embodiments, the subject anti-IL-7Rα antibody comprises a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 1 (*e.g.*, any one of SEQ ID NOs: 7-22, such as SEQ ID NO: 7 (GFTFDDHAMH)); a heavy chain CDR2 of the amino acid sequence set forth in SEQ ID NO: 2 (GISWNSRGIGYADSVKG); a heavy chain CDR3 of the amino acid sequence set forth in SEQ ID NO: 3 (DEYSRGYYVLDV); a light chain CDR1 of the amino acid sequence set forth in SEQ ID NO: 4 (RASQGISSALA); a light chain CDR2 of the amino acid sequence set forth in SEQ ID NO: 5 (DASSLES); and a light chain CDR3 of the amino acid sequence set forth in SEQ ID NO: 6 (QQFNSYPLWIT).

[0159] In some embodiments, the subject anti-IL-7Rα antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth in SEQ ID NO: 25. In some embodiments, the VL comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth in SEQ ID NO: 26.

[0160] In some embodiments, the subject anti-IL-7Rα antibody disclosed herein specifically binds to the alpha-chain of the human IL-7 receptor at an epitope selected from the group consisting of: ^{24}SQLEVNGSQHSLTCAF^{39} (SEQ ID NO: 27);

^{73}FIETKKFLLIGKSNIC^{88} (SEQ ID NO: 28); ^{89}VKVGEKSLTCKKIDLTT^{105} (SEQ ID NO: 29); ^{136}QKKYVKVLMHDVAY^{149} (SEQ ID NO: 30); ^{181}YEIKVRSIPDHYFKGF^{196} (SEQ ID NO: 31); and combinations thereof.

[0161] In some embodiments, an anti-IL-7Rα antibody specifically binds to the alpha-chain of the human IL-7 receptor at an epitope comprising one or more amino acid residues selected from the group consisting of H33, E75, F79, I82, K84, M144, R186, H191, Y192, and combinations thereof.

[0162] In some embodiments, an anti-IL-7R antibody of is selected from the group consisting of an IgGl, IgG2, IgG3, IgG4, and a variant thereof.

[0163] In some embodiments, an IL-7R antibody is an IgGl antibody. In some embodiments, an anti-IL-7R antibody comprises an effectorless IgG1 Fc.

[0164] In some embodiments, the subject anti-IL-7Rα antibody or antigen binding portion thereof comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises the amino acid sequence set forth in SEQ ID NO: 25 and the VL comprises the amino acid sequence set forth in SEQ ID NO: 26.

[0165] In some embodiments, the subject anti-IL-7Rα antibody or antigen binding portion thereof comprises a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence set forth in SEQ ID NO: 23 and wherein the light chain comprises the amino acid sequence set forth in SEQ ID NO: 24.

[0166] In some embodiments, an anti-IL-7Rα antibody binds to the alpha-chain of the human IL-7 receptor with a K_D of less than 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, or 1 nM (*e.g.*, 1.3 nM), as measured by surface plasmon resonance. In some embodiments, an anti-IL-7Rα antibody binds to the alpha-chain of the cynomolgus IL-7 receptor with a K_D of less than 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, or 1 nM (*e.g.*, 1.7 nM), as measured by surface plasmon resonance. In some embodiments, the binding to the alpha-chain of the human IL-7 receptor or the alpha-chain of the cynomolgus IL-7 receptor is pH-dependent. In some embodiments, an anti-IL-7Rα antibody binds to the alpha-chain of the human IL-7 receptor with a K_D of about 1.3 nM at pH 7.4 and with a K_D of about 5.3 nM at pH 6. In some embodiments, an anti-IL-7Rα antibody binds to the alpha-chain of the cynomolgus IL-7 receptor with a K_D of about 1.7 nM at pH 7.4 and with a K_D of about 7.0 nM at pH 6.

[0167] In some embodiments, the isolated antibody or antigen binding portion thereof, which specifically binds to an alpha-chain of a human IL-7 receptor ("anti-IL-7Rα antibody") comprising a heavy chain (HC) CDR1, CDR2, and CDR3, and a light chain (LC) CDR1,

CDR2, and CDR3, wherein: (i) the heavy chain CDR1 comprises an amino acid sequence set forth in any one of SEQ ID NOs: 7 to 22; (ii) the heavy chain CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 2 (GISWNSRGIGYADSVKG); (iii) the heavy chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 3 (DEYSRGYYVLDV); (iv) the light chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 4 (RASQGISSALA); (v) the light chain CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 5 (DASSLES); and (vi) the light chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 6 (QQFNSYPLWIT). In certain aspects, the heavy chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 8 (GYTFDDHAMH), SEQ ID NO: 19 (GFDFDDHAMH), or SEQ ID NO: 20 (GFEFDDHAMH).

[0168] The relevant sequences of the exemplary antibodies are provided below.

[0169] **Table 1: Amino acid sequences of anti- IL-7Rα antibodies**

SEQ ID NO	DESCRIPTION	SEQUENCE
1	VH CDR1	DHAMH
7	VH CDR1 (18B1)	GFTFDDHAMH
8	VHCDR1 (F27Y)	GYTFDDHAMH
9	VH CDR1 (T28P)	GFPFDDHAMH
10	VH CDR1 (T28A)	GFAFDDHAMH
11	VH CDR1 (T28V)	GFVFDDHAMH
12	VH CDR1 (T28L)	GFLFDDHAMH
13	VH CDR1 (T28I)	GFIFDDHAMH
14	VH CDR1 (T28M)	GFMFDDHAMH
15	VH CDR1 (T28H)	GFHFDDHAMH
16	VH CDR1 (T28F)	GFFFDDHAMH
17	VH CDR1 (T28Y)	GFYFDDHAMH
18	VH CDR1 (T28N)	GFNFDDHAMH
19	VH CDR1 (T28D)	GFDFDDHAMH
20	VH CDR1 (T28E)	GFEFDDHAMH
21	VH CDR1 (T28Q)	GFQFDDHAMH
22	VH CDR1 (M34L)	GFTFDDHALH
2	VH CDR2	GISWNSRGIGYADSVKG
3	VH CDR3	DEYSRGYYVLDV
4	VL CDR1	RASQGISSALA
5	VL CDR2	DASSLES
6	VL CDR3	QQFNSYPLWIT
25	Heavy Chain Variable Region, VH	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDHAM HWVRQAPGKGLEWVSGISWNSRGIGYADSVKGRF TIFRDNAKNSLYLQMNSLRAEDTALYYCAKDEYS RGYYVLDVWGQGTTVTVSS
26	Light Chain Variable Region, VL	AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWY QQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFT LTISSLQPEDFATYYCQQFNSYPLWITFGQGTRLEI K
23	Heavy Chain	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDHAM HWVRQAPGKGLEWVSGISWNSRGIGYADSVKGRF TIFRDNAKNSLYLQMNSLRAEDTALYYCAKDEYS

		RGYYVLDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAEGAP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
24	Light Chain	AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWY QQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFT LTISSLQPEDFATYYCQQFNSYPLWITFGQGTRLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC

[0170] In some embodiments, the anti-IL-7Rα antibody binds to the alpha-chain of the human IL-7 7Rα with a K_D of less than 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, or 1 nM (*e.g.*, 1.3 nM), as measured by surface plasmon resonance. In some embodiments, an anti-IL-7Rα antibody binds to the alpha-chain of the cynomolgus IL-7 receptor with a K_D of less than 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, or 1 nM (*e.g.*, 1.7 nM), as measured by surface plasmon resonance. In some embodiments, the binding to the alpha-chain of the human IL-7 receptor or the alpha-chain of the cynomolgus IL-7 receptor is pH-dependent. In some embodiments, an anti- IL-7Rα antibody binds to the alpha-chain of the human IL-7 receptor with a K_D of about 1.3 nM at pH 7.4 and with a K_D of about 5.3 nM at pH 6. In some embodiments, an anti-IL-7R antibody binds to the alpha-chain of the cynomolgus IL-7 receptor with a K_D of about 1.7 nM at pH 7.4 and with a K_D of about 7.0 nM at pH 6.

[0171] In some embodiments, an anti-IL-7Rα antibody is formulated for administration to the subject at a flat dose or a body weight-based dose. In some embodiments, an anti-IL-7Rα antibody is formulated for administration to the subject at a body weight-based dose (*e.g.*, mg/kg). In some embodiments, an anti-IL-7Rα antibody is formulated for administration intravenously, subcutaneously, intramuscularly, intradermally, or intraperitoneally. In some embodiments, an anti-IL-7Rα antibody is formulated for administration intravenously (*i.v.*) or subcutaneously (*s.c.*).

[0172] Provided herein are compositions comprising an anti-IL-7Rα antibody or antigen-binding portion thereof described herein having the desired degree of purity in a physiologically acceptable carrier, excipient or stabilizer. Acceptable carriers, excipients, or

stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt- forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as TWEEN®, PLURONICS® or polyethylene glycol (PEG).

[0173] In a specific embodiment, pharmaceutical compositions comprise an antibody or antigen binding portion thereof, a bispecific molecule, or a immunoconjugate described herein, and optionally one or more additional prophylactic or therapeutic agents, in a pharmaceutically acceptable carrier. In a specific embodiment, pharmaceutical compositions comprise an effective amount of an antibody or antigen-binding portion thereof described herein, and optionally one or more additional prophylactic of therapeutic agents, in a pharmaceutically acceptable carrier. In some embodiments, the antibody is the only active ingredient included in the pharmaceutical composition. Pharmaceutical compositions described herein can be useful in modulating (*e.g.*, reducing or inhibiting) IL-7 activity in a T cell (*e.g.*, pathogenic T cell) and treating a disease or disorder, such as an inflammatory disease, *e.g.*, inflammatory bowel disease.

[0174] As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. In some embodiments, the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (*e.g.*, by injection or infusion). Depending on the route of administration, the active compound, *i.e.*, antibody, immunoconjugate, or bispecific molecule, can be coated in a material to protect the compound from the action of acids and other natural conditions that can inactivate the compound.

[0175] Also provided is a pharmaceutical formulation, which improves the stability of the anti-IL-7Rα antibodies and thus, allows for their long-term storage. In some embodiments,

the pharmaceutical formulation disclosed herein comprises: (a) an anti-IL-7R antibody; (b) a buffering agent; (c) a stabilizing agent; (d) a salt; (e) a bulking agent; and/or (f) a surfactant. In some embodiments, the pharmaceutical formulation is stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 1 year, at least 2 years, at least 3 years, at least 5 years or more. In some embodiments, the formulation is stable when stored at 4°C, 25°C, or 40°C.

[0176] Buffering agents can be a weak acid or base used to maintain the acidity (pH) of a solution near a chosen value after the addition of another acid or base. Suitable buffering agents can maximize the stability of the pharmaceutical formulations by maintaining pH control of the formulation. Suitable buffering agents can also ensure physiological compatibility or optimize solubility. Rheology, viscosity and other properties can also dependent on the pH of the formulation. Common buffering agents include, but are not limited to, histidine, citrate, succinate, acetate and phosphate. In some embodiments, a buffering agent comprises histidine (*e.g.*, L-histidine) with isotonicity agents and potentially pH adjustment with an acid or a base known in the art. In some embodiments, the buffering agent is L- histidine. In some embodiments, the pH of the formulation is maintained between about 2 and about 10, or between about 4 and about 8.

[0177] Stabilizing agents are added to a pharmaceutical product in order to stabilize that product. Such agents can stabilize proteins in a number of different ways. Common stabilizing agents include, but are not limited to, amino acids such as glycine, alanine, lysine, arginine, or threonine, carbohydrates such as glucose, sucrose, trehalose, raffmose, or maltose, polyols such as glycerol, mannitol, sorbitol, cyclodextrins or dextrans of any kind and molecular weight, or PEG. In some embodiments, the stabilizing agent is chosen in order to maximize the stability of FIX polypeptide in lyophilized preparations. In some embodiments, the stabilizing agent is sucrose and/or arginine.

[0178] Bulking agents can be added to a pharmaceutical product in order to add volume and mass to the product, thereby facilitating precise metering and handling thereof. Common bulking agents include, but are not limited to, lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate, or magnesium stearate.

[0179] Surfactants are amphipathic substances with lyophilic and lyophobic groups. A surfactant can be anionic, cationic, zwitterionic, or nonionic. Examples of nonionic surfactants include, but are not limited to, alkyl ethoxylate, nonylphenol ethoxylate, amine ethoxylate, polyethylene oxide, polypropylene oxide, fatty alcohols such as cetyl alcohol or oleyl alcohol, cocamide MEA, cocamide DEA, polysorbates, or dodecyl dimethylamine

oxide. In some embodiments, the surfactant is polysorbate 20 or polysorbate 80.

[0180] In some embodiments, the pharmaceutical formulation comprises: (a) about 0.25 mg/mL to 250 mg/mL (*e.g.*, 10 to 200 mg/mL) of an anti-IL-7Rα antibody; (b) about 20 mM histidine; (c) about 260 mM sucrose; (d) about 0.5 mM DTPA; and (e) about 0.05% Tween-80; optionally further comprising 0.05 mM pentetic acid.

[0181] In some embodiments, the pharmaceutical formulation comprises about 100 mg/mL of an anti-IL-7Rα antibody in 20 mM histidine, 260 mM sucrose, and 0.05% (w/v) polysorbate 80 at pH 6.0, with an optional 0.05 mM pentetic acid.

[0182] The formulation can further comprise one or more of a buffer system, a preservative, a tonicity agent, a chelating agent, a stabilizer and/or a surfactant, as well as various combinations thereof. The use of preservatives, isotonic agents, chelating agents, stabilizers and surfactants in pharmaceutical compositions is well-known to the skilled person.

[0183] In some embodiments, the pharmaceutical formulation is an aqueous formulation. Such a formulation is typically a solution or a suspension, but may also include colloids, dispersions, emulsions, and multi-phase materials. The term "aqueous formulation" is defined as a formulation comprising at least 50% w/w water. Likewise, the term "aqueous solution" is defined as a solution comprising at least 50 % w/w water, and the term "aqueous suspension" is defined as a suspension comprising at least 50 % w/w water.

[0184] In some embodiments, the pharmaceutical formulation is a freeze-dried formulation, to which the physician or the patient adds solvents and/or diluents prior to use.

[0185] Pharmaceutical compositions described herein also can be administered in combination therapy, *i.e.*, combined with other agents. For example, the combination therapy can include an IL-7R antibody described herein combined with at least one other therapeutic agent. Examples of therapeutic agents that can be used in combination therapy can include other compounds, drugs, and/or agents used for the treatment of a disease or disorder (*e.g.*, an inflammatory disorder). Such compounds, drugs, and/or agents can include, for example, anti-inflammatory drugs or antibodies that block or reduce the production of inflammatory cytokines. In some embodiments, therapeutic agents can include an anti -IP- 10 antibody, an anti-TNF-a antibody (*e.g.*, adalimumab (HUMIRA®), golimumab (SIMPONI®), infliximab (REMICADE®), certolizumab pegol (CIMZIA®)), interferon beta-la (*e.g.*, AVONEX®, REBIF®), interferon beta- lb (*e.g.*, BETASERON®, EXTAVIA®), glatiramer acetate (*e.g.*, COPAXONE®, GLATOPA®), mitoxantrone (*e.g.*, NOVANTRONE®), non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids, and combinations thereof. In

some embodiments, therapeutic agents can include compounds, drugs, and/or agents that can induce the generation of regulatory T cells (*e.g.*, induced regulatory T cells). Non-limiting examples of such therapeutic agents include TGF-b, IL-10, IL-2, and combinations thereof.

[0186] The pharmaceutical compounds described herein can include one or more pharmaceutically acceptable salts. A "pharmaceutically acceptable salt" refers to a salt that retains the desired biological activity of the parent compound and does not impart any undesired toxicological effects. Examples of such salts include acid addition salts and base addition salts. Acid addition salts include those derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, phosphorous and the like, as well as from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl- substituted alkanoic acids, hydroxy alkanoic acids, aromatic acids, aliphatic and aromatic sulfonic acids and the like. Base addition salts include those derived from alkaline earth metals, such as sodium, potassium, magnesium, calcium and the like, as well as from nontoxic organic amines, such as N,N'-dibenzylethylenediamine, N-methylglucamine, chloroprocaine, choline, diethanolamine, ethylenediamine, procaine and the like.

[0187] A pharmaceutical composition described herein can also include a pharmaceutically acceptable anti-oxidant. Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0188] Examples of suitable aqueous and nonaqueous carriers that can be employed in the pharmaceutical compositions described herein include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0189] These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of presence of microorganisms can be ensured both by sterilization procedures, supra, and by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid,

and the like. It can also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0190] Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions described herein is contemplated. A pharmaceutical composition can comprise a preservative or can be devoid of a preservative. Supplementary active compounds can be incorporated into the compositions.

[0191] Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, the compositions can include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

[0192] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by sterilization microfdtration. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated herein. In the case of sterile powders for the preparation of sterile injectable solutions, some methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0193] The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the subject being treated, and the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the composition which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 0.01 percent to about ninety-nine percent of active ingredient, from about 0.1 percent to about 70 percent, or from about 1 percent to about 30 percent of active ingredient in combination with a pharmaceutically acceptable carrier.

[0194] Dosage regimens are adjusted to provide the optimum desired response (*e.g.*, a therapeutic response). For example, a single bolus can be administered, several divided doses can be administered over time or the dose can be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms described herein are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

[0195] In some embodiments, the anti-IL-7Rα antibody is administered at a flat dose (flat dose regimen).

[0196] In some embodiments, for administration of an anti-IL-7Rα antibody, *e.g.*, described herein, the dosage range for each dose is from about 10 mg – about 800 mg per dose, about 20 mg – about 500 mg per dose, about 50 mg – about 300 mg per dose, or about 100 mg – about 250 mg per dose.

[0197] In some embodiments, the anti-IL-7Rα antibody is administered to the subject at about 25, 50, 100, 150, 200, 250, 300, or 350 mg per dose.

[0198] In some embodiments, the anti-IL-7Rα antibody is administered at a dose based on body weight.

[0199] In some embodiments, for administration of an anti-IL-7Rα antibody, *e.g.*, described herein, the dosage ranges from about 0.1 mg/kg – about 10 mg/kg per dose, about

0.2 mg/kg – about 8 mg/kg per dose, about 0.5 mg/kg – about 5 mg/kg per dose, about 1 mg/kg – about 4 mg/kg per dose, or about 2 mg/kg – about 3 mg/kg per dose.

[0200] In some embodiments, the anti-IL-7Rα antibody is administered to the subject at about 0.2 mg/kg per dose, about 0.5 mg/kg per dose, about 1 mg/kg per dose, about 2 mg/kg per dose, about 3 mg/kg per dose, about 4 mg/kg per dose, about 5 mg/kg per dose, about 6 mg/kg per dose, about 7 mg/kg per dose, about 8 mg/kg per dose, about 9 mg/kg per dose, or about 10 mg/kg per dose.

[0201] In some embodiments, the anti-IL-7Rα antibody is administered at a fixed dose with another antibody.

[0202] Antibody is usually administered on multiple occasions. Intervals between single dosages can be, for example, weekly, bi-weekly (*i.e.*, once every two weeks), monthly, every three months or yearly. Intervals can also be irregular as indicated by measuring blood levels of antibody to the target antigen in the patient.

[0203] An exemplary treatment regime entails administration once per week, once every two weeks, once every three weeks, once every four weeks, once a month, once every 3 months or once every three to 6 months.

[0204] In some embodiments, the anti-IL-7Rα antibody, *e.g.*, those described herein, is administered once a week.

[0205] In some embodiments, the anti-IL-7Rα antibody, *e.g.*, those described herein, is administered once every two weeks.

[0206] In some embodiments, the treatment comprises 5-10 (*e.g.*, 5, 6, 7, 8, 9, or 10) consecutive doses, administered once every two weeks. For example, the treatment may comprise 5, 6, 7, 8, 9, or 10 consecutive doses, with each dose administered every two weeks apart.

[0207] In some embodiments, the antibody is administered for a period of up to 10 weeks, 13 weeks, 26 weeks, 52 weeks, 2 years, 3 years, 5 years, 10 years, or lifetime / permanently. In some embodiments, the antibody is administered as needed when there is AD symptom.

[0208] In some methods, two or more monoclonal antibodies with different binding specificities are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated.

[0209] In some methods, dosage is adjusted to achieve a plasma antibody concentration of about 0.1 – about 10 μg/mL, about 0.2 – about 9 μg/mL, about 0.5 – about 8 μg/mL, about

1 – about 7 μg/mL, about 2 – about 6 μg/mL, about 4 – about 5 μg/mL or about 5 - about 10 μg/mL.

[0210] In some methods, dosage is adjusted to achieve a plasma antibody concentration of about 2 μg/mL, about 3 μg/mL, about 4 μg/mL, about 5 μg/mL, about 6 μg/mL, about 7 μg/mL, or about 8 μg/mL.

[0211] An antibody can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the antibody in the patient. In general, human antibodies show the longest half-life, followed by humanized antibodies, chimeric antibodies, and nonhuman antibodies. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patient can be administered a maintenance regime.

[0212] Actual dosage levels of the active ingredients in the pharmaceutical compositions described herein can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions described herein employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0213] A composition described herein can be administered via one or more routes of administration using one or more of a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. Routes of administration for the anti-IL-7R antibodies described herein can include intravenous, intramuscular, intradermal, intraperitoneal, subcutaneous, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase "parenteral administration" as used herein means modes of

administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrastemal injection and infusion.

[0214] Alternatively, an antibody described herein could potentially be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally, sublingually or topically.

[0215] The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and poly lactic acid. Many methods for the preparation of such formulations are generally known to those skilled in the art.

[0216] Therapeutic compositions can be administered with medical devices known in the art. For example, in a particular embodiment, a therapeutic composition described herein can be administered with a needleless hypodermic injection device. Examples of well-known implants and modules for use with anti-IL-7R antibodies described herein include an implantable micro-infusion pump for dispensing medication at a controlled rate; a therapeutic device for administering medicaments through the skin; a medication infusion pump for delivering medication at a precise infusion rate; a variable flow implantable infusion apparatus for continuous drug delivery; an osmotic drug delivery system having multi-chamber compartments; and an osmotic drug delivery system. Many other such implants, delivery systems, and modules are known to those skilled in the art.

Combination Therapy

[0217] In some embodiments, the method described herein comprises administering to the mammalian subject a second / additional therapeutic agent effective for treating AD.

[0218] In some embodiments, the second / additional therapeutic agent comprises a topical immunomodulator. In some embodiments, the topical immunomodulator comprises a calcineurin inhibitor. In some embodiments, the topical immunomodulator comprises a PDE-4 inhibitor. In some embodiments, the topical immunomodulator comprises a JAK inhibitor (such as tofacitinib, ruxolitinib, upadacitinib, abrocitinib, and baricitinib). In some

embodiments, the topical immunomodulator comprises one or more of calcineurin inhibitor, PDE-4 inhibitor, and JAK inhibitor.

[0219] In some embodiments, the second / additional therapeutic agent comprises a systemic steroid, such as corticosteroid.

[0220] In some embodiments, the second / additional therapeutic agent comprises a topical corticosteroid.

[0221] In some embodiments, the second / additional therapeutic agent comprises tacrolimus and/or pimecrolimus.

[0222] In some embodiments, the second / additional therapeutic agent comprises phototherapy. In some embodiments, the phototherapy comprises narrow band ultraviolet B [NBUVB]. In some embodiments, the phototherapy comprises ultraviolet B [UVB]. In some embodiments, the phototherapy comprises ultraviolet A1 [UVA1]. In some embodiments, the phototherapy comprises psoralen and ultraviolet A [PUVA].

[0223] In some embodiments, the second / additional therapeutic agent comprises an allergen immunotherapy.

[0224] In some embodiments, the second / additional therapeutic agent comprises a leukotriene inhibitor.

[0225] In some embodiments, the second / additional therapeutic agent comprises an oral chemical synthetic immunomodulator. For example, the oral chemical synthetic immunomodulator may comprises one or more of: methotrexate, mycophenolate mofetil, interferon (IFN)-γ, azathioprine, cyclosporine, a systemic biologic, a systemic targeted synthetic JAK inhibitor, a topical synthetic JAK inhibitor, or a PDE-4 inhibitor.

[0226] In some embodiments, the systemic biologic comprises one or more of dupliumab, ustekinumab, tralokinumab, and nemolizumab.

[0227] In some embodiments, the systemic targeted synthetic JAK inhibitor comprises one or more of tofacitinib, ruxolitinib, upadacitinib, abrocitinib, and/or baricitinib.

[0228] In some embodiments, the topical synthetic JAK inhibitor comprises delgocitinib.

[0229] In some embodiments, the PDE-4 inhibitor comprises crisaborole.

[0230] With the general aspects and embodiments described above, the following illustrative (non-limiting) example is provided to further demonstrates specific embodiments.

EXAMPLES

Example 1: A Phase 2a, Randomized, Double-blind, Placebo-Controlled, Trial of COMPOUND A for the Treatment of Moderate to Severe Atopic Dermatitis

[0231] COMPOUND A (the antibody having the heavy chain amino acid sequence of SEQ ID NO: 23 and the light chain amino acid sequence of SEQ ID NO: 24) is a fully human, high affinity anti-interleukin-7 receptor α (IL-7Rα) antagonist monoclonal antibody (mAb) developed from human immunoglobulin transgenic mice. It exhibits high affinity as an anti-interleukin-7 receptor α (IL-7Rα) and reduced affinity to FcγR (Type I, II, or III), the receptors that mediate effector functions, and to complement component 1 (C1q), the mediator of complement cell lysis. COMPOUND A is demonstrated here as an effective treatment for atopic dermatitis.

[0232] Nonclinical pharmacology studies confirm IL-7Rα receptor occupancy (RO) and inhibition of IL-7Rα-mediated pharmacodynamic (PD) responses and T-cell mediated biology. Both interleukin (IL)-7 and thymic stromal lymphopoietin (TSLP) receptors are heterodimeric, and share the common IL-7Rα subunit.

[0233] In a Phase 1 study in healthy participants, COMPOUND A single doses up to 4 mg/kg and repeat doses of 1 mg/kg every two weeks were safe and well tolerated. Results from that Phase 1 study demonstrated that doses of COMPOUND A that achieved ≥95% receptor occupancy were associated with >90% inhibition of IL-7 signaling via phosphorylation of signal transducer and activator of transcription-5 (STAT5). Repeat administration of COMPOUND A at 1 mg/kg demonstrated durable inhibition of IL-7Rα after the 2nd dose over the 2-week dose regimen. In addition, the lymphocyte subsets and T cell immune function assessments exhibited modest, dose-dependent effects on these biomarkers. Based on the available nonclinical and Phase 1 safety data, no expected adverse events have been identified. Thus, the Phase 1 study has shown that COMPOUND A have acceptable tolerability and safety, has confirmed the expected pharmacology, and has allowed for the generation of a predictive pharmacokinetic (PK)-PD model, supporting initiation of the present Phase 2a study.

[0234] Mechanistically, COMPOUND A is a high affinity effector-minimized anti-IL-7Rα antagonist antibody that blocks the IL-7 cytokine binding to human IL-7Rα (CD127) and inhibits IL-7 receptor (IL-7R) (CD127/CD132) mediated intracellular signaling pathways. In addition to forming the heterodimeric IL-7R, the IL-7Rα chain heterodimerizes with TSLPR(CRLF2) to form a high affinity TSLP receptor (TSLPR) complex. TSLP is an

epithelial-cell-derived cytokine that promotes inflammation in response to environmental stimuli. While COMPOUND A also inhibits TSLPR activity on monocytes *in vitro*, studies to date have been focused on the effects of COMPOUND A on IL-7R -mediated activity *in vitro* and *in vivo*.

[0235] In recent years, significant progress has been made in our understanding of the complex phenotype and mechanisms that underlie AD, offering multiple new potential targets for pharmacological intervention. It is now generally appreciated that varied and diverse mechanisms generate an "immunologic march" consisting of discernible and likely overlapping stages. Of central importance, early disease is characterized by activation of the skin innate immune response alongside a core TH2-T helper cell adaptive response. Later in the disease, a widening of the adaptive immunity is evident with TH1, TH17 and TH22 responses becoming more relevant (Bieber *et al* 2021). Within this framework, TSLP and IL-7 may act as sequential mediators of AD initiation (via TH2 pathways) and progression (via TH1 and/or TH17), respectively (Gittler *et al* 2012). Thus, blocking these two cytokines may address both the acute and chronic phases of the disease.

[0236] This example demonstrates that the anti-IL7Ra antibody COMPOUND A is effective to treat atopic dermatitis in patients with moderate to severe AD, at least by Week 14 after commencement of treatment based on the dosing regimen described herein. COMPOUND A's ability for dual IL-7/TSLP blockade has potential benefits in all AD phases and could represent an important therapeutic modality considering the evolving understanding of the immunopathology underlying AD in humans.

[0237] The primary objective of the trial is to show the efficacy of COMPOUND A vs placebo at Week 14 after the commencement of the treatment, in participants with AD (*e.g.*, moderate to severe chronic atopic dermatitis). This primary objective is assessed based on the primary endpoint of mean percentage change from baseline in Eczema Area and Severity Index (EASI) score at Week 14 (as though no use of rescue therapy and as though no treatment interruption or discontinuation of treatment for any reason), for COMPOUND A vs placebo.

[0238] A secondary objective of the trial is to show the efficacy of COMPOUND A vs placebo on treating AD through 14 weeks of treatment in participants with AD. This secondary objective is assessed through analyzing a number of secondary endpoints, including:

- Mean percentage change from baseline in EASI score at Weeks 4, 8, 12, 16, and 24.
- Mean percentage change from baseline in Scoring Atopic Dermatitis (SCORAD) score at Weeks 4, 8, 12, 14, 16, and 24.
- Proportion of subjects achieving EASI 50, 75 and 90 at Weeks 4, 8, 12, 14, 16, and 24.
- Proportion of subjects achieving Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score of 0 or 1 with at least 2 grades of reduction from Baseline at Weeks 4, 8, 12, 14, 16, and 24.

[0239] Patients receiving treatment (*e.g.*, baseline COMPOUND A group) have statistically significant improvement over matched placebo control (*e.g.*, patients receiving placebo) in mean percentage change from baseline in EASI score at Week 4, 8, 12, 16, and/or 24.

[0240] Further, patients receiving treatment (*e.g.*, baseline COMPOUND A group) have statistically significant improvement over matched placebo control (*e.g.*, patients receiving placebo) in mean percentage change from baseline in Scoring Atopic Dermatitis (SCORAD) score at Week 4, 8, 12, 14, 16, and/or 24.

[0241] Further, a significant proportion of subjects achieve EASI 50, 75 and 90 at Week 4, 8, 12, 14, 16, and/or 24.

[0242] Further, a significant proportion of subjects achieve Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score of 0 or 1 with at least 2 grades of reduction from Baseline at Week 4, 8, 12, 14, 16, and/or 24.

[0243] The treatment also evaluates a number of Secondary and Exploratory Objectives and Endpoints, including:

- Mean percentage change from baseline at Weeks 4, 8, 12, 14, 16, and 24 in following Patient-Reported Outcomes (PROs)
- Peak Pruritis Numerical Rating Scale (NRS)
- Patient-Oriented Eczema Measures (POEM)
- Dermatology Life Quality Index (DLQI)
- Atopic Dermatitis Control Tool (ADCT)
- Sleep Disturbance (SD)
- Sleep Related Impairment (SRI)

- Proportion of subjects achieving improvement from Baseline at Weeks 4, 8, 12, 14, 16, and 24 in peak pruritis NRS score of ≥4 points, and
- Mean percentage change from baseline in involved Body Surface Area (BSA) at Weeks 4, 8, 12, 14, 16, and 24

[0244] Pharmacokinetics (PK) and immunogenicity of COMPOUND A in treated patients are also characterized to be desirable, based on assays including serum COMPOUND A concentrations based on Schedule of Assessments (SoA), and anti-drug antibody (ADA) rate.

[0245] Finally, the safety and tolerability of COMPOUND A are evaluated, including acceptable numbers or percentages of adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) including injection site tolerability, in view of laboratory evaluations, physical examinations, vital signs, and 12-lead electrocardiogram (ECG).

[0246] The trial described herein also includes several additional exploratory objectives and endpoints, including:

- Serum pharmacokinetics of subcutaneously administered COMPOUND A, as assessed by population PK analysis using nonlinear mixed-effects modeling
- Incidence and titer of serum anti-COMPOUND A antibodies and associated effects on PK, PD, efficacy, and safety
- Changes in whole blood IL-7Rα RO on circulating CD3+ T cells
- Changes in lymphocytes, including T and B cell subsets
- Changes in disease-specific biomarkers, which may include but are not limited to total eosinophil count, total IgE, CCL17 (TARC), CCL18 (PARC), and LDH
- Skin tape and optional skin biopsy samples will be collected for potential analysis of biomarkers related to COMPOUND A treatment responses and/or AD disease biomarkers
- Serum, plasma, PBMC, and whole blood RNA and DNA (DNA is optional) are collected and stored for potential future assessment of biomarkers related to COMPOUND A treatment responses and/or AD disease biomarkers
- To explore the relationships between PK, RO, PD, AE profiles, exploratory biomarkers, clinical laboratory data, and clinical activity of COMPOUND A

Trial Design:

[0247] The clinical study was designed as a Phase 2a, multicenter, placebo controlled, proof-of-concept trial to assess the preliminary efficacy, safety, tolerability, PK, and PD of COMPOUND A in in adult subjects with persistent moderate to severe AD. COMPOUND A or matching placebo is administered subcutaneously in the clinic setting post-randomization and every 2 weeks for a total of 7 doses. Subjects with chronic AD (duration of disease ≥3 years) as diagnosed by the Eichenfield revised criteria of Hanifin and Rajka (Eichenfield *et al* 2014, incorporated herein by reference) who have moderate to severe disease activity at the time of enrollment, and who has a history of inadequate response to previous therapy are eligible for treatment.

[0248] In a previous Phase 1 study, subcutaneous dosing of COMPOUND A or placebo was well tolerated in healthy subjects for 13 weeks following single doses up to 4 mg/kg and for approximately 18 weeks following 4 doses of 1 mg/kg administered every 2 weeks. The T lymphocyte reductions observed in healthy subjects in that Phase 1 study were not associated with any clinical adverse events and were consistent with expected changes based on the biology of IL-7 signaling and prior clinical data for similar anti-IL-7Rα mAb.

[0249] Maintenance of serum COMPOUND A concentrations ≥5 μg/mL throughout dosing is expected to result in maximal RO at the site of action in skin and corresponding clinical efficacy in AD. Preliminary population PK simulations project that a dose of 2 mg/kg administered every 2 weeks results in a median steady-state serum trough concentration of about 8.78 μg/mL. Considering the potential for increased target expression in patients with AD compared to healthy subjects, a dose of 3 mg/kg is evaluated in Part A. Steady-state is predicted to occur by approximately 10 weeks following initiation of dosing every 2 weeks; predicted steady-state exposures at 2 mg/kg fall within the range of exposures previously tested in healthy subjects in Phase 1 study, while 3 mg/kg exposures are up to approximately 40% higher than previously tested. Predicted observed maximum serum concentration after administration (Cmax) and area under the concentration time curve (AUC) are >120 times and >40 times lower than exposures observed at the no observed adverse effect level (NOAEL) of 150 mg/kg/week SC COMPOUND A in cynomolgus monkeys.

[0250] More specifically, the trial is a two-part, Phase 2a, randomized, double-blind, placebo-controlled, multi-center proof of concept study in adult subjects with persistent moderate to severe AD. Both Part A and Part B of the study have three periods: Screening up

to 4 weeks, treatment with COMPOUND A or placebo for 12 weeks, and follow-up for 12 weeks. COMPOUND A or matching placebo is administered subcutaneously (*e.g.*, in the abdomen or anterior thigh) in the clinic setting post-randomization and every 2 weeks for a total of 7 doses. Subjects with chronic AD (duration of disease ≥3 years) as diagnosed by the Eichenfield revised criteria of Hanifin and Rajka (Eichenfield *et al* 2014) who have moderate to severe disease activity at the time of consent and who have a history of inadequate response to previous therapy are eligible for the study.

[0251] After informed consent, subjects are screened for eligibility for up to 4 weeks before enrollment in the study. BSA, EASI, IGA, and other specified qualifying measures of AD disease activity are performed to determine eligibility. The pre-randomization assessments constitute the baseline reference measures. All subjects use an additive free bland emollient twice daily for 7 days or more before baseline and during the study. Subjects continue the same emollient throughout the study. Subjects who are not compliant with specified AD therapeutic exclusions for any reason during the screening period are not enrolled.

[0252] Efficacy, PK, PD, and immunology assessments are conducted at scheduled visits throughout the study. Clinical laboratory assessments, vital signs and physical examination, 12-lead ECG, and AE assessments are conducted at scheduled visits throughout the study. The study schema is provided in FIG. 1.

[0253] In more detail, in Part A, the intent is to demonstrate initial safety and generate confirmatory PK/PD data in AD subjects to support the use of a safe and pharmacologically active dose for Part B. Up to 20 eligible subjects are enrolled. Study conduct in Part A are the same as in Part B with the following exceptions:

- There are additional sparse PK sampling in Part A
- The cohorts are studied in an escalating fashion in Part A.

[0254] In Part A Cohort 1, on Day -1, a minimum of 6 subjects are randomized in a 2:1 fashion to either COMPOUND A at a dose of 2 mg/kg or placebo administered subcutaneously every 2 weeks for a total of 7 doses. Safety data from the first 6 subjects who have completed a minimum of 2 weeks of study participation are reviewed by the Safety Review Committee (SRC) to support a recommendation regarding initiation of Cohort 2. In Cohort 2, a minimum of 6 subjects are randomized in a 2:1 fashion to either COMPOUND A at a dose of 3 mg/kg or placebo administered subcutaneously every 2 weeks for a total of 7 doses.

[0255] Based on emerging data, an additional cohort (Cohort 3) is opened to evaluate COMPOUND A administered SC Q2W for a total of 7 doses, at an intermediate or lower weight-based dose with respect to Cohorts 1 and 2, or at a fixed dose with predicted exposures ≤ those at 3 mg/kg. Consistent with the other Part A cohorts, a minimum of 6 subjects are randomized to receive either COMPOUND A or placebo in a 2:1 fashion. Safety and available PK/PD data from all subjects who have completed a minimum of 2 weeks of study participation are reviewed by the SRC prior to initiation of Cohort 3.

[0256] Repeat-dose safety and available PK, RO, and clinical laboratory data from the first 6 subjects in Cohort 1 who have completed a minimum of 6 weeks of study participation are reviewed by the SRC and as necessary the same data from Cohort 2, and any additional cohorts, in order to confirm dose selection and to schedule initiation of Part B.

[0257] In Part B, subjects are randomized in a 1:1 ratio to COMPOUND A or matching placebo at the dose finalized in Part A (e.g., 200 mg COMPOUND A administered as a single 2-mL subcutaneous injection every 2 weeks) . Approximately 82 subjects are enrolled. For Part B, randomization is stratified by disease severity (EASI Score <30, ≥30) at baseline, using block randomization.

[0258] Both Part A and Part B have three periods: Screening up to 4 weeks, treatment with COMPOUND A or placebo for 12 weeks, and follow-up for 12 weeks. The total duration of the study including the Screening period is 28 weeks.

[0259] Efficacy is evaluated by assessment of clinician reported outcome measures (ClinRO), patient-reported outcomes (PRO), and disease activity assessments as defined in further detail below.

[0260] For pharmacokinetic assessments, blood samples are collected from all participants for the measurement of serum COMPOUND A concentrations using a validated immunoassay for pharmacokinetic analysis. Population pharmacokinetic model-based analysis are applied.

[0261] Immunogenicity assessments are performed by collecting blood samples from all subjects for the measurement of antibodies to COMPOUND A using a validated immunoassay for anti-drug antibody (ADA) analysis. The incidence and level of antibodies against COMPOUND A are summarized for all subjects who received at least one dose of IP.

[0262] Receptor occupancy (RO) and pharmacodynamic (PD) assessments are performed by collecting blood samples from all subjects for assessment of PD and target engagement. IL-7Rα RO on circulating T cells is evaluated to assess target engagement. Changes in

circulating lymphocytes (T, B and NK cells, T-cell subsets and B cell subsets), and changes in PD and/or disease biomarkers related to COMPOUND A treatment are also evaluated.

[0263] Safety is assessed by collecting Aes (Adverse Events), SAEs (Serious Adverse Events), AESIs (Adverse events of special interest), performing local injection site reactions and tolerability assessment, recording vital signs, performing physical examinations and 12-lead ECGs, and evaluating clinical laboratory results. Analysis of AESIs focus on 1) Injection site reactions, 2) Clinical monitoring for infection and viral surveillance studies, and 3) Reduction in lymphocyte counts. Subjects with an absolute lymphocyte count <LLN at screening are excluded. For subjects who experience a reduction in their lymphocyte count to < 800/μL, their COMPOUND A dosing are managed carefully.

[0264] Thus, the overall duration of the trial is at least 28 weeks, including screening of up to 4 weeks, treatment with COMPOUND A or placebo for 12 weeks, and follow-up for 12 weeks in Part B, which is preceded by at least 10 more weeks in in Part A, which evaluates the planned doses of COMPOUND A in Cohorts 1 and 2 at 2 mg/kg or 3 mg/kg, administered SC once every 2 weeks (Q2W), for 12 weeks (7 doses total) following 4 weeks of screening for Part A. An additional cohort may be enrolled to investigate COMPOUND A administered SC every 2 weeks, at a lower or intermediate weight-based dose with respect to Cohorts 1 and 2, or a fixed dose with predicted exposures ≤ those at 3 mg/kg Q2W Dose for Part B will be dependent on Part A data. See FIG. 1.

Dose and Frequency (Dosing Regimen)

[0265] Participants are administered either COMPOUND A or matching placebo.

[0266] COMPOUND A is formulated as 100 mg/mL drug product solution for *s.c.* injection, provided in aseptic filled, sterile, 2R borosilicate glass vials with a Flurotec serum stopper and a matte cap flip-off seal. Each vial contains an extractable volume of 2 mL COMPOUND A. That is, each dose of COMPOUND A contains 200 mg of COMPOUND A antibody, which is administered as a flat dose once every two weeks according to the Schedule of Activities (SoA) detailed below (also see FIG. 1), for a total of 7 doses. The total volume per injection is less than or equal to 2 mL. This dosing regimen (*i.e.*, 200 mg of COMPOUND A administered *s.c.* Q2W) is expected to result in steady-state serum trough concentrations >5 μg/mL, and maximum RO on circulating T cells in >90% of subjects throughout dosing. Additionally, exposures after 200 mg are predicted to fall within the range of previously tested exposures at 3 mg/kg, and is expected to be safe and well tolerated.

[0267] Specifically, following COMPOUND A doses of 2 to 3 mg/kg administered every 2 weeks, median effective half-life is approximately 17 days (95% prediction interval 7 to 40 days). Model-predicted IL-7Rα RO on circulating CD3+ T cells for the dosing regimens show complete return to baseline by Study Week 20. Therefore, considering the duration and magnitude of lymphocyte reductions observed in toxicology studies and COMPOUND A clinical study and the PK/RO model projections, the 12-week follow-up period in the Phase 2a study is considered appropriate.

[0268] Preliminary PK and RO data supports this assessment. Predicted median maximum concentration (C_{max}) at steady state (29.5 µg/mL) and AUC_{ss} (8531 µg*h/mL) in patients with AD after a dose of 200 mg SC Q2W are >100-fold and >50-fold lower, respectively, than exposures at the NOAEL of 150 mg/kg/week SC COMPOUND A in cynomolgus monkeys in the 6-month GLP study (C_{max} of 3260 µg/mL and AUC of 466,000 µg*h/mL for non-sexually mature animals, and C_{max} of 3780 µg/mL and AUC of 540,000 µg*h/mL for sexually mature animals).

[0269] The placebo is identically formulated with volume matched to active dose, and is identical in appearance to COMPOUND A. The formulations are stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with limited access to the authorized personnel until use.

[0270] TEAEs experienced by subjects, standard safety laboratory data and systematic assessment of ADAs are routinely monitored to ensure subject safety and to identify the occurrence of events that meet the criteria for IP discontinuation (see below).

Stopping Criteria

Event	**Criteria for IP Discontinuation in Any Subject**
Any TEAE	Drug-related TEAE that is Grade ≥3
Immunological TEAE	Grade ≥3 or serious immunological event of any severity
Lymphocyte counts	Absolute lymphocyte count ≤500/µL sustained for 2 weeks on repeat testing
Viral reactivation or infection	≥ Grade 3 viral reactivation or serious infection

[0271] The Sponsor conducts blinded periodic safety reviews as the study progresses described in a Safety Monitoring Plan.

Patient Inclusion Criteria

[0272] Participants meeting all of the following criteria are eligible for trial participation:

1. Age ≥18 years, inclusive, at time of informed consent, with chronic AD (duration of disease ≥3 years) diagnosed by the Eichenfield revised criteria of Hanifin and Rajka.
2. Moderate to severe disease activity at baseline and screening defined as:
    a. BSA affected ≥10%
    b. EASI Score ≥12
    c. Investigators Global Score (IGA) ≥3
3. Who have a history of inadequate response to at least one of the following:
    a. at least 4 week course of medium-potency topical steroids or other approved topical immunomodulators (calcineurin, PDE-4 and JAK inhibitors)
    b. systemic steroids or phototherapy
    c. oral chemical synthetic immunomodulators (methotrexate [MTX], mycophenolate mofetil, azathioprine, cyclosporine, systemic approved biologics [dupliumab, ustekinumab or tralokinumab]), or approved systemic targeted synthetic JAK inhibitors (upadacitinib, abrocitinib)
4. Subject has been using an additive-free bland emollient once or twice daily for at least 7 days prior to Day 1 (except on visit days before the visit) and agrees to continue using that same emollient at the same frequency throughout the study.

    Note: Every effort should be made to keep the same additive-free bland emollient throughout the study for the same body region. However, the chosen emollient may differ depending on the body region (e.g., body vs face emollient may be different).

Patient Exclusion Criteria:

[0273] Participants are ineligible for trial participation if there is any of the following criteria is met at the screening and/or Day 1 visits, as applicable:

1. Body weight ≤ 50.0 kg for men and ≤ 45.0 kg for women or >100 kg (e.g., >120 kg), at Screening.
2. Rescue therapy, topical or systemic, need anticipated within 4 weeks of randomization.

3. Have a history of, recent or current clinically serious viral, bacterial, fungal, or parasitic infection or mycobacterial infection

a. History of organ or bone marrow transplant

b. History of a primary immunodeficiency disorder

c. History of infected joint prosthesis or other implanted device remaining in place

d. History of opportunistic infection, *e.g.*, pneumocystis pneumonia

e. History of disseminated Staphylococcus aureus or Eczema herpeticum infection

4. Recent (within 2 months of informed consent) or current clinically serious viral, bacterial, fungal, or parasitic infection or mycobacterial infection including but not limited to:

a. Symptomatic *H. zoster* infection within 12 weeks prior to study entry or any history of disseminated/complicated *H. zoster* (*e.g.*, multi-dermatomal involvement, ophthalmic zoster, central nervous system involvement, postherpetic neuralgia)

b. Active *H. simplex virus* (HSV) type 1 or 2 at the time of Screening or during the screening period up to Day 1. This includes individuals who have clinically active disease and are asymptomatic on suppressive therapy

c. Positive serology for HIV type 1 or 2

d. Evidence of active HAV. Subjects with a positive HAV total antibody should have HAV IgM reflexively performed. Subjects with positive HAV IgM are excluded. If HAV IgM is not available at the time of randomization, randomization may proceed if there is a reliable history of vaccination to HAV or the subject has no clinical or laboratory evidence of HAV infection including normal liver function tests.

e. Evidence of active HCV infection. Subjects with a positive HCV antibody require reflexive HCV RNA testing. Subjects with positive HCV RNA are excluded. Subjects previously treated for HCV with positive HCV antibody, but negative HCV RNA may be enrolled with ongoing monitoring to ensure they remain negative.

f. Evidence of active HBV infection. Subjects with positive HBV surface antigen (HbsAg) are excluded. Subjects with positive HBV core antibody and negative HbsAg require reflexive testing for HBV DNA. Subjects with positive HBV DNA are excluded.

g. Evidence of active CMV or EBV infection by PCR. Note: PCR must be available and negative prior to enrollment only if clinical CMV/EBV infection is suspected

h. On any therapy for chronic infection, *e.g.*, CMV, *H. zoster*, atypical mycobacterium

5. A positive QuantiFERON®TB Gold test at Screening or history of tuberculosis (TB) unless the subject has a negative chest x-ray and has been treated with 9 months of isoniazid (INH) or appropriate therapeutic regimen per World Health Organization (WHO) or national guidelines. It is the responsibility of the Investigator to verify and document the adequacy of previous anti-tuberculous treatment. The QuantiFERON®TB Gold test may be repeated one time for subjects with an indeterminate test and subjects with two indeterminate tests may be enrolled.

6. Have been exposed to a live vaccine within 12 weeks prior to planned randomization or are expected to receive a live vaccine during the study.

7. Received a vaccine for COVID-19 (eg, RNA-based vaccines, protein-based vaccines, and nonreplicating viral vector–based vaccines) within 4 weeks before Day 1.

8. Systemic, topical, or device-based therapy of AD or immunotherapy required for any other condition except as noted:

a. allergen immunotherapy within 4 weeks before randomization; patients on a stable allergy immunotherapy regimen may be enrolled provided the therapy is continued unchanged throughout the study duration

b. leukotriene inhibitors within 4 weeks before randomization

c. systemic corticosteroids within 4 weeks before randomization

d. topical corticosteroids, tacrolimus, and/or pimecrolimus, topical JAK inhibitor or PDE-4 inhibitor within 1 week before randomization. Note: Intranasal and inhaled corticosteroids are allowed; eye and ear drops containing corticosteroids are also allowed

e. immunosuppressive/immunomodulating therapy, *e.g.*, cyclosporine, mycophenolate mofetil, interferon (IFN)-γ, azathioprine, methotrexate within 4 weeks prior to the randomization

f. any other biologic therapy for atopic dermatitis within 3 months or oral JAK inhibitors within 1 month prior to the randomization

g. phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]), within 4 weeks before randomization.

9. Have Screening laboratory results at the central laboratory that meet any of the following criteria. These may be repeated once before declaring the subject a screen failure. In addition, no subject with a clinically significant lab value and graded according to the modified Common Terminology Criteria for Adverse Events (CTCAE Version 5) laboratory abnormality greater than Grade 1, should be enrolled.

a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 × upper limits of normal (ULN).

b. Bilirubin ≥1.5 × ULN (isolated bilirubin ≥1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

c. Hemoglobin <10 g/dL

d. White blood cell (WBC) count <3.0 × 109/L

e. Platelet count <150 × 109/L

f. Total lymphocyte counts must be ≥LLN at Screening.

9. Have confirmed QTc interval >470 msec for women and >450 msec for men. Atrioventricular (AV) block, bundle branch block, intraventricular conduction delay (IVCD), or atrial fibrillation. Other clinically significant electrocardiographic findings must be discussed with the Medical Monitor prior to enrolling the subject in the study.

10. Other Screening laboratory values outside the reference range of the central laboratory for the population or investigative study site that, in the opinion of the Investigator, pose an unacceptable risk for the subject's participation in the study.

11. History or the presence of other cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, hematological, neurological, psychiatric disorders, or any other serious and/or uncontrolled disease that, in the opinion of the Investigator, could constitute a risk when taking IP or could interfere with the interpretation of data.

12. Current or history of renal disease or individual estimated glomerular filtration rate (eGFR) by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) calculation <60 mL/min at Screening (CKD-EPI Calculator).

13. Serious concomitant illness that could require the use of systemic corticosteroids or otherwise interfere with study participation or require active frequent monitoring.

14. Other concomitant skin conditions that would interfere with evaluations of the effect of study medication on atopic dermatitis (*e.g.*, scabies, seborrheic dermatitis, contact dermatitis, ichthyoses, cutaneous T-cell lymphoma, psoriasis, photosensitivity dermatoses, immune deficiency disease, erythroderma of other causes).

15. Any history of malignancy with the exception of non-melanomatous skin cancer that in the opinion of the Investigator has been appropriately treated without recurrence; or cervical carcinoma in situ that have been resected.

16. Other active autoimmune disease other than those above that would make it difficult to appropriately assess AD disease activity or pose a risk to the subject's participation in the trial

17. History of sensitivity to any of the study treatments, or components thereof, or a history of drug or other allergy that, in the opinion of the Investigator, contraindicates their participation.

18. Symptoms of presumed or documented COVID-19 infection in the past 30 days. Any history of severe COVID-19 infection defined as requiring hospitalization for treatment.

Efficacy Analyses

[0274] For efficacy assessments, both clinician reported outcome assessments and patient-reported outcomes are assessed. The former comprises assessments of the Eczema Area and Severity Index (EASI), Scoring Atopic Dermatitis (SCORAD), Validated Investigator Global Assessment for atopic dermatitis, and Body Surface Area (BSA) involvement of atopic dermatitis. The latter comprises Peak Pruritis Numerical Rating Scale (NRS), Patient-Oriented eczema measure, Dermatology Life Quality Index (DLQI), Atopic Dermatitis control tool (ADCT), and PROMIS Sleep Disturbance (SD) and Sleep Related Impairment (SRI).

Peak Pruritis Numerical Rating Scale (NRS)

[0275] The Peak Pruritus Numerical Rating Scale (NRS) is an 11-point scale to evaluate itch intensity. Subjects are asked to rate the overall severity of their itch in the past 24 hours using this scale. See Yosipovitch *et al.* (*Br J Dermatol.* 181(4):761-769, 2019, incorporated herein by reference).

Patient-Oriented Eczema Measure

[0276] The Patient-Oriented Eczema Measure (POEM) is a self-assessed, repeatable measurement tool for measuring atopic dermatitis (AD) severity. Patients answer questions about the frequency of seven symptoms: itch, sleep disturbance, skin bleeding, skin weeping/oozing, skin cracking, skin flaking, and skin dryness/roughness over the last week. The total score from this assessment reflects overall disease activity. The POEM utilizes a 5-point Likert scale for each question. POEM scores can range from 0 to 28 where lower total scores reflect lower disease activity and higher scores reflect higher disease activity. See Charman *et al.* (*Arch Dermatol.* 140(12):1513-9, Erratum in: *Arch Dermatol.* 141(3):381 (2005), 2004, incorporated herein by reference); Kido-Nakahara *et al.*, (*Acta Derm Venereol.* 100(10):adv00159, 2020, incorporated herein by reference).

Dermatology Life Quality Index (DLQI)

[0277] The Dermatology Life Quality Index (DLQI) is a self-administered questionnaire designed to measure the health-related quality of life of adult patients suffering from a skin disease. The DLQI consists of 10 questions concerning symptoms and feelings, daily activities, leisure, work, and school, personal relationships and treatment. Each question is answered by a tick box: “not at all”, “a little”, “a lot” or “very much.” Each question is scored from 0 to 3 and the scores summed, giving a range from 0 (no impairment of life quality) to 30 (maximum impairment). All questions relate “to the last week.” See Lewis and Finlay (*J Investig Dermatol Symp Proc.* 9(2):169-180, 2004, incorporated herein by reference).

Atopic Dermatitis Control Tool (ADCT)

[0278] The Atopic Dermatitis Control Tool (ADCT) is a brief patient self-administered instrument designed and validated to assess AD control; six AD symptoms and impacts are evaluated over the past week, including overall severity of symptoms, days with intense episodes of itching, intensity of bother, problem with sleep, impact on daily activities, and

impact on mood or emotions. See Simpson *et al.* (*BMC Dermatol.* 19(1):15, 2019, incorporated herein by reference).

PROMIS Sleep Disturbance (SD) and Sleep Related Impairment (SRI)

[0279] Sleep is assessed using questions about self-reported sleep duration and the Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaires for SD and SRI. PROMIS SD assesses perceptions of sleep quality, sleep depth, and restoration associated with sleep; perceived difficulties and concerns with getting to sleep or staying asleep; and perceptions of the adequacy of and satisfaction with sleep. PROMIS SRI assesses perceptions of alertness, sleepiness, and tiredness during usual waking hours, and the perceived functional impairments during wakefulness associated with sleep problems or impaired alertness. These instruments were previously validated and found to strongly correlate with both objective and other PRO measures of sleep quality. See Li *et al.* (*Dermatitis*. 29(5):270-277, 2018, incorporated herein by reference).

Eczema Area and Severity Index

[0280] The Eczema Area and Severity Index (EASI) is an Investigator-assessed instrument measuring the severity of clinical signs in atopic dermatitis (AD). See Leshem *et al.* (*Br J Dermatol.* 172(5):1353-7, 2015, incorporated herein by reference).

[0281] Investigator assesses following 4 body regions and assigns area score and severity score: Head and neck; trunk (including genital area); upper limbs; and lower limbs (including buttocks) (Hanifin *et al* 2001).

[0282] Area score is recorded for each of the four regions of the body. The area score is the percentage of skin affected by eczema for each body region.

Area score	**Percentage of skin affected by eczema in each region**
0	No active eczema in this region
1	1–9%
2	10–29%
3	30–49%
4	50–69%
5	70–89%

6	90–100%: the entire region is affected by eczema

[0283] Severity score is recorded for each of the four regions of the body. The severity score is the sum of the intensity scores for four signs. The four signs are:

- Redness (erythema, inflammation)
- Thickness (induration, papulation, swelling—acute eczema)
- Scratching (excoriation)
- Lichenification (lined skin, furrowing, prurigo nodules—chronic eczema).

[0284] The average intensity of each sign in each body region is assessed as: none (0), mild (1), moderate (2) and severe (3).

Score	Intensity of redness, thickness/swelling, scratching, lichenification
0	None, absent
1	Mild (just perceptible)
2	Moderate (obvious)
3	Severe

Scoring Atopic Dermatitis (SCORAD)

[0285] SCORAD is a clinical tool used to assess the extent and severity of eczema (SCORing Atopic Dermatitis) and includes three components: area (A), intensity (B), and subjective symptoms (C) (SCORAD index, *Dermatology* 186(1):23-31, 1993, incorporated herein by reference). The method of deriving the SCORAD score uses the following formula: SCORAD score = A/5 + B*3.5 + C. The total SCORAD score ranges between 0 and 103.

[0286] To determine extent of disease, the sites affected by eczema are shaded on a drawing of a body. The rule of 9 is used to calculate the affected area (A) as a percentage of the whole body:

- Head and neck 9%
- Upper limbs 9% each
- Lower limbs 18% each
- Anterior trunk 18%
- Back 18%
- Genitals 1%.

[0287] The score for each area is added up. The total area is 'A', which has a possible maximum of 100%.

[0288] A representative area of eczema is selected. In this area, the intensity of each of the following signs is assessed as none (0), mild (1), moderate (2) or severe (3).

- Redness
- Swelling
- Oozing/crusting
- Scratch marks
- Skin thickening (lichenification)
- Dryness (this is assessed in an area where there is no inflammation)

[0289] The intensity scores are added together to give 'B' (maximum 18).

[0290] Subjective symptoms (itch and sleeplessness) are each scored by the subject or relative using a visual analogue scale where 0 is no itch (or no sleeplessness) and 10 is the worst imaginable itch (or sleeplessness). These scores are added to give 'C' (maximum 20).

Validated Investigator Global Assessment for Atopic Dermatitis

[0291] The vIGA is an assessment scale used in clinical studies to determine severity of AD and clinical response to treatment based on a 5-point scale ranging from 0 (clear) to 4 (severe) (Simpson *et al.*, *J Am Acad Dermatol.* 83(3):839-846, 2020, incorporated herein by reference).

Body Surface Area (BSA) Involvement of Atopic Dermatitis

[0292] Body surface area affected by AD is assessed for each major section of the body (head, trunk, arms, and legs) and is reported as a percentage of all major body sections combined.

Time Period and Frequency for Collecting AE and SAE Information

[0293] An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to the IP. An AE can, therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an IP, whether considered related to the IP or not.

[0294] Events meeting the AE definition include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after IP administration that occur during the reporting periods, even though it may have been present prior to the start of the study

[0295] A treatment-emergent adverse event (TEAE) is defined as any event that occurs from the first administration of IP or an adverse event that worsens in either intensity or frequency after exposure to the IP. Events that occur from the time of consent to the administration of IP are considered pretreatment adverse events.

[0296] Subjects in whom study medication is discontinued for any reason prior to the end of the 12-week treatment period are followed for a minimum of 12 weeks after the last dose is administered. Subjects who receive rescue therapy during the follow-up period continue to be followed to the 24-week end of study.

[0297] Anticipated day-to-day fluctuations of pre-existing diseases or conditions present or detected at the start of the study that do not worsen would not be considered AEs. Laboratory results of disease/disorders being studied, or medical/surgical procedures are not AEs but rather the condition/event that leads to it are defined as an AE.

[0298] The severity of AEs is graded using the most current version of the National Cancer Institute CTCAE 5-point scale:

- Mild (Grade 1): Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate (Grade 2): Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- Severe (Grade 3): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Life-threatening (Grade 4): Life-threatening consequences; urgent intervention indicated.
- Death (Grade 5): Death related to AE.

[0299] If an AE has multiple aspects, the aspect with the highest severity will be graded.

[0300] An SAE is defined as any event that

- results in death
- is immediately life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event

[0301] An important medical event is an event that does not result in death, is not life-threatening, or does not require hospitalization; however, based upon appropriate medical judgement, these events may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

[0302] A suspected unexpected serious adverse reaction (SUSAR) is defined as an adverse reaction that is assessed as serious and related to the IP, and the nature or severity of which is not consistent with the applicable product information.

[0303] An AESI (serious or nonserious) is defined as an AE or SAE of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor could be appropriate. Following events are considered AESIs for this study and are reported using the same process as for AEs:

- Injection site reactions (also recorded on the injection site reaction CRF).
- Infection AEs including viral reactivation infections.
- Lymphopenia ≥ CTCAE Grade 3 (<500/μL) (Subesinghe *et al.*, *Rheumatology (Oxford).* 59(4):762-766, 2020).

Pharmacokinetics

[0304] In all subjects, serum samples are collected for assessment of pharmacokinetics. COMPOUND A concentrations are measured in samples from COMPOUND A-treated subjects at a central laboratory using a validated ligand-binding assay.

[0305] Population PK analysis using nonlinear mixed-effects modeling are performed to characterize COMPOUND A PK in serum and are reported separately. Non-compartmental analysis may also be performed, as feasible. Preliminary analyses are conducted during the study in support of the Part A dose confirmation objective, while maintaining blinding procedures.

Biomarkers

[0306] Blood samples are collected to assess the PD properties of COMPOUND A, which may include, but are not limited to, changes in immune cell subsets, and the treatment effect of COMPOUND A on AD disease biomarkers (including total eosinophil count, total IgE, serum CCL17(TARC), serum CCL18 (PARC), and lactate dehydrogenase [LDH]). Immune cell subsets may include, but are not limited to total T cells, helper T cells, cytotoxic T cells, total natural killer cells, and total B cells. Additional T-cell subsets are evaluated, which include, but are not limited to regulatory, naïve, memory, and regulatory T-cell subsets. Additional B cell subsets are evaluated, which include, but are not limited to transitional, naïve, and memory B cells, and plasma blast/plasma cells.

[0307] The following exploratory biomarker collections are performed:

[0308] Serum and plasma samples are collected and stored for testing of exploratory markers related to COMPOUND A treatment response. Exploratory markers may include, but not be limited to, soluble IL-7Rα, chemokines, cytokines, and/or other markers of inflammation, COMPOUND A activity, or AD disease biomarkers.

[0309] Peripheral blood mononuclear cells are separated from whole blood samples and frozen for testing at a later time for potential evaluation of additional immune cell subsets and/or immune function related to COMPOUND A treatment responses, *e.g.*, inhibition of IL7 and TSLPmediated effects.

[0310] Whole blood cell samples are collected (*i.e.*, PAXgene® tubes) and stored for potential ribonucleic acid (RNA) expression profiling of COMPOUND A treatment response. The purpose of RNA collection is to potentially evaluate the effect of COMPOUND A on transcripts related to the IL7Rα pathway (*e.g.*, immune cell signatures, IL7/TSLP pathway signatures, *etc.*). The RNA samples are utilized for genome-wide or candidate gene expression studies.

[0311] Skin tape and optional skin biopsy samples are collected for potential analysis of biomarkers related to COMPOUND A treatment responses and/or AD disease biomarkers, which may include but not limited to protein, gene expression and immunohistochemical

(biopsy only) analyses of biomarkers related to COMPOUND A treatment effects and/or AD disease biomarkers.

Genetics

[0312] A DNA sample is collected for exploratory research related to AD disease activity and/or the response to COMPOUND A. Genetic polymorphism in genes encoding drug targets or the downstream pathways may affect the efficacy and safety of the study treatment. In the event of an unusual response or observation of unexplained AEs, DNA samples are used to determine if there are any pharmacogenetic associations with drug response. As the understanding of the role of IL-7 and TSLP pathways in AD increases, additional genetic analyses may be warranted to refine the knowledge of the molecular basis of the disease, drug response, and to advance the development of novel therapeutics.

Example 2: Stability of COMPOUND A Formulation

[0313] COMPOUND A (the antibody having the heavy chain amino acid sequence of SEQ ID NO: 23 and the light chain amino acid sequence of SEQ ID NO: 24) was formulated as 100 mg/mL drug product in 20 mM histidine, 260 mM sucrose, and 0.05% (w/v) polysorbate 80 at pH 6.0. Based on ongoing long-term stability studies, this formulation has a shelf life of about 24 months when stored at -20°C (±5°C) away from direct light.

[0314] Formulation characterization studies were performed on the COMPOUND A bulk drug substance (BDS) excipients and formulation including photostability, thermal, agitation, and freeze-thaw in 2R glass vials. The studies were performed in 2R glass vials to generate formulation data in drug product container closures.

[0315] The photostability of COMPOUND A was evaluated in 2R glass vials at 10 and 60 mg/mL in the BDS formulation of 20 mM histidine, 260 mM sucrose, 0.05% (w/v) polysorbate 80, and 0.05 mM pentetic acid at pH 6.0 for up to five days at room temperature under room light. When compared to samples held at room temperature away from direct light, the appearance, protein concentration by A280, SE-HPLC, cIEF, pH, and subvisible particulates counts were similar, indicating that COMPOUND A BDS at these concentrations and formulation is stable under these light stress conditions.

[0316] The buffer histidine and excipient sucrose were shown to have good conformational stability in comparison to other buffers such as citrate, phosphate and excipients arginine and sodium chloride at pH ranges of 5.5 to 6.5. Conformation stability assessment utilized differential scanning fluorimetry to evaluate unfolding temperature and dynamic light scattering to evaluate hydrodynamic radius.

[0317] The addition of polysorbate 80 as a stabilizing surfactant in the COMPOUND A BDS was evaluated in agitation and freeze thaw studies at a protein concentration of 60 mg/mL. The study showed that agitation stress up to one week had no observable effect on aggregation or significant increase of subvisible particulates in both formulations with and without polysorbate 80. Up to 5 freeze thaw cycles at -80°C of COMPOUND A BDS at 60 mg/mL was also evaluated in formulations with and without polysorbate 80. In the freeze thaw study, an increase in subvisible particulates by micro-flow imaging (MFI) was observed in the formulation without polysorbate 80. This indicated that polysorbate 80 is an important excipient for the freeze stability of COMPOUND A.

[0318] Development stability studies of COMPOUND A in the BDS formulation at pH 5.5, 6.0, 6.5 at 10 and 60 mg/mL over 12 weeks were performed at 2-8°C, 25°C, and 40°C. The pH, SE-HPLC, cIEF, CE-SDS, and particle analysis by MFI particle counts of the samples were trended. The data shows that the samples showed similar trends across all stability conditions.

[0319] The formulation of COMPOUND A 100 mg/mL rBDS was determined by various screening studies. This formulation development was intended to explore the design space of COMPOUND A 70 mg/mL BDS formulation without implementing major changes to pH and the buffering system. Therefore, histidine buffer at pH 6.0 was tested with several excipient combinations targeting a protein concentration of 100 mg/mL. Formulation combinations tested sucrose, trehalose, mannitol, sorbitol, sodium chloride and arginine. Pentetic acid, a chelator that was part of the BDS formulation, was also evaluated and compared to ethylenediaminetetraacetic acid (EDTA). Polysorbate 80 was included with each formulation combination. Based on the results of the initial studies, it was determined that histidine buffer with sucrose/pentetic acid in polysorbate 80 had the capability to stabilize COMPOUND A at 100 mg/mL.

[0320] The formulation combination and role of pentetic acid were evaluated further. An accelerated stability study was performed comparing COMPOUND A 100 mg/mL formulations with and without pentetic acid at 40°C for 14 days and at 50°C for 7 days. The data from these studies are shown below in Tables 2-1, 2-2, 2-3, and 2-4.

Table 2-1: Accelerated stability study for COMPOUND A reformulated BDS without pentetic acid Formulation ID (100 mg/mL COMPOUND A, 20mM Histidine, 260 mM Sucrose, 0.05% polysorbate 80, pH 6.0) at 40°C

Analytical Test	**T_0**	**T1d**	**T2d**	**T3d**	**T5d**	**T7d**	**T14d**
Appearance (visible particles)	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles
% Monomer (SE-HPLC)	97%	97%	97%	97%	97%	97%	95%
% HMW	2.8%	3.0%	3.2%	3.3%	2.8%	3.2%	3.8%
% LMW	ND	ND	ND	ND	ND	ND	0.9%
% Acidic species (CEX)	41.6%	41.1%	41.0%	35.3%	38.9%	36.6%	36.4%
% Main peak (CEX)	55.0%	55.4%	53.7%	64.7%	55.9%	54.1%	46.1%
% Basic species (CEX)	3.4%	3.5%	5.3%	ND	5.2%	9.2%	17.5%
% Purity CE-SDS (NR)	98.2%	98.6%	98.8%	99.3%	99.2%	96.3%	99.1%
% Sum of minor peaks > LOQ CE-SDS (NR)	1.8%	1.4%	1.2%	0.7%	0.8%	3.7%	0.9%
% Purity CE-SDS (R)	99.4%	99.7%	99.9%	99.3%	99.1%	98.6%	99.0%
% Sum of minor peaks > LOQ CE-SDS (R)	0.6%	0.3%	0.1%	0.7%	0.9%	1.4%	1.0%
Particle size (DLS) nm	12.7	12.9	12.9	12.8	13.0	12.9	13.5
Particle size (DLS) PDI	0.26	0.26	0.25	0.26	0.27	0.26	0.26

Table 2-2: Accelerated stability study for COMPOUND A reformulated BDS with pentetic acid Formulation ID (100 mg/mL COMPOUND A, 20 mM Histidine, 260 mM Sucrose, 0.05 mM DTPA, 0.05% polysorbate 80, pH 6.0) at 40°C

Analytical Test	**T_0**	**T1d**	**T2d**	**T3d**	**T5d**	**T7d**	**T14d**
Appearance (visible particles)	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles
% Monomer (SE-HPLC)	97%	97%	97%	97%	97%	97%	95%
% HMW	2.8%	3.1%	3.3%	3.4%	3.0%	3.2%	3.9%
% LMW	ND	ND	ND	ND	ND	ND	0.9
% Acidic species (CEX)	41.4%	41.4%	41.4%	36.0%	39.0%	37.5%	37.5%
% Main peak (CEX)	56.1%	54.5%	53.3%	64.0%	56.2%	53.5%	43.2%
% Basic species (CEX)	2.5%	4.1%	5.3%	ND	4.8%	9.0%	19.3%
CE-SDS (NR)	98.7%	98.3%	98.3%	99.3%	98.5%	96.1%	98.4%
% Sum of minor peaks > LOQ CE-SDS (NR)	1.3%	1.7%	1.8%	0.7%	1.5%	3.9%	1.6%
CE-SDS (R)	99.3%	98.0%	96.5%	99.3%	98.2%	98.9%	99.0%
% Sum of minor peaks > LOQ CE-SDS (R)	0.7%	2.0%	3.5%	0.7%	1.8%	1.1%	1.0%
Particle size (DLS)	14.8%	15.2%	15.1%	15.2%	15.3%	15.4%	15.5%
Particle size (DLS) PDI	0.29	0.31	0.30	0.31	0.31	0.32	0.31

Table 2-3: Accelerated stability study for COMPOUND A reformulated BDS without pentetic acid Formulation ID (100 mg/mL COMPOUND A, 20 mM Histidine, 260 mM Sucrose, 0.05% polysorbate 80, pH 6.0) at 50°C

Analytical Test	T_0	T1d	T2d	T3d	T5d	T7d
Appearance (visible particles)	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles
% Monomer (SE-HPLC)	97%	97%	96%	95%	97%	96%
% HMW	2.8%	3.0%	3.2%	3.4%	2.1%	2.9%
% LMW	ND	ND	1.0%	1.2%	1.3%	1.5%
% Acidic species (CEX)	41.6%	41.0%	41.5%	37.7%	43.5%	45.3%
% Main peak (CEX)	55.0%	51.0%	49.1%	49.1%	44.6%	41.2%
% Basic species (CEX)	3.4%	7.9%	9.4%	13.2%	11.9%	13.6%
% Purity CE-SDS (NR)	98.2%	98.2%	98.4%	98.9%	98.8%	92.5%
% Sum of minor peaks > LOQ CE-SDS (NR)	1.8%	1.8%	1.6%	1.1%	1.2%	7.5%
% Purity CE-SDS (R)	99.4%	99.2%	98.9%	98.5%	97.1%	96.6%
% Sum of minor peaks > LOQ CE-SDS (R)	0.6%	0.8%	1.1%	1.5%	2.9%	3.4%
Particle size (DLS) nm	12.7	13.1	13.2	13.6	14.1	15.6
Particle size (DLS) PDI	0.26	0.26	0.28	0.29	0.30	0.33

Table 2-4: Accelerated stability study for COMPOUND A reformulated BDS with pentetic acid Formulation ID (100 mg/mL COMPOUND A, 20 mM Histidine, 260 mM Sucrose, 0.05mM DTPA, 0.05% polysorbate 80, pH 6.0) at 50°C

Analytical Test	T_0	T1d	T2d	T3d	T5d	T7d
Appearance (visible particles)	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles
% Monomer (SE-HPLC)	97%	97%	96%	95%	96%	95%
% HMW	2.8%	3.1%	3.4%	3.6%	2.3%	3.3%
% LMW	ND	ND	1.0%	1.2%	1.6%	1.9%

Analytical Test	T_0	T1d	T2d	T3d	T5d	T7d
% Acidic species (CEX)	41.4%	41.7%	42.3%	38.4%	45.6%	48.1%
% Main peak (CEX)	56.1%	50.9%	48.5%	49.4%	42.3%	37.9%
% Basic species (CEX)	2.5%	7.4%	9.1%	12.2%	12.2%	14.1%
CE-SDS (NR)	98.7%	98.8%	98.5%	98.2%	98.6%	91.3%
% Sum of minor peaks > LOQ CE-SDS (NR)	1.3%	1.7%	1.5%	1.8%	1.4%	8.7%
CE-SDS (R)	99.3%	99.8%	99.6%	97.2%	96.4%	95.9%
% Sum of minor peaks > LOQ CE-SDS (R)	0.7%	0.2%	0.4%	2.8%	3.6%	4.1%
Particle size (DLS)	14.8	15.2	15.3	15.4	18.1	19.9
Particle size (DLS) PDI	0.29	0.30	0.30	0.30	0.46	0.53

[0321] Due to instrument availability, a CEX method was utilized in the accelerated stability studies in place of the cIEF method that was utilized in long-term stability studies. The number of assays was also reduced to focus on assays believed to be the most stability indicating. For accelerated stability studies, protein concentration by A280 and potency by binding ELISA were not monitored whereas these tests would be conducted for all timepoints and conditions during long-term stability studies. Additionally, particle size and Polydispersity Index (PDI) by dynamic light scattering (DLS) were monitored for accelerated stability studies as the growth in particle size and/or PDI could be indicative of protein aggregation especially during accelerated stability conditions. Particle size by DLS and PDI are not part of release and stability testing panel for long term stability testing.

[0322] The presence of pentetic acid did not impact stability positively or negatively in accelerated stability studies for a period of 7 days at 50°C and for 14 days at 40°C. In

addition, the increased concentration of COMPOUND A to 100 mg/mL from 70 mg/mL did not have any impact on accelerated stability over a period of 7 days at 50°C and for 14 days at 40°C.

[0323] A freeze-thaw stability study was also performed comparing COMPOUND A 25 mg/mL formulations with and without pentetic acid for up to 5 freeze-thaw cycles. Appearance and purity testing by SEC were evaluated. The data from these studies are shown below in

[0324] Table 2-5 and 2-6.

Table 2-5: Freeze-thaw stability study for COMPOUND A reformulated BDS without pentetic acid Formulation ID (125 mg/mL COMPOUND A, 20 mM Histidine, 260 mM Sucrose, 0.05mM DTPA, 0.05% polysorbate 80, pH 6.0)

Analytical Test	T_0	1 F/T	3 F/T	5 F/T
Appearance (visible particles)	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles
% Monomer (SE-HPLC)	96.8%	96.0%	96.0%	95.8%
% HMW	3.2%	3.2%	3.2%	3.4%
% LMW	ND	0.76%	0.76%	0.77%

Table 2-6: Freeze-thaw stability study for COMPOUND A reformulated BDS with pentetic acid Formulation ID (125 mg/mL COMPOUND A, 20 mM Histidine, 260 mM Sucrose, 0.05mM DTPA, 0.05% polysorbate 80, pH 6.0)

Analytical Test	T_0	1 F/T	3 F/T	5 F/T
Appearance (visible particles)	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles	Clear and Colorless with no visible particles
% Monomer (SE-HPLC)	96.8%	95.8%	96.0%	96.0%
% HMW	3.2%	3.4%	3.2%	3.2%
% LMW	ND	0.79%	0.76%	0.78%

[0325] No instability was observed across all freeze-thaw cycles for formulations with and without pentetic acid. Both formulations at 125 mg/mL were considered stable up to 5 freeze-thaw cycles.

[0326] Based on the results from the formulation process development, pentetic acid was determined to be optional in the formulation. The formulation of COMPOUND A 100 mg/mL rBDS was determined to be 20 mM histidine, 260 mM sucrose, 0.05% polysorbate 80 at pH 6.0. The concentrated 100 mg/mL rBDS without the chelator is expected to be stable at the intended storage temperature of -20 ± 5°C for the intended duration of storage.

[0327] Furthermore, an in-use clinical compatibility study was performed during development to verify the stability of the above COMPOUND A drug product across the range of potential doses over 4 hours at ambient room temperature without light protection in the clinical presentation (polypropylene syringe and stainless-steel needles). The drug product was demonstrated to be compatible and stable with the administration materials over a 4-hour period by enzyme-linked immunosorbent assay (ELISA) analysis of binding potency, protein concentration, and size-exclusion high-performance liquid chromatography for antibody purity.

Example 3: Preliminary Results

[0328] Partly based on the interim results from Part A, the dose for Part B was selected as 200 mg COMPOUND A administered as a single 2-mL subcutaneous injection every 2 weeks (Q2W). The dose selected for Part B was based on the totality of available data for COMPOUND A as described above and also considering:

- Emerging preliminary data from Part A demonstrates acceptable clinical safety of COMPOUND A in subjects with AD following doses up to 3 mg/kg administered Q2W for a total of 7 doses.
- Flat dosing of 200 mg is predicted to achieve concentrations similar to and within the range of exposures achieved following 3 mg/kg SC administered Q2W.
- Preliminary population PK simulations project that a dose of 200 mg administered Q2W will result in a median steady-state serum trough concentration of 20.0 μg/mL and the majority of subjects maintaining concentrations >5 μg/mL throughout dosing.

Example 4: Binding properties of COMPOUND A

SPR analysis of binding to FcγR by a COMPOUND A precursor

[0329] Fcγ receptors are found on hematopoietic cells and mediate antibody-antigen-induced effector functions. These include antibody-dependent cell-mediated cytotoxicity and antibody dependent cellular phagocytosis. The binding of specific non-variable regions of

IgG1 with FcγRs expressed on immune cells mediates effector functions of the antigen-antibody complexes.

[0330] The precursor of COMPOUND A (C1GM/2hIgG1) was tested for its binding to human and monkey Fcγ receptors (types I, II, and III) by surface plasma resonance (SPR). The FcγRs screened included FcγRI (hCD64 and cynoCD64), FcγRII (hCD32a-H131 and hCD32a-R131, hCD32b, cynoCD32a, and cynoCD32b), and FcγRIII (hCD16a-V158, hCD16b-NA2, and cynoCD16) subtypes. The C1GM/2hIgG1 antibody demonstrated the expected binding profiles for human and cynomolgus monkey FcγRI, FcγRII and FcγRIII (data not shown)

Lack of binding by COMPOUND A to cynomolgus monkey and human Fcγ receptors

[0331] Three amino acid substitutions were engineered into the Fc chain of the precursor CICM/2hG1 to attenuate effector function, arriving at COMPOUND A. The mutations included a leucine to alanine substitution at position 234 (L234A), a leucine to glutamic acid substitution at position 235 (L235E), and a glycine to alanine substitution at position 237 (G237A). COMPOUND A was expressed in HEK293 and CHO cells.

[0332] COMPOUND A (1 μM) was purified from cell supernatants and assessed for binding to human and cynomolgus monkey FcγRs by SPR. The FcγRs screened included FcγRI (hCD64 and cynoCD64), FcγRII (hCD32a-H131, hCD32a-R131, hCD32b, cynoCD32a, and cynoCD32b), and FcγRIII (hCD16a-V158, hCD16b-NA2, and cynoCD16) subtypes.

[0333] The binding of COMPOUND A to all FcγRs was below detectable limits when tested at a high concentration (1 μM) (data not shown). In contrast, an IgG1-positive control antibody showed the expected high degree of binding to human FcγRI, with moderate binding to both FcγRII and FcγRIII (data not shown).

[0334] Taken together, these data confirm that the combined L234A, L235E, and G237A substitutions engineered into the Fc domain of COMPOUND A effectively minimize potential effector function.

Lack of binding by COMPOUND A to C1q

[0335] C1q binding to the Fc domain of IgG1 antibodies can mediate complement-mediated cell lysis. The ability of COMPOUND A to bind C1q was evaluated using an ELISA assay. Briefly, microtiter plates were coated with human IL-7Rα, and COMPOUND A from 2 different lots were added at varying concentrations to the coated plates, followed by

a saturating concentration of C1q purified from human serum. Bound C1q was detected with a sheep anti-human C1q antibody. Positive control included human IgG1. Positive control IgG1 showed the expected affinity for C1q; however, neither lot of COMPOUND A showed any measurable binding to C1q at concentrations of up to 1000 ng/mL (6.7 nM).

[0336] This data shows that COMPOUND A can evade C1q-mediated complement-mediated cell lysis when administered to human.

Binding properties of COMPOUND A to human and cynomolgus monkey FcRn at pH 6.0 and 7.4

[0337] Neonatal Fc receptor (FcRn), expressed on endothelial and bone marrow-derived cells, extends the half-life of IgGs by facilitating their transport out of epithelial cell endosomes (pH 6.0) where they would otherwise be degraded, and back into the bloodstream as functional immunoglobulins (pH 7.4). Endosomal recycling is facilitated by a pH shift (tight binding at pH 6.0 and low binding/high dissociation at pH 7.4) in the IgG-FcRn interaction.

[0338] The binding of COMPOUND A to a panel of human and cynomolgus neonatal Fc receptors (hFcRn and cFcRn, respectively) were assessed using a single cycle Biacore analysis. The Kd of COMPOUND A binding to human and cynomolgus monkey FcRn was 686 and 866 nM, respectively, at pH 6.0. COMPOUND A did not bind to FcRn from either human or monkey at pH 7.4. This pH-dependent shift in antigen affinity facilitates the release of complexed COMPOUND A in lysosome from lysosomal degradation. Irrelevant human IgG1 and IgG4 wild-type antibodies were run as controls.

[0339] These findings suggest that endosomal recycling is expected to enhance the biostability/half-life of COMPOUND A in vivo.

SPR analysis of binding to human and cynomolgus IL-7Rα at pH 6.0 and 7.4

[0340] COMPOUND A was evaluated for binding to purified recombinant human and cynomolgus monkey IL-7Rα via SPR. The Kd of COMPOUND A for human IL-7Rα is 1.3 nM and for cynomolgus monkey IL-7Rα is 1.7 nM at pH 7.4. The binding affinity of COMPOUND A for both human and cynomolgus monkey IL-7Rα was 4-fold weaker at pH 6.0, with Kd values of 5.3 nM for human IL-7Rα (hIL-7Rα), and 7.0 nM for cynomolgus monkey IL-7Rα (cIL-7Rα) (see Table 3 below).

Table 3: Binding Affinity of COMPOUND A to Human and Cynomolgus Monkey IL-7Rα

Target	Temperature	pH	Kd (nM)
hIL-7Rα	37°C	7.4	1.3
		6.0	5.3
cIL-7Rα	37°C	7.4	1.7
		6.0	7.0

Kd: receptor binding affinity dissociation constant; SPR: surface plasmon resonance.

[0341] These data demonstrate that COMPOUND A bound with equivalent high affinity to human and cynomolgus monkey IL-7Rα at pH 6.0 and 7.4. For both species the binding affinity was roughly 4-fold higher at pH 7.4 compared with pH 6.0. This pH-dependent shift in antigen affinity may further facilitate the release of complexed COMPOUND A from the lysosomal to avoid lysosomal degradation of COMPOUND A.

Example 5: In vitro assessment of efficacies of COMPOUND A

Receptor Occupancy and Inhibition of IL-7 Stimulated Phosphorylation of STAT5 (pSTAT5) in CD4 T Cells From Healthy Volunteers

[0342] The effect of COMPOUND A on IL-7–induced pSTAT5 expression was evaluated in $CD4^+$ T cells in healthy human volunteers (n = 3). Anticoagulated whole blood from healthy volunteers was incubated with increasing concentrations of COMPOUND A in the presence of recombinant human IL-7 (10 ng/mL). The percentage of pSTAT5 in $CD4^+$ T cells was measured by flow cytometry using fluorescent probes for $CD3^+$, $CD4^+$, $CD45RA^+$, and pSTAT5.

[0343] COMPOUND A showed potent inhibition of pSTAT5 on naïve $CD4^+$ T cells from all 3 healthy volunteers (n = 3) with mean IC_{50} values of 0.16 to 0.27 nM (23.7 to 40.4 ng/mL, respectively).

Inhibition of pSTAT5 in Naïve CD4+ and CD8 T-Cells From Healthy Volunteers

[0344] COMPOUND A was evaluated for target engagement and inhibition of IL-7 induced IL-7R signaling on human T cells from normal healthy volunteers. Freshly drawn blood was incubated ex vivo with IL-7 (100 ng/mL) for 15 minutes, and pSTAT5 levels were measured by flow cytometry.

[0345] As shown in Table 4, COMPOUND A potently inhibited IL-7–induced phosphorylation of STAT5 in naïve ($CD45RA^+$) and memory ($CD45RA^-$) T cells (both CD4

and CD8 phenotypes) from normal healthy volunteers with IC50 values ranging between 0.38 and 0.54 nM (equivalent to about 57 to 81 ng/mL).

Table 4: Inhibition of IL-7–Induced pSTAT5 in T Cells by COMPOUND A (IC_{50} in nM)

	IC_{50} (nM)			
	$CD4^+CD45RA^+$	**$CD4^+CD45RA^-$**	**$CD8^+CD45RA^{+a}$**	**$CD8^+CD45RA^{-a}$**
NHV (n = 19)	0.54±0.32	0.52±0.35	0.42±0.29	0.38±0.30

Abbreviations: IC_{50}: half maximal inhibitory concentration; NHV: normal healthy volunteers; CD45RO: marker of naïve CD3+ T cells.

[a] IC_{50} values were calculated only when CD8 T cells responded to IL-7.

COMPOUND A is an IL-7R antagonist antibody with no partial agonist activity

[0346] To determine if COMPOUND A had any partial agonist capabilities, whole blood or purified peripheral blood monocyte cells (PBMCs) were collected from healthy volunteers (n = 3). COMPOUND A was incubated in each matrix at 8 concentrations ranging from 1 to 100 nM. Signal transduction was assessed by AlphaLISA® SureFire®Ultra™ pSTAT5 to detect pSTAT5. Negative control used a non-targeting IgG isotype, and the positive control was IL-7 (2 nM). IL-7 increased pSTAT5 levels by an average of 4.7-fold (±1.6) and 21.1-fold (±2.8) in whole blood and PBMCs, respectively. No significant induction of pSTAT5 was observed at any concentration of COMPOUND A (1, 2, 3, 6, 13, 25, 50, or 100 nM) in either whole blood or PBMCs, demonstrating that COMPOUND A is a full antagonist at the IL-7R with no partial agonist activity. These data are presented in Table 5.

Table 5. COMPOUND A is an Antagonist With no Intrinsic Partial Agonist Activity

COMPOUND A (nM)	Peripheral blood mononuclear cells					
	Donor 1		Donor 2		Donor 3	
	pSTAT5 AlphaLISA units	pSTAT5 % control (IL-7)	pSTAT5 AlphaLISA units	pSTAT5 % control (IL-7)	pSTAT5 AlphaLISA units	pSTAT5 % control (IL-7)
100	786	1.73	1836	6.32	1083	1.53
50	868	2.48	915	0.47	1386	3.16
25	894	2.72	1072	1.46	1333	2.88
13	1038	4.03	1060	1.39	1373	3.09
6	941	3.14	1031	1.21	1476	3.65
3	938	3.12	1467	3.98	1711	4.91
2	896	2.73	1075	1.49	1582	4.22
1	1174	5.28	1467	3.98	1787	5.32
0	597	0.00	841	0.00	797	0.00
Isotype ctrl	934	3.09	1174	2.12	1325	2.84
IL-7 (2 nM)	11520	100	16575	100.00	19406	100.00
COMPOUND A (nM)	Whole blood					
	Donor 4		Donor 5		Donor 6	
	pSTAT5 AlphaLISA units	pSTAT5 % control (IL-7)	pSTAT5 AlphaLISA units	pSTAT5 % control (IL-7)	pSTAT5 AlphaLISA units	pSTAT5 % control (IL-7)
100	14704	-5.39	1055	-1.99	8328	-9.41
50	17982	-0.55	1001	-2.87	9524	-4.13
25	16463	-2.79	1140	-0.62	11526	4.71
13	15041	-4.90	1031	-2.37	11212	3.33
6	19004	0.97	976	-3.26	10891	1.91
3	15281	-4.54	958	-3.55	9132	-5.86
2	21046	3.99	1016	-2.62	14779	19.08
1	17489	-1.27	1045	-2.16	10224	-1.04
0	18350	0.00	1178	0.00	10459	0.00
Isotype ctrl	18648	0.44	952	-3.65	14024	15.74
IL-7 (2 nM)	85954	100	7371	100	33102	100.00

COMPOUND A Inhibits TSLP-Induced TARC Production by PBMCs

[0347] Thymus-activated regulated chemokine (TARC, also known as CCL17) is an important chemokine released from monocytes and dendritic cells in response to thymic stromal lymphopoietin (TSLP) stimulation. TARC drives the maturation of dendritic cells and their production of IL-23 as well as the proliferation of $CD4^+$ T cells. TSLP is highly expressed in atopic dermatitis (AD) skin lesions. Signaling through IL-7Rα/TLSPR and IL-7Rα/CD132 has been demonstrated to produce additive inflammatory effects.

[0348] COMPOUND A binds to the IL-7Rα subunit that is common to both the IL-7 receptor (IL-7Ra/CD132) and the TSLP receptor complex (IL-7Rα/TSLPR). COMPOUND A

inhibited TSLP-induced production of TARC from PBMCs enriched for monocytes (3 independent assays with 1-2 donors) with an average IC_{50} of 2.9 nM (428 ng/mL).

[0349] Thus, in addition to blocking IL-7–induced signaling, COMPOUND A also inhibits TSLP induced signaling at low nM concentrations.

Example 6: Assessment of efficacies of COMPOUND A in humanized mouse model

Efficacy of COMPOUND A in a Humanized Mouse Graft versus Host Disease Model

[0350] Graft-versus-host disease (GvHD) is a systemic disease, and skin is often one of the target organs.

[0351] COMPOUND A was evaluated with prophylactic treatment in a humanized non-obese diabetic severe combined immune deficiency-mice with a humanized immune system (NOD-SCID-IL2rγ^{null} [Hu-NSG]) mouse model of GvHD. NSG mice are immunodeficient due to the lack of mature murine lymphocytes and natural killer (NK) cells, which allows human peripheral blood mononuclear cells (PBMCs) to engraft with high efficiency. NSG mice were injected intravenously (IV) with human PBMCs that engrafted and led to the development of a robust xenogeneic-GvHD response, reproducing many aspects of the human disease.

[0352] A reference IL-7Rα antagonist antibody (A3312F, which epitope residues appear to include all epitope residues of COMPOUND A) was evaluated in 2 treatment regimens (prophylactic and therapeutic modes), and the data from the prophylactic regimen was presented herein, with A3312F serving as a positive control for COMPOUND A in this model of GvHD.

[0353] In the prophylactic treatment study, COMPOUND A, administered subcutaneously twice weekly (5 mg/kg) for 3 weeks starting on Day (-1) (the day before adoptive PBMC transfer) to NSG mice (n = 7 females), showed robust inhibition of GvHD as demonstrated by a reduction in body weight loss, inflammatory cytokine expression, and immune cell proliferation (see FIGs. 2A-2C). A3312F, tested in the same study, showed comparable efficacy to COMPOUND A.

[0354] In a separate experiment, target engagement was assessed by evaluating the level of pSTAT5 in cells from whole blood and spleens. COMPOUND A treatment (0.2, 1, or 5 mg/kg 2×/week SC) was initiated 5 days after human PBMC transfer to NSG mice. Whole blood and spleens were collected 72 and 120 hours, respectively, after the fourth dose of COMPOUND A. Cells were collected and stimulated with human IL-7 for 15 minutes, and pSTAT5 levels were analyzed in human $CD4^+$ and $CD8^+$ T cells by flow cytometry.

COMPOUND A demonstrated complete target engagement and inhibition of IL-7–induced pSTAT5 at 1 and 5 mg/kg treatments (see FIG. 3A-3B). This confirms that inhibition of IL-7Rα signaling with COMPOUND A is protective in a humanized mouse model of GvHD and that complete target engagement can be achieved.

[0355] In several related experiments, a mouse surrogate antibody (SB14) was used to further assess the role of IL-7Rα inhibition to treat other disease indications in mouse models of such disease indications (COMPOUND A was not used in these experiments partly because COMPOUND A does not cross-react with the mouse IL-7Rα (data not shown)). Collectively, these additional *in vivo* studies demonstrated that short-term inhibition of IL-7Rα signaling provides a durable, efficacious response, and suggested the potential for an infrequent dosing paradigm to sustain clinical efficacy. Furthermore, it demonstrated the importance of IL-7R signaling in driving T cell-mediated disease processes.

[0356] Interestingly, in at least one such disease model, a different inhibitor of T cell activation, CTLA4-Ig, did not exhibit efficacy in that disease model using the same treatment strategy (data not shown), thus demonstrating a clear differentiation between anti-IL-7Rα mAb and CTLA4-Ig treatment, and highlighting the potential for a durable, drug-free response with IL-7Rα mAb treatment.

Example 7: Pharmacokinetics/Pharmacodynamics (PK/PD) in Cynomolgus Monkeys

Single-dose intravenous pharmacokinetics and pharmacodynamics

[0357] This study was conducted to compare the PK and PD profiles of low doses of COMPOUND A with a reference positive control IL-7Rα antagonist antibody (A3312F) when administered to cynomolgus monkeys, and to provide data to support the use of COMPOUND A in humans. COMPOUND A and A3312F were administered by IV injection at doses of 0 (vehicle), 0.1 (low dose), 0.5 (mid dose), or 3.0 (high dose) mg/kg to groups of 1 or 2 monkeys per sex. All doses were administered at 1 mL/kg in a vehicle/carrier consisting of 20 mM histidine, 260 mM sucrose, 0.05 mM diethylenetriaminepentaacetic acid (DTPA), and 0.05% Tween 80, pH 6.0.

[0358] Criteria for PD evaluation included total and soluble IL-7R levels in blood and plasma, inhibition of IL-7–induced pSTAT5, receptor occupancy (RO), and peripheral lymphocyte phenotyping. Pharmacokinetic endpoints included AUC, C_{max}, and T_{max} and immunogenicity endpoint included anti-drug antibody (ADA).

[0359] On Day 1, 100% RO was achieved at 4 hours after dosing and maintained on Days 2-4 at all doses for both COMPOUND A and A3312F. The vehicle control group consistently

exhibited no RO for the duration of the study. RO decreased for the remainder of the study, starting with the low dose of A3312F falling below 95% RO on Day 4, while the other drug-treated groups maintained 100% RO. On Day 7, the RO of both low dose groups fell below 50%. On Day 10, the RO of low dose of A3312F returned to vehicle control levels, the mid dose below 50% and the high dose below 90%. The low dose of COMPOUND A also returned to vehicle control, while the mid dose averaged below 50% (with variability), and the high dose remained at 100% RO. On Day 14, all A3312F dose groups returned to vehicle control levels (no RO), whereas the COMPOUND A low and mid doses both returned to vehicle levels but the high dose of COMPOUND A maintained >50% RO. All doses for both COMPOUND A and A3312F were comparable to vehicle control levels by Day 17.

[0360] Cynomolgus monkey IL-7–induced pSTAT5 was strongly inhibited by both COMPOUND A and A3312F. The low dose of 0.1 mg/kg showed notable inhibition of pSTAT5 (≥80%) at early time points (Days 1-3) with COMPOUND A being slightly more effective than A3312F. The intermediate dose of 0.5 mg/kg COMPOUND A was more effective than A3312F at maintaining complete inhibition of pSTAT5 through Day 5, with an approximate 4-fold higher suppression on Day 5. At the high dose of 3 mg/kg, complete inhibition of pSTAT5 activity was sustained through Day 8 with COMPOUND A treatment, while A3312F treatment demonstrated lesser inhibition of pSTAT5 over the same time period. Moreover, COMPOUND A at Day 11 continued to substantially inhibit IL-7 induced pSTAT5 while A3312F exhibited a complete loss of this inhibitory activity.

[0361] Both mean total (blood) and soluble (plasma) IL-7R concentrations, which encompass both free and bound IL-7R, increased after administration of COMPOUND A and maximum levels were generally reached by 8 to 11 days. Mean soluble (plasma) IL-7R concentrations increased to a greater extent compared to total (blood) IL-7R levels. The cell surface IL-7R levels measured using flow cytometry did not significantly change after COMPOUND A or A3312F administration, suggesting that decreased elimination of soluble IL-7R– COMPOUND A complexes is the cause for increase in total IL-7R levels in blood.

[0362] On Day 8, there was a trend of reduction in peripheral lymphocytes as compared to baseline in both COMPOUND A and A3312F treated animals, which was most prominent at the highest dose (3 mg/kg). However, no overt differences in peripheral lymphocyte subsets were observed for either COMPOUND A or A3312F during the study. There was variability in lymphocyte populations among animals in the same group, however, suggesting that the variability may be due to stress (*i.e.*, handling of the monkeys, *etc.*) and the study's small sample size per dose group (n = 3).

[0363] COMPOUND A exposure was evaluated after single IV doses of ≤3 mg/kg and compared to A3312F. Mean exposures (AUCs) at 3 mg/kg in the first week, before anti-drug antibody (ADA) formation, were higher for COMPOUND A compared to A3312F with a mean AUC from 0 extrapolated to infinity (AUC_{inf}) ≤287 µg*day/mL and AUC_{inf} ≤135 µg*day/mL, respectively) (see Table 6). ADA formation was accompanied by concomitant accelerated decline of serum concentrations, RO, and inhibition of pSTAT5 for COMPOUND A and A3312F.

Table 6. Mean Serum COMPOUND A and A3312F Pharmacokinetic Parameters

Parameter	COMPOUND A IV dose (mg/kg)			A3312F-IV dose (mg/kg)		
	0.1	**0.5**	**3**	**0.1**	**0.5**	**3**
C_{max} (µg/mL)[a]	3.1	12.4	79.1	2.61	12.5	71
T_{max} (h)[a]	0.5	0.5	0.5	0.5	0.5	0.5
AUC_{inf} (µg*day/mL)[b]	3.7	33.3	287.2	2.4	19.4	134.9
CL (mL/h/kg)[a]	1.15	0.64	0.44	1.76	1.16	0.94

Abbreviations: AUC_{inf}: area under the concentration-time curve from 0 extrapolated to infinity; C_{max}: maximum plasma concentration; CL: clearance; IV: intravenous; PK: pharmacokinetic; T_{max}: time of maximum plasma concentration.

[0364] ADAs were detected in all monkeys dosed with COMPOUND A. ADAs were detected in 3, 3, and 2 of 3 monkeys dosed with A3312F at 0.1, 0.5, and 3 mg/kg, respectively, by Day 11. The presence of ADAs led to generally lower serum COMPOUND A and A3312F concentrations and lower individual COMPOUND A and A3312F systemic exposures on and after Day 11 (240 hours post dose) in all monkeys.

[0365] In summary, COMPOUND A and A3312F were well tolerated by monkeys after single IV doses of up to 3 mg/kg. There were no drug-related clinical observations or effects on body weight observed during the study. Good correlation was observed between the inhibition pSTAT5 in the CD4+CD45RA+ T cell population and serum concentration of anti-human IL-7R antibodies. More than 95% RO resulted in 90% inhibition of pSTAT5. The inhibition of pSTAT5 levels, a proximal biomarker of IL-7R signaling, by COMPOUND A was similar but more prolonged than that by A3312F and suggests that COMPOUND A exhibits improved PK, but similar *in vivo* potency compared to A3312F. No significant change in lymphocyte phenotypes was observed for either COMPOUND A or A3312F after a single-dose administration. Despite the impact of ADAs on COMPOUND A's concentration, meaningful exposure and evaluation of toxicological endpoints were achieved.

Single-dose subcutaneous pharmacokinetics and pharmacodynamics

[0366] Systemic toxicokinetic profile, tolerability, RO, and PD changes as a measure of target engagement, assess immune responses was determined for subcutaneous (SC) administration of COMPOUND A at doses of 0 (vehicle), 3, and 30 mg/kg to groups of 2 male and 2 female cynomolgus monkeys. Criteria for PD evaluation included assessments of IL-7–induced pSTAT5, IL-7 RO, peripheral blood lymphocyte phenotyping (T cell, B cell, and NK cell [T/B/NK]), T cell-dependent antibody response (TDAR) to keyhole limpet hemocyanin (KLH) immunization, and total and soluble IL-7R levels.

[0367] In the 3 mg/kg SC dose group, the RO was 100% through Day 8, 98% on Day 11, 16% on Day 15, 12% on Day 22, and below the limit of quantitation (BLQ) on Day 36. In the 30 mg/kg SC dose group, RO was 100% through Day 11, 70% on Day 15, and BLQ on Day 22.

[0368] Inhibition of IL-7–induced pSTAT5 on CD3+ T cells was observed in all dose groups, 4 hours post dose (between 92% and 99% mean inhibition), indicating significant PD activity. In the 3 mg/kg SC group, the mean % pSTAT5 levels were 100% through Day 8, 79% on Day 11, and returned to baseline levels on Day 22. In the 30 mg/kg SC dose group the % pSTAT5 inhibition was 100% through Day 11, 30% on Day 15, and returned to baseline on Day 22. Inhibition of pSTAT5 generally correlated with the degree of IL-7 RO and systemic exposure of COMPOUND A that was decreased due to the presence of ADAs in all monkeys by Day 11.

[0369] Mean exposures ($AUC_{0\text{-}336h}$ and C_{max}) generally increased approximately dose-proportionally by SC injection between 3 and 30 mg/kg. No substantial sex differences were noted. The systemic exposure after a single SC dose of 3 mg/kg was comparable to that after a single IV dose of 3 mg/kg, and the bioavailability was 78% by calculating with the first week data.

[0370] Overall, COMPOUND A was well tolerated by monkeys after a single SC dose ≤30 mg/kg ($AUC_{0\text{-}336h}$ ≤61,314 μg*h/mL). COMPOUND A–related PD activity was noted at all doses, as demonstrated by inhibition of IL-7–induced pSTAT5, and generally correlated with IL-7 RO and COMPOUND A exposure, which was decreased due to the presence of ADAs in all monkeys by Day 11. Decreased lymphocyte subpopulations observed as early as on Day 8 was consistent with hematology findings of decreased lymphocytes (at ≥3 mg/kg SC). Despite the impact of ADAs on COMPOUND A's concentration, meaningful exposure and evaluation of toxicological endpoints were achieved.

Six-week intermittent-dose (QW) SC toxicity study with an 8-week recovery period

[0371] COMPOUND A was administered SC once weekly at doses of 0 (vehicle), 2, 10, or 50 mg/kg to groups of 5 monkeys per sex. Scheduled necropsies were conducted after 6 weeks of dosing (7 doses) (3/sex/group) and after an 8-week recovery period (2/sex/group).

[0372] At all doses near-complete (>95%) inhibition of IL-7 induced pSTAT5 on CD3+ T cells (PD activity) and near-complete (≥98%) IL-7 RO on CD3+ T cells (target engagement) were observed at 4 hours post dose on Day 1 through Day 8. Recovery of pSTAT5 and loss of IL-7 RO were noted on Day 22 and correlated with decreased systemic exposures to COMPOUND A due to the presence of higher levels of ADAs. Overall, target engagement and PD activity correlated with sustained systemic exposures in monkeys with minimal or no ADA responses.

[0373] At all doses, there were decreases in total T (as low as 0.51× relative to vehicle control group mean), helper T (CD4+, as low as 0.51×), and cytotoxic T (CD8+, as low as 0.48×) cells on Day 8 consistent with the hematology findings of a decrease in total lymphocyte counts on Day 8, but no decrease in B and NK cells. Due to reduced systemic exposures of COMPOUND A as a result of ADA, T cell subset counts returned to baseline levels by Day 22 with the exception of the highest dose group of 50 mg/kg in which drug levels remained in circulation. In the 50 mg/kg dose group, the decreases in T cell subsets were maintained through the end of the recovery period (Day 97/99) and consistent with drug maintained in circulation.

[0374] After doses up to 50 mg/kg, there were no COMPOUND A–related changes in qualitative and quantitative electrocardiographic evaluations. Additional examinations demonstrated no COMPOUND A–related changes in neurological endpoints, respiratory rates, body temperatures, evaluations of lung sounds and mucus membrane color, and arterial oxygen saturation determinations.

[0375] Overall, COMPOUND A was well tolerated by monkeys for 6 weeks at SC, once weekly doses of 2, 10, or 50 mg/kg. SC toxikinetic profile was approximately dose-proportional on Day 1 across the dose range tested but was later affected by the development of ADA in most animals. High-dose animals maintained exposure, albeit variable, allowing for meaningful interpretation of toxicological endpoints and the definition of a NOAEL. At all doses, PD activity (inhibition of IL-7 induced pSTAT5) generally correlated with IL-7 RO (target engagement) and COMPOUND A exposure and was decreased due to high levels of ADAs (more prominently at the lower doses).

Three-month repeat dose toxicity study of COMPOUND A by subcutaneous injection with a 6-month recovery period

[0376] COMPOUND A was administered SC once weekly at doses of 0 (vehicle), 10, 50, and 150 mg/kg to groups of 5 monkeys per sex.

[0377] During Week 1 of the ECG evaluations, 7 ventricular premature complexes (VPCs) were observed in 1 male monkey over a 10-second interval in the high dose group (150 mg/kg QW). The relationship of the VPCs to COMPOUND A is unclear for the following reasons: VPCs were observed in only 1 of 30 animals in this study; and VPCs can be an incidental finding in naïve cynomolgus monkeys (~8% of animals with 1 minute ECGs performed 2 weeks apart) as well as spontaneous incidence over time can be quite variable and their occurrence sporadic when evaluated over 24 hours. Additionally, there were no histologic correlations or QT/QTc interval changes to predispose this animal to ventricular arrhythmias. The presence of VPCs in this animal was not associated with any clinical signs and hence the arrhythmia was not considered adverse.

[0378] Overall, administration of COMPOUND A to cynomolgus monkeys, administered by weekly subcutaneous injection for 3 months was well tolerated at doses of 10, 50, and 150 mg/kg. Greater than 95% RO was maintained at 50 mg/kg (7/10 animals) and at 150 mg/kg (10/10 animals) through the 3-month dosing phase. Loss of >95% RO at 10 mg/kg (9/10 animals) and 50 mg/kg (3/10 animals) was observed on Day 29 or Day 57 and correlated with detectable ADA. A decline in CD4+ and CD8+ T cell populations were observed, with the largest impact on naïve and CM T-cells at doses of COMPOUND A ≥50 mg/kg. These reductions are related to the pharmacological effects of COMPOUND A and were generally correlated with observed RO. Total T lymphocyte counts, T cell subsets and B cells were partially or completely recovered to baseline in the males, but decreases in T lymphocyte counts, T cell subsets and B cells were maintained with minimal or no recovery in female monkeys, which are generally correlated with observed durability of RO. There were no histological correlations with the decreased lymphocytes at end of the recovery phase.

[0379] Exposure of COMPOUND A was maintained ≥60,800 μg*h/mL through the dosing phase in 7/10 animals at 50 mg/kg and 10/10 animals at 150 mg/kg despite detectable ADA. Based on the non-adverse nature of the COMPOUND A–related pathology changes at the end of the dosing period, the no-observed-adverse-effect level (NOAEL) was considered to be 150 mg/kg, the highest dose tested. At the phase NOAEL, the mean C_{max} and AUC sex combined values were 3570 μg/mL and 314,000 μg*h/mL, respectively.

Six-month study of COMPOUND A by subcutaneous injection in sexually mature and not sexually mature cynomolgus monkeys with an 8-month recovery period (ongoing)

[0380] COMPOUND A was administered SC weekly at doses of 0 (vehicle), 25, 50, and 150 mg/kg to groups of sexually mature and not sexually mature monkeys. Scheduled necropsy was conducted after 6 months of dosing (27 doses) (2-4/sex/group) and after an 8-month recovery period (1-2/sex/group). All doses were administered at 1 mL/kg in a vehicle/carrier consisting of 20 mM histidine, 260 mM sucrose, and 0.05% PS80, pH 6, which is consistent with the clinical formulation.

[0381] In the dosing phase, low signals of anti–COMPOUND A antibody (most below 10,000 mean signal responses) were detected in 10 of 12 animals in the control groups as observed in the control animals in the 3-month GLP study. Similarly, it was determined that the bridging method used to detect the presence of ADAs in serum can detect ADA against all parts of the COMPOUND A molecule, including the human IgG1 Fc region and the complementarity determining regions. No adverse clinical signs were observed in the 10 control animals with detectable ADA. In addition, COMPOUND A exposure was not detected in the control animals; thus, the reason for the detected ADA in control animals was determined to be unlikely related to COMPOUND A exposure but rather possibly due to generic reactivity to IgG of unknown etiology.

[0382] In the thymus, decreased lymphoid cellularity was observed in the thymus of sexually mature males administered ≥25 mg/kg (mild to moderate), and sexually mature females and not sexually mature males and females administered ≥50 mg/kg (moderate to marked), correlating with decreased thymus weights (absolute and relative to body and brain weights), small thymus size noted macroscopically, and decreases in lymphocyte counts. The COMPOUND A–related decreased lymphoid cellularity observed in the thymus and associated hematology effects during the dosing phase of the study were considered non-adverse because of the low incidence and severity of the changes. There were no significant differences between the findings noted in not sexually mature and sexually mature animals. To date, no effects on reproductive organs have been observed in general toxicology studies.

[0383] Systemic exposure of COMPOUND A was mostly independent of sex or sexual maturity. At 25 mg/kg, exposure disparities were observed, likely due to ADA presence. Systemic exposure ($AUC_{0\text{-}t}$ and C_{max} values) generally increased with increasing dose in an approximately dose-proportional manner with a mean accumulation ratio ranging

approximately 2- to 5-fold from Day 1 to the end of the dosing phase. Exposure of COMPOUND A was maintained at ≥141,000 µg*h/mL on Day 92 throughout the dosing phase in 22 of 28 animals at ≥50 mg/kg despite detectable ADA.

[0384] In summary, weekly SC administration of COMPOUND A to not sexually mature and sexually mature cynomolgus monkeys for 6 months at dose levels of 25, 50, and 150 mg/kg was well tolerated. The NOAEL was considered to be 150 mg/kg/week. At the NOAEL, the mean C_{max} and AUC_{0-t} values for not sexually mature animals (sex combined) were 3260 µg/mL and 466,125 µg*h/mL, and for sexually mature animals (sex combined) were 3780 µg/mL and 540,200 µg*h/mL, respectively, after 6 months of SC weekly dosing. This corresponds to >50-fold greater than the projected steady-state Cmax (Cmax,ss) and steady-state AUC over the dosing interval ($AUC_{tau,ss}$) of the proposed dose of 200 mg COMPOUND A for Phase 2 studies. The preliminary data reported here are considered sufficient to support the dose frequency, dosing duration, and dose regimen in Phase 2 studies.

Example 8 Phase 1, double-blind, placebo-controlled, single and multiple ascending dose study to assess the safety, PK, and PD of COMPOUND A after SC administration in healthy subjects

[0385] The example demonstrates that COMPOUND A is safe and well tolerated in healthy human subjects (male and female subjects aged 18 to 50 years old). Further, PK studies based on the data collected in these healthy human subjects show that COMPOUND A can be administered at relatively low doses and still achieve high receptor occupancy (RO) with respect to the IL-7R receptor. Additional analysis revealed that COMPOUND A administration in healthy human subjects led to minimal ADA host response due to the low immunogenecity of COMPOUND A.

[0386] For Part 1, SAD (single ascending dose) study, the protocol defined up to 6 cohorts of 8 subjects per cohort. In each cohort, subjects were randomly assigned in a 3:1 ratio to receive either COMPOUND A or matching placebo. SAD cohort 6 was optional and was not utilized. A minimum of 7 dosed subjects evaluable for safety were required for each cohort in order to escalate to the subsequent cohort. The 5 SAD cohorts dosed in the study were 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 2 mg/kg and 4 mg/kg.

[0387] For Part 2, MAD (multiple ascending dose) study, the protocol defined up to 3 cohorts of 8 subjects per cohort. In each cohort, subjects were to be randomly assigned in a 3:1 ratio to receive either COMPOUND A or matching placebo. In the end, MAD Cohorts 2

and 3 were not enrolled per termination decision due to COVID-19 caseload and COVID-19 operational concerns where the study was being conducted.

[0388] Overall, the PD analyses demonstrated that COMPOUND treatment at doses that achieved ≥95% RO also demonstrated >90% inhibition of IL-7 signaling via phosphorylation of STAT5 (FIGs. 4A-4B). Single doses of COMPOUND A administered at 2 mg/kg or higher demonstrated sustained full RO for at least 2 weeks. Repeat administration of COMPOUND A at 1 mg/kg demonstrated durable saturation of IL-7Rα after the second dose (see FIG. 4A). In addition, the lymphocyte subsets and T cell immune function assessments demonstrated modest, dose-dependent effects on these biomarkers, consistent with the expected pharmacology when COMPOUND A fully occupies IL-7Rα. An attenuation of T-dependent antibody responses to a neo-antigen was observed at dose levels where full RO was maintained over the evaluation period while the impact of COMPOUND A treatment on delayed-type hypersensitivity (DTH) responses to a recall antigen was more variable.

[0389] The presence of ADA against COMPOUND A in human serum samples from treated subjects in phase 1 was measured using a 3-tier approach (screen, confirm, and titer) using a validated assay. After single and multiple SC administrations of COMPOUND A, generally, there was an increase in the incidence of positive ADA with time for all cohorts. While most ADA-positive samples had low titers near the sensitivity threshold of the assay, there was an increase in ADA titer with time and dose level. Based on the surrogate antibody positive control for the ADA assay, titer values ≤80 ng/mL reflect ADA detectable below the US FDA recommended sensitivity guideline of 100 ng/mL. Most subjects had ADA levels below this 100 ng/mL threshold, and only 8 of 34 (23.5%) subjects had titer values >80 ng/mL during the observation period.

[0390] In the context of repeat dosing with COMPOUND A in MAD Cohort 1, all 6 subjects treated with active drug developed treatment-emergent ADA responses with titers that increased to 40, 80, or 320 by Day 85, but then a decrease in ADA titer was observed upon reaching the end of the study (Day 127).

[0391] Given the ability to detect low titer antibodies in the presence of circulating drug, the assay can detect both clinically relevant and irrelevant anti-COMPOUND A antibodies. The impact of ADA on COMPOUND A exposure and PD activity was also evaluated.

[0392] Where evaluable, no impact of ADA on PK or RO was observed since the PK and RO profiles for treatment-emergent ADA-positive subjects fell within the range of observed PK profiles for ADA-negative subjects. Where the impact of ADA on PK profiles compared

with ADA-negative subjects was not evaluable, concentrations generally fell within the range of expected exposures and no accelerated clearance was observed.

[0393] Across cohorts, there were no associations between the timing of positivity and any observations in the PK profiles. Many treatment-emergent ADA-positive samples occurred at or beyond Day 50 when COMPOUND A concentrations were BLQ.

[0394] Similarly, there was no apparent impact on RO, substantiating that the low titers of ADA observed in the study are unlikely to be clinically relevant. No ADA-related AEs were observed in the study. Immunogenicity and its potential clinical impact will continue to be evaluated throughout the clinical development of COMPOUND A.

[0395] In Part 1 study (SAD), while 85.7% of the subjects receiving COMPOUND 1 and 70% of the subjects receiving placebo reported treatment-emergent adverse events (TEAEs), all TEAEs were mild or moderate in intensity. 57.1% of subjects who received COMPOUND A and 30.0% subjects who received placebo reported at least one injection site reaction (ISR) event; no ISRs were reported as severe. Transient reductions in lymphocyte counts were observed after COMPOUND A treatment centered on the Day 3 time point, corresponding to C_{max}, with a more prolonged time course for the highest dose (2 mg/kg and 4 mg/kg). None of the lymphocyte count reduction events were considered clinically significant.

[0396] In Part 2 study (MAD), similarly, all TEAEs were mild or moderate in intensity and no ISR were reported as severe. Reductions in absolute lymphocyte counts were observed after COMPOUND A treatment, but none of the lymphocyte count events were considered clinically significant. A total lymphocyte count of $<0.5 \times 10^9$/L, a prespecified protocol stopping criterion, was not observed in any of the subjects during the study. There were no cases of lymphopenia as defined by the CTCAE guidance.

[0397] Overall, Phase 1 data indicates that dose up to 4 mg/kg is well tolerated in healthy human volunteers, with no observable impact on pharmacology or safety by ADA. Doses less than 3 mg/kg SC was observed to achieve full RO, and multiple administration of COMPOUND A at 1 mg/kg SC every two weeks also achieved full RO and pSTAT5 inhibition. A total lymphocyte count of $<0.5 \times 10^9$/L, a prespecified protocol stopping criterion, was not observed in any of the study subjects during the study. There were no cases of lymphopenia as defined by the Common Terminology Criteria for Adverse Events (CTCAE) guidance.

Example 9: Preliminary Phase 2 Clinical Data in Human

Assessment of Antibody Serum Concentration and Receptor Occupancy (RO) by COMPOUND A in AD patients

[0398] Serum PK and blood IL-7Rα RO of COMPOUND A were evaluated in subjects dosed with 2 mg/kg (N = 5) or 3 mg/kg (N = 5) subcutaneous administration. The interim cutoff date for this analysis resulted in inclusion of data of at least 98 days (14 weeks) or 14 days (2 weeks) postdose for PK. Analyses were performed by an external unblinded pharmacometrician and results were reblinded for the Sponsor. To maintain blinding, time points or groups with N <2 were not included in the analysis. Nominal doses and nominal times of dosing and sampling were used in the analyses.

[0399] The preliminary mean serum concentration versus time profiles of free COMPOUND A after 2 and 3 mg/kg SC administration every 2 weeks are shown in FIG. 5A. After SC dosing of 2 or 3 mg/kg COMPOUND A, apparent dose-dependent exposures were observed over the first 2 weeks post-dose, with mean Day 15 trough concentrations (at pre-dose) of 5.8 and 7.76 µg/mL, respectively. With continued dosing of 2 mg/kg every 2 weeks, 60% to 80% of patients maintained trough concentrations above 5 µg/mL, the target therapeutic concentration. Trough serum concentrations demonstrated generally high variability, with CV% ranging from approximately 40% to 90%.

[0400] Preliminary RO (mean ± standard deviation [SD]) versus time profiles after dosing of 2 and 3 mg/kg COMPOUND A SC Q2W are presented in FIG. 5B. The preliminary mean IL-7Rα RO on circulating CD3+ T cells reached complete saturation (ie, >90% RO) by Day 3 after a dose of 2 or 3 mg/kg COMPOUND A. Upon repeat subcutaneous administration of 2 mg/kg COMPOUND A Q2W, 100% of patients maintained complete RO at all time points except for one outlier at Day 43. After administration of 3 mg/kg COMPOUND A SC Q2W, 100% patients maintained complete RO above 90% up to Study Day 15.

[0401] COMPOUND A has an acceptable safety profile at doses up to 3 mg/kg every 2 weeks in subjects with AD. All adverse events (AEs) were assessed as mild or moderate, and there were no reported severe AEs. Reductions in lymphocyte count below 1000/µL, consistent with the mechanism of action, were observed in 5 subjects across both cohorts. The minimum lymphocyte count observed was 750/µL and no adverse sequelae were reported; the subject's lymphocyte count returned to normal upon retesting approximately 1 week later with no further reduction below normal values observed. No dose-dependent reduction in lymphocyte count was observed. The lymphocyte count reductions were

generally transient and trended to within normal limits at follow-up visits. No CTCAE Grade ≥3 lymphopenia or associated AEs or infections were observed. No doses were delayed due to TEAEs or due to a subject's absolute lymphocyte count (ALC) being <800/μL (as per protocol). No other clinically significant findings in laboratory values related to COMPOUND A have been observed.

[0402] In summary, both 2 and 3 mg/kg dose groups maintained target PK threshold > 5 μg/mL (dose expected to achieve full target engagement in tissue). Maximal RO (>90%) was achieved in all subjects of both dose groups by day 3 and maintained through the entire dosing period. Safety profile is also acceptable at these two doses; particularly, no lymphopenia-associated AEs, including viral infections, have been observed.

[0403] Based on these preliminary data, a dose of 200 mg (~2.7 mg/kg) administered SC Q2W is expected to result in steady-state serum trough concentrations >5 μg/mL and maximum RO on circulating T cells in >90% of subjects throughout dosing, while expected to cause no or only minimal lymphopenia. In patients with AD, predicted median $C_{max,ss}$ and $AUC_{tau,ss}$ after a dose of 200 mg SC administered Q2W are >100-fold and >50-fold lower, respectively, than exposures at the NOAEL of 150 mg/kg/week SC in cynomolgus monkeys from the 6-month GLP toxicology study (Example 7).

[0404] The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, applications, and publications to provide yet further embodiments.

[0405] These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

CLAIMS

1. A method of treating atopic dermatitis (AD) in a subject (*e.g.*, a human) in need thereof, the method comprising administering an effective amount of a composition comprising an antibody for IL-7Rα, wherein the antibody comprises:
   (a) a heavy chain variable region (HCVR) that comprises a VH CDR1 comprising the sequence of SEQ ID NO: 1 (DHAMH, such as any one of SEQ ID NOs: 7-22), a VH CDR2 sequence of SEQ ID NO: 2 (GISWNSRGIGYADSVKG), and a VH CDR3 sequence of SEQ ID NO: 3 (DEYSRGYYVLDV); and
   (b) a light chain variable region (LCVR) that comprises a VL CDR1 sequence of SEQ ID NO: 4 (RASQGISSALA), a VL CDR2 sequence of SEQ ID NO: 5 (DASSLES), and a VL CDR3 sequence of SEQ ID NO: 6 (QQFNSYPLWIT),
   and wherein the composition comprising the antibody is administered to the subject to maintain serum concentration of the antibody at ≥5 μg/mL throughout dosing, such that atopic dermatitis is treated in the subject.

2. The method of claim 1, wherein the antibody has a heavy chain sequence of SEQ ID NO: 23 and a light chain sequence of SEQ ID NO: 24.

3. The method of claim 1 or 2, wherein the subject:
   (1) has moderate to severe AD (*e.g.*, chronic AD having a disease duration of ≥3 years, as diagnosed by the Eichenfield revised criteria of Hanifin and Rajka);
   (2) has moderate to severe disease activity characterized by:
      a) BSA affected ≥10%,
      b) EASI Score ≥12, and/or
      c) Investigators Global Score (IGA) ≥3; and/or,
   (3) has inadequate response to treatment by:
      i) a (medium-potency) topical steroid or a topical immunomodulator (such as a calcineurin inhibitor, a PDE-4 inhibitor, or a JAK inhibitor), optinally, said inadequate response is observed after at least 4 weeks of treatment;
      ii) a systemic steroid or phototherapy; and/or,
      iii) an oral chemical synthetic immunomodulator (such as methotrexate (MTX), mycophenolate mofetil, azathioprine, cyclosporine, a systemic

biologic (*e.g.*, dupliumab, ustekinumab or tralokinumab)), or a systemic targeted synthetic JAK inhibitor (*e.g.*, upadacitinib or abrocitinib).

4. The method of any one of claims 1-3, wherein the antibody is administered to the subject subcutaneously (*s.c.*).

5. The method of any one of claims 1-4, wherein the antibody is administered once a week (Q1W), once every two weeks (Q2W), once every three weeks (Q3W), once every four weeks (Q4W), once every eight weeks (Q8W), once every twelve weeks (Q12W), or any intermittent PRN (*pro re nata*).

6. The method of any one of claims 1-5, wherein the antibody is administered for 5-10 (*e.g.*, 5, 6, 7, 8, 9, or 10) consecutive doses.

7. The method of any one of claims 1-6, wherein efficacy of treatment is measured by mean difference in percentage reduction from baseline level (just prior to commencement of treatment) of Eczema Area and Severity Index (EASI) score, at 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 14 weeks, 16 weeks, and/or 24 weeks after the first dose at Week 0, for treatment vs. placebo / untreated control.

8. The method of any one of claims 1-7, wherein ≥50% , ≥75%, or ≥90% mean difference in percentage reduction from baseline level of EASI score is achieved at 4 weeks (Week 4), 8 weeks (Week 8), 12 weeks (Week 12), 16 weeks (Week 16), and/or 24 weeks (Week 24) after the first dose at Week 0, in the treated subject compared to placebo / untreated control.

9. The method of any one of claims 1-6, wherein efficacy of treatment is measured by mean percentage change from baseline level (just prior to commencement of treatment) in Scoring Atopic Dermatitis (SCORAD) score, at 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 14 weeks, 16 weeks, and/or 24 weeks after the first dose at Week 0, for treatment vs. placebo / untreated control.

10. The method of any one of claims 1-6 and 9, wherein ≥50% , ≥75%, or ≥90% mean percentage change from baseline level in SCORAD score is achieved at 4 weeks (Week 4), 8 weeks (Week 8), 12 weeks (Week 12), 16 weeks (Week 16), and/or 24 weeks (Week 24) after the first dose at Week 0 in the treated subject compared to placebo / untreated control.

11. The method of any one of claims 1-10, wherein ≥50% , ≥75%, or ≥90% of all treated subject achieve EASI 50, EASI 75 and/or EASI 90 at Week 4, 8, 12, 14, 16, and/or 24.

12. The method of any one of claims 1-10, wherein ≥50% , ≥75%, or ≥90% of all treated subject achieve Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score of 0 or 1 with at least 2 grades of reduction from Baseline at Week 4, 8, 12, 14, 16, and/or 24.

13. The method of any one of claims 1-12, wherein the antibody is formulated as 100 mg/mL solution in 20 mM histidine, 260 mM sucrose, and 0.05% (w/v) polysorbate 80 at pH 6.0, with an optional 0.05 mM pentetic acid.

14. The method of any one of the preceding claims, wherein the antibody is administered to the subject at about 0.1 mg/kg – about 10 mg/kg per dose, about 0.2 mg/kg – about 8 mg/kg per dose, about 0.5 mg/kg – about 5 mg/kg per dose, about 1 mg/kg – about 4 mg/kg per dose, about 2 mg/kg – about 3 mg/kg per dose, about 0.2 mg/kg per dose, about 0.5 mg/kg per dose, about 1 mg/kg per dose, about 2 mg/kg per dose, about 3 mg/kg per dose, about 4 mg/kg per dose, about 5 mg/kg per dose, about 6 mg/kg per dose, about 7 mg/kg per dose, about 8 mg/kg per dose, about 9 mg/kg per dose, or about 10 mg/kg per dose.

15. The method of any one of the preceding claims, wherein the antibody is administered to the subject at about 10 mg – about 800 mg per dose, about 20 mg – about 500 mg per dose, about 50 mg – about 300 mg per dose, about 100 mg – about 250 mg per dose, about 25 mg per dose, about 50 mg per dose, about 100 mg per dose, about 150 mg per dose, about 200 mg per dose, about 250 mg per dose, about 300 mg per dose, or about 350 mg per dose.

16. The method of any one of the preceding claims, wherein the subject has impaired renal function (*e.g.*, mildly impaired renal function (such as a glomerular filtration rate <60 mL/min and/or the presence of albuminuria >30 mg/d), moderately impaired renal function (such as a glomerular filtration rate <45 mL/min), or severely impaired renal function (such as a glomerular filtration rate <30 mL/min).

17. The method of any one of the preceding claims, wherein the subject is further being treated by or has been treated by a second therapeutic agent effective to treat atopic dermatitis.

18. The method of claim 17, wherein the second therapeutic agent comprises a topical immunomodulator (*e.g.*, a calcineurin, PDE-4, and/or JAK inhibitor); a systemic steroid (corticosteroid); a topical corticosteroid; tacrolimus; pimecrolimus; phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]); allergen immunotherapy; a leukotriene inhibitor; or an oral chemical synthetic immunomodulator (*e.g.*, methotrexate, mycophenolate mofetil, interferon (IFN)-γ, azathioprine, cyclosporine, a systemic biologic (dupliumab, ustekinumab, tralokinumab, or nemolizumab), a systemic targeted synthetic JAK inhibitor (tofacitinib, ruxolitinib, upadacitinib, abrocitinib, and baricitinib), a topical synthetic JAK inhibitor (delgocitinib), or a PDE-4 inhibitor (crisaborole)).

19. The method of any one of the preceding claims, comprising administering the antibody to the subject subcutaneously one dose every two weeks (Q2W), at about 200 mg per dose, for (at least) about 7 doses.

20. A method of treating atopic dermatitis (AD) in a subject (*e.g.*, a human) in need thereof, the method comprising administering an effective amount of a composition comprising an antibody for IL-7Rα, wherein the antibody comprises:

(a) a heavy chain variable region (HCVR) that comprises a VH CDR1 comprising the sequence of SEQ ID NO: 1 (DHAMH, such as any one of SEQ ID NOs: 7-22), a VH CDR2 sequence of SEQ ID NO: 2 (GISWNSRGIGYADSVKG), and a VH CDR3 sequence of SEQ ID NO: 3 (DEYSRGYYVLDV); and

(b) a light chain variable region (LCVR) that comprises a VL CDR1 sequence of SEQ ID NO: 4 (RASQGISSALA), a VL CDR2 sequence of SEQ ID NO: 5 (DASSLES), and a VL CDR3 sequence of SEQ ID NO: 6 (QQFNSYPLWIT);

wherein 200 mg of the antibody is administered subcutaneously every 2 weeks;

wherein the antibody comprises an effectorless IgG1 Fc; and,

wherein the subject optionally:

(1) has moderate to severe AD (*e.g.*, chronic AD having a disease duration of ≥3 years, as diagnosed by the Eichenfield revised criteria of Hanifin and Rajka);

(2) has moderate to severe disease activity characterized by:

a) BSA affected ≥10%,

b) EASI Score ≥12, and/or

c) Investigators Global Score (IGA) ≥3; and/or,

(3) has inadequate response to treatment by:

i) a (medium-potency) topical steroid or a topical immunomodulator (such as a calcineurin inhibitor, a PDE-4 inhibitor, or a JAK inhibitor), optinally, said inadequate response is observed after at least 4 weeks of treatment;

ii) a systemic steroid or phototherapy; and/or,

iii) an oral chemical synthetic immunomodulator (such as methotrexate (MTX), mycophenolate mofetil, azathioprine, cyclosporine, a systemic biologic (*e.g.*, dupliumab, ustekinumab or tralokinumab)), or a systemic targeted synthetic JAK inhibitor (*e.g.*, upadacitinib or abrocitinib);

such that atopic dermatitis is treated in the subject.

21. The method of claim 20, wherein the composition comprising the antibody is administered to the subject to maintain serum concentration of the antibody at ≥5 μg/mL throughout dosing.

22. The method of claim 20 or 21, wherein the VH CDR1 comprises SEQ ID NO: 7 (GFTFDDHAMH).

23. The method of any of claims 20-22, wherein the composition comprises 100 mg/ml of the antibody in 20 mM histidine, 260 mM sucrose, and 0.05% (w/v) polysorbate 80 at pH 6.0, with an optional 0.05 mM pentetic acid.

24. The method of any of claims 20-23, wherein the subject has an absolute lymphocyte count (ALC) of ≥ 800 per microL.

25. The method of any of claims 20-24, wherein administration of the antibody is stopped when the subject's ALC is < 500 per microL.

26. The method of any preceding claims, wherein the antibody is administered to the subject at about 200 mg per dose.

27. The method of any preceding claims, wherein the antibody is administered once every two weeks (Q2W).

28. The method of any preceding claims, wherein the antibody is administered for at least about 7 doses.

29. The method of any preceding claims, wherein the antibody comprises an effectorless IgG1 Fc.

30. A pharmaceutical composition comprising an antibody having two heavy chains and two light chains, wherein each said heavy chain has the amino acid sequence of SEQ ID NO: 23, and each said light chain has the amino acid sequence of SEQ ID NO: 24; and wherein the antibody is formulated in a pharmaceutically acceptable solution comprising about 50-200 mg/mL (*e.g.*, about 100 mg/mL) of the antibody in about 15-25 mM (*e.g.*, about 20 mM) histidine, 200-300 mM (*e.g.*, about 260 mM) sucrose, and about 0.03-0.07% (w/v) (*e.g.*, about 0.05% (w/v)) polysorbate 80 at pH 6.0.

31. The pharmaceutical composition of claim 30, wherein the solution further comprises about 0.01-0.10 mM (*e.g.*, about 0.05 mM) of pentetic acid.

32. The pharmaceutical composition of claim 30, comprising, consisting essentially of, or consisting of the antibody formulated as 100 mg/mL of the antibody in 20 mM histidine, 260 mM sucrose, and 0.05% (w/v) polysorbate 80 at pH 6.0.

33. The pharmaceutical composition of claim 30, comprising, consisting essentially of, or consisting of the antibody formulated as 100 mg/mL of the antibody in 20 mM histidine, 260 mM sucrose, 0.05 mM of pentetic acid, and 0.05% (w/v) polysorbate 80 at pH 6.0.

34. A container (*e.g.*, a polycarbonate bottle) containing about 2 mL of extractable volume of the pharmaceutical composition of claim 32 or 33.

35. The container of claim 34, comprising about 2.26 mL of the pharmaceutical composition of claim 32 or 33.