

TREATMENT OF CORTICOSTEROID DEPENDENT ASTHMA WITH ANTI-TSLP ANTIBODY

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the priority benefit of U.S. Provisional Patent Application No. 63/503,089, filed May 18, 2023, U.S. Provisional Patent Application No. 63/597,219, filed November 8, 2023, and U.S. Provisional Patent Application No. 63/547,945, filed November 9, 2023, each of which is incorporated by reference here in its entirety.

INCORPORATION BY REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0002] Incorporated by reference in its entirety is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: Filename: 59127_SeqListing.xml; Size: 15,642 bytes; Created: May 7, 2024.

FIELD OF THE INVENTION

[0003] The present disclosure relates, in general, to methods of treating corticosteroid dependent severe asthma using an antibody specific for thymic stromal lymphopoietin (TSLP).

BACKGROUND

[0004] Asthma is a chronic inflammatory airway disease characterized by bronchial hyperreactivity and reversible airflow limitation that causes wheezing, shortness of breath, cough, and chest tightness. Although several treatments are available (e.g., ICS, LABA, and long-acting muscarinic antagonists [LAMA]), there continues to be a clear unmet medical need among patients with severe asthma.

[0005] Biologic therapies can provide additional asthma control for patients with severe asthma. Omalizumab may be suitable for a subgroup of patients with proven reactivity to an aeroallergen and elevated serum immunoglobulin E (IgE) levels who remain inadequately controlled with ICS plus LABA (XOLAIR US PI 2019). Additional biologics, such as mepolizumab, reslizumab, benralizumab, and dupilumab, have been approved for severe asthma with an eosinophilic phenotype (NUCALA US PI 2019, CINQAIR US PI 2020, FASENRA US 2017, DUPIXENT US 2017). Biologics targeting IL-5, IgE, and IL-4 are now included in international treatment guidelines (Global Initiative for Asthma [GINA 2022]) as

an add-on treatment for patients whose asthma remains uncontrolled despite high dose ICS/LABA treatment.

[0006] However, even when using currently available biologics, substantial proportions of patients continue to experience exacerbations and may benefit from agents that target different molecular pathways (Wenzel 2012, Froidure et al 2016, Swedin et al 2017). Therefore, despite these additional therapeutic options, there remains a clear unmet medical need among patients with severe asthma, independent of IgE status or eosinophil level, who are unable to gain complete asthma control using currently available therapies.

[0007] Thymic stromal lymphopoietin is an epithelial cell-derived cytokine that is produced in response to proinflammatory stimuli (e.g., infectious, allergic, and environmental stimuli) and trauma. TSLP has an upstream and central role in the initiation of inflammatory responses and can activate a broad range of cell types including eosinophils, mast cells, T cells, dendritic cells, type 2 innate lymphoid cells and basophils (Tedeschi et al 2017, Watson and Gauvreau, 2014). Classically, TSLP may be a critical component in the initiation and perpetuation of the T helper 2 (Th2) response and the resulting cascade of cytokines associated with Th2 driven asthma (Kaur and Brightling 2012). Asthma is now recognized as a heterogeneous disease with subsets of patients that do not exhibit Th2-associated disease (Wenzel 2012). There are emerging data that TSLP may also mediate non-allergic (non-T helper cell 2) inflammation (Tanaka et al., 2009, Ziegler et al., 2013). Given that TSLP is an upstream and pleiotropic cytokine, the blockade of TSLP is therefore anticipated to have broad impact on the spectrum of inflammatory responses seen in asthma.

[0008] Tezepelumab (also known as AMG 157) (Gilliet, et al., J Exp Med 2003; 197:1059-63) is a fully human monoclonal antibody (immunoglobulin G2 λ) that targets the thymic, stromal lymphopoietin (TSLP), an epithelial-cell-derived cytokine that promotes inflammatory responses to environmental stimuli through its activities on multiple pathways, including (but not limited to) activities on dendritic cells (Gilliet, et al., 2003; Soumelis et al., Nat Immunol. 3:673-680, 2002; Reche, et al., J Immunol 2001; 167:336-43) and mast cells (Allakhverdi et al., J Exp Med. 204:253-258, 2007). By binding to TSLP, tezepelumab prevents its interaction with the TSLP receptor complex and inhibits multiple downstream inflammatory pathways.

SUMMARY

[0009] The anti-TSLP antibody described herein addresses an unmet need in patients with corticosteroid-dependent asthma, in which other medications may not control

symptoms. For example, the antibody therapy may reduce or eliminate the need for therapies such as oral corticosteroids.

[0010] The disclosure provides a method for treating corticosteroid-dependent asthma in a subject comprising administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant in a dose of 140 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0011] The disclosure provides a method for treating corticosteroid-dependent asthma in a subject comprising administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant in a dose of 140 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain comprising a. a light chain variable domain selected from the group consisting of: i. a sequence of amino acids at least 80% identical to SEQ ID NO:12; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and b. a heavy chain variable domain selected from the group consisting of: i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0012] The disclosure further provides a method for treating corticosteroid-dependent asthma in a subject comprising selecting a subject in need of treatment for corticosteroid-

dependent asthma and administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant to the subject in a dose of 140 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0013] Also provided is a method for treating corticosteroid-dependent asthma in a subject comprising selecting a subject in need of treatment for corticosteroid-dependent asthma, administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant to the subject in a dose of 140 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain selected from the group consisting of: i. a sequence of amino acids at least 80% identical to SEQ ID NO:12; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and b. a heavy chain variable domain selected from the group consisting of: i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0014] In various embodiments, the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0015] In various embodiments, the antibody or antibody variant is administered every 4 weeks.

[0016] In various embodiments, the antibody or antibody variant is administered at a dose of 210 mg every 2 weeks. In various embodiments, the antibody or antibody variant is administered at a dose of 210 mg every 4 weeks.

[0017] In various embodiments, the subject is also receiving treatment with corticosteroids. In various embodiments the corticosteroids are oral corticosteroids. In various embodiments, the oral corticosteroids are one or more of prednisone, prednisolone, cortisone, hydrocortisone, methylprednisolone, triamcinolone, betamethasone, dexamethasone, and deflazacort.

[0018] In various embodiments, the method comprises administering an anti-TSLP antibody or antibody variant in conjunction with an oral corticosteroid, wherein the subject goes through an optimization phase of OCS therapy, a reduction phase of OCS therapy and a maintenance phase of OCS therapy.

[0019] In various embodiments, the method comprises reducing the dose of corticosteroids when the subject receives a reduction phase of treatment. In various embodiments, the dose of corticosteroid is reduced every 4 weeks for approximately 20 weeks. In various embodiments, the dose of corticosteroid is reduced by 5 mg/day or 2.5 mg/day at each reduction interval.

[0020] In various embodiments, provided is a method for treating corticosteroid-dependent asthma in a subject comprising selecting a subject in need of treatment for oral corticosteroid (OCS)-dependent asthma, administering a therapeutically effective amount of a oral corticosteroid and an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg at an interval of every 2 weeks or every 4 weeks, wherein the subject receives an optimization phase of OCS therapy, a reduction phase of OCS therapy and a maintenance phase of OCS therapy, and wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0021] The disclosure further provides a method for treating corticosteroid-dependent asthma in a subject comprising selecting a subject in need of treatment oral corticosteroid (OCS)-dependent asthma, administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg at an interval of every 2 weeks or every 4 weeks, wherein the subject receives an optimization phase of OCS therapy, a reduction phase of OCS therapy and a maintenance phase of OCS therapy, and wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain selected from the group consisting of: i. a sequence of amino acids at least 80% identical to SEQ ID NO:12; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and b. a heavy chain variable domain selected from the group consisting of: i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0022] In various embodiments, provided is a method for treating corticosteroid-dependent asthma in a subject comprising selecting a subject in need of treatment for corticosteroid-dependent asthma, administering a therapeutically effective amount of a systemic corticosteroid and an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg at an interval of every 4 weeks, wherein the subject receives an optimization phase of OCS therapy, a reduction phase of OCS therapy and a maintenance phase of OCS therapy, and wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the

antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0023] The disclosure further provides a method for treating corticosteroid-dependent asthma in a subject comprising selecting a subject in need of treatment of oral corticosteroid (OCS)-dependent asthma, administering a therapeutically effective amount of a systemic corticosteroid and anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg at an interval of every 4 weeks, wherein the subject receives an optimization phase of OCS therapy, a reduction phase of OCS therapy and a maintenance phase of OCS therapy, and wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain selected from the group consisting of: i. a sequence of amino acids at least 80% identical to SEQ ID NO:12; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and b. a heavy chain variable domain selected from the group consisting of: i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0024] In various embodiments, the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0025] In various embodiments, the optimization phase comprises a dose of OCS of 30 mg/day, 25 mg/day, 20 mg/day, 15 mg/day, 10 mg/day, 7.5 mg/day or 5 mg/day.

[0026] In various embodiments, the reduction phase comprises a dose of OCS of 25 mg/day, 20 mg/day, 15 mg/day, 10 mg/day, 7.5 mg/day, 5 mg/day, 2.5 mg/day or 0 mg/day.

[0027] In various embodiments, the maintenance phase comprises a dose of OCS of 15 mg/day, 10 mg/day, 7.5 mg/day, 5 mg/day, 2.5 mg/day or 0 mg/day.

[0028] In various embodiments, the anti-TSLP antibody variant has substantially similar pK characteristics as tezepelumab-ekko in humans.

[0029] In various embodiments, the antibody or antibody variant is administered for a period of at least 4 months, 6 months, 9 months, 1 year, 2 years or more.

[0030] In various embodiments, the anti-TSLP antibody or antibody variant thereof is bivalent and selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a monoclonal antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a monomeric antibody, a diabody, a triabody, a tetrabody, a Fab fragment, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody.

[0031] In one embodiment, the anti-TSLP antibody variant is selected from the group consisting of a diabody, a triabody, a tetrabody, a Fab fragment, a single domain antibody, an scFv, wherein the dose is adjusted such that the binding sites are equimolar to those dosed by bivalent antibodies.

[0032] In various embodiments, the antibody is an IgG2 antibody.

[0033] In one embodiment, the antibody or antibody variant is a human antibody.

[0034] In various embodiments, the antibody is tezepelumab. In various embodiments, the tezepelumab is an IgG2 antibody having the full length heavy and light chain amino acid sequences set out in SEQ ID NOs: 13 and 14, respectively.

[0035] In various embodiments, the antibody or antibody variant is administered to the subject in a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient.

[0036] In various embodiments, the corticosteroid-dependent asthma is in a subject with severe asthma.

[0037] In various embodiments, the antibody is tezepelumab or another anti-TSLP antibody described in the art. Exemplary antibodies are described further in the Detailed Description.

[0038] In various embodiments, the subject is an adult. In various embodiments, the subject is a child or adolescent.

[0039] In various embodiments, the administration reduces frequency of or levels of administered corticosteroids in the subject. In various embodiments, the corticosteroids are oral corticosteroids. In various embodiments, the oral corticosteroids are selected from the group consisting of prednisone, prednisolone, cortisone, hydrocortisone, methylprednisolone, triamcinolone, betamethasone, dexamethasone, and deflazacort.

[0040] In various embodiments, the reduction of levels of corticosteroids is reduction from baseline in daily maintenance OCS compared to baseline in a subject having corticosteroid dependent asthma comprising wherein the reduction is 90% to 100% reduction, 75% to 90%

reduction, 0% to 75% reduction, or 30% to 50% reduction. In various embodiments, the method results in discontinued OCS without loss of asthma control.

[0041] In various embodiments, the administration reduces frequency of or levels of co-administered therapy in the subject. Optionally, the co-administered therapy is inhaled corticosteroids (ICS), long-acting β 2 agonist (LABA), leukotriene receptor antagonists (LTRA), long-acting anti-muscarinics (LAMA), cromones, short-acting β 2 agonist (SABA), and theophylline. In various embodiments, the inhaled corticosteroids are selected from the group consisting of beclomethasone dipropionate, beclomethasone dipropionate, ciclesonide, fluticasone furoate, (Arnuity® Ellipta®), fluticasone propionate, budesonide, mometasone furoate, mometasone furoate, beclomethasone dipropionate (e.g., Fostair®), fluticasone propionate (e.g., Seretide®, Advair®), fluticasone furoate (e.g., Relvar® Ellipta®, Breo® Ellipta®), budesonide (e.g., Symbicort®), and mometasone furoate (e.g., Dulera®).

[0042] It is further provided that administration of the anti-TSLP antibody or antibody variant decreases levels of Th2 cytokines in the subject.

[0043] In various embodiments, administration of the anti-TSLP antibody or antibody variant improves one or more measures of corticosteroid dependent asthma in a subject selected from the group consisting of forced expiratory volume (FEV), FEV₁ reversibility, forced vital capacity (FVC), FeNO, Asthma Control Questionnaire-6 score and AQLQ(S)+12 score, change from baseline in pre-BD FEV₁, reduction from baseline in daily maintenance OCS dose, daily maintenance OCS dose $\leq$ 5 mg, and $\geq$ 50% reduction from baseline in daily maintenance OCS dose, asthma exacerbations as measured by AAER, time to first asthma exacerbation, rate of asthma exacerbations associated with emergency room (ER) visit, urgent care visit or hospitalization, and proportion of participants who did not experience an asthma exacerbation, weekly mean home PEF (morning and evening), and/or St George's Respiratory Questionnaire (SGRQ) score. It is further provided that the administration reduces the incidence of adrenal insufficiency in a subject.

[0044] In one embodiment, the administration improves one or more symptoms of asthma as measured by an asthma symptom diary.

[0045] In various embodiments, treatment with anti-TSLP antibody or antibody variant modulates the levels of one or more biomarkers of corticosteroid-dependent asthma, including, cytokines, IgE, CCL17, CCL18, CCL22, and RNA transcriptional changes in nasal epithelium. In various embodiments, treatment with anti-TSLP reduces the level of Th2 cytokines. In various embodiments, the treatment modulates (reduces or moderates) levels

of or activity of one or more of IL-4, IL-5, IL-13, IL-17, IL-22, IL-23, IL-31, IL-33, or combinations thereof.

[0046] Provided herein is a method to reduce daily maintenance oral corticosteroid (OCS) compared to baseline in a subject having OCS-dependent asthma comprising administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant in a dose of 140 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0047] Further provided is a method to reduce daily maintenance oral corticosteroid (OCS) compared to baseline in a subject having OCS-dependent asthma comprising administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant in a dose of 1400 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain selected from the group consisting of: i. a sequence of amino acids at least 80% identical to SEQ ID NO:12; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and b. a heavy chain variable domain selected from the group consisting of: i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b).

[0048] Also provided herein is a method for reducing ACQ-6 score in a subject having corticosteroid dependent asthma comprising administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant in a dose of 140 mg to 420 mg at an interval of

every 2 weeks or every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0049] Further provided is a method for reducing ACQ-6 score in a subject having corticosteroid dependent asthma comprising administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant in a dose of 1400 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain selected from the group consisting of: i. a sequence of amino acids at least 80% identical to SEQ ID NO:12; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and b. a heavy chain variable domain selected from the group consisting of: i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b).

[0050] Further provided is a method for treating corticosteroid dependent asthma in a subject comprising selecting a subject in need of treatment for corticosteroid dependent asthma, administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant to the subject in a dose of 140 to 420 mg at an interval of every 2 or every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light

chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and
b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2, wherein the antibody is an IgG2 antibody.

[0051] Provided herein is a method a method of reducing the frequency of corticosteroid-dependent asthma exacerbation in a subject having corticosteroid dependent asthma comprising selecting a subject in need of treatment for corticosteroid-dependent asthma, administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant to the subject in a dose of 140 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and
b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0052] Further provided is a method of reducing the frequency of corticosteroid-dependent asthma exacerbation in a subject having corticosteroid dependent asthma comprising selecting a subject in need of treatment for corticosteroid-dependent asthma, administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant to the subject in a dose of 140 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain selected from the group consisting of: i. a sequence of amino acids at least 80% identical to SEQ ID NO:12; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and
b. a heavy chain variable domain selected from the group consisting of: i. a sequence of

amino acids that is at least 80% identical to SEQ ID NO:10; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b).

[0053] Also provided is a method of reducing the frequency of corticosteroid-dependent asthma exacerbation in a subject comprising selecting a subject in need of treatment for corticosteroid-dependent asthma, administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg at an interval of every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0054] Also provided is a method of reducing the frequency of corticosteroid-dependent asthma exacerbation in a subject comprising selecting a subject in need of treatment for corticosteroid-dependent asthma, administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg at an interval of every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain selected from the group consisting of: i. a sequence of amino acids at least 80% identical to SEQ ID NO:12; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and b. a heavy chain variable domain selected from the group consisting of: i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately

stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b).

[0055] In various embodiments, the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0056] In various embodiments, the antibody is tezepelumab.

[0057] In various embodiments, the antibody or antibody variant is administered every 4 weeks. In various embodiments, the antibody or antibody variant is administered at a dose of 210 mg every 2 weeks. In various embodiments, the antibody or antibody variant is administered at a dose of 210 mg every 4 weeks.

[0058] In various embodiments, the methods comprise administering anti-TSLP antibody or antibody variant in conjunction with an oral corticosteroid, wherein the subject goes through an optimization phase of OCS therapy, a reduction phase of OCS therapy and a maintenance phase of OCS therapy.

[0059] In various embodiments, the disclosure provides a method for eliminating the need for oral corticosteroids in a subject having corticosteroid dependent asthma comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody or antibody variant for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0060] In various embodiments, the disclosure provides a method for eliminating the need for oral corticosteroids in a subject having corticosteroid dependent asthma comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody or antibody variant for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a light chain variable domain selected from the group consisting of: i. a sequence

of amino acids at least 80% identical to SEQ ID NO:12; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and b. a heavy chain variable domain selected from the group consisting of: i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b).

[0061] In various embodiments, the disclosure provides a method for reducing the amount of daily maintenance oral corticosteroids in a subject having corticosteroid dependent asthma to ≤ 5 mg/day comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody or antibody variant for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0062] In various embodiments, the disclosure provides a method for reducing the amount of daily maintenance oral corticosteroids in a subject having corticosteroid dependent asthma to ≤ 5 mg/day comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody or antibody variant for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a light chain variable domain selected from the group consisting of: i. a sequence of amino acids at least 80% identical to SEQ ID NO:12; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide

consisting of SEQ ID NO:11; and b. a heavy chain variable domain selected from the group consisting of: i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b).

[0063] In various embodiments, the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0064] It is provided that the dosing and antibody and antibody variant types referenced above apply to each method described herein.

[0065] In various embodiments, the antibody or antibody variant is administered to the subject in a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient.

[0066] In various embodiments, the administration delays the time to a corticosteroid-dependent asthma exacerbation compared to a subject not receiving the anti-TSLP antibody.

[0067] In various embodiments, the administration reduces frequency of or levels of co-administered therapy in the subject. Optionally, the co-administered therapy is dupilumab, immunosuppressive or immunomodulating drugs (e.g., systemic corticosteroids, cyclosporine, mycophenolate-mofetil, interferon (IFN)-gamma, Janus kinase inhibitors, azathioprine, methotrexate), anti-IL-13 antibodies, anti-IL-5 pathway antibodies (benralizumab, mepolizumab, reslizumab), or combinations thereof.

[0068] In various embodiments, the administration eliminates the need for corticosteroid therapy.

[0069] In various embodiments, the administration is subcutaneous or intravenous.

[0070] In various embodiments, the antibody is tezepelumab or another anti-TSLP antibody described in the art, e.g., in Table A. Exemplary antibodies are described further in the Detailed Description.

[0071] Also provided is an anti-TSLP antibody or antibody variant for use in the methods described herein.

[0072] In one embodiment, the disclosure provides an anti-TSLP antibody or antibody variant for use in the treatment of corticosteroid-dependent asthma in a subject comprising

administering a therapeutically effective amount of a dose of 140 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0073] Also provided is the use of an anti-TSLP antibody or antibody variant for the manufacture of a medicament for use in the methods described herein.

[0074] In one embodiment, the disclosure provides the use of an anti-TSLP antibody or antibody variant for the manufacture of a medicament for use in the treatment of corticosteroid-dependent asthma in a subject comprising administering a therapeutically effective amount of a dose of 140 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises a. a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0075] It is understood that each feature or embodiment, or combination, described herein is a non-limiting, illustrative example of any of the aspects of the invention and, as such, is meant to be combinable with any other feature or embodiment, or combination, described herein. For example, where features are described with language such as “one embodiment”, “some embodiments”, “certain embodiments”, “further embodiment”, “specific exemplary embodiments”, and/or “another embodiment”, each of these types of

embodiments is a non-limiting example of a feature that is intended to be combined with any other feature, or combination of features, described herein without having to list every possible combination. Such features or combinations of features apply to any of the aspects of the invention. Where examples of values falling within ranges are disclosed, any of these examples are provided as possible endpoints of a range, any and all numeric values between such endpoints are provided, and any and all combinations of upper and lower endpoints are envisioned.

[0076] The headings herein are for the convenience of the reader and not intended to be limiting. Additional aspects, embodiments, and variations of the invention will be apparent from the Detailed Description and/or Drawings and/or claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0077] Figure 1 depicts the oral corticosteroid titration schema.

[0078] Figures 2A and 2B show estimated daily doses for inhaled corticosteroids. Figure 2C shows estimated OCS dose therapy equivalence.

[0079] Figure 3 shows the reductions from baseline (week 0) in daily OCS dose in patients originally from NAVIGATOR and SOURCE over time in the DESTINATION study.

[0080] Figures 4A-4B show mean daily OCS dose in the tezepelumab and placebo group at week 104 in patients from NAVIGATOR (Figure 4A) and in patients from SOURCE (Figure 4B).

[0081] Figure 5. Sequences of anti-TSLP antibody tezepelumab.

[0082] Figure 6 depicts an example OCS dose titration schedule during the OCS reduction and maintenance phase.

[0083] Figure 7A shows the proportion of patients receiving a maintenance OCS dose of ≤ 5 mg/day. Data are presented as the number of patients with a maintenance OCS dose ≤ 5 mg/day divided by the number of patients who reached the time point. Figure 7B shows the proportions of patients with $\geq 50\%$ reduction in OCS dose. Data are presented as the number of patients with $\geq 50\%$ reduction in OCS dose divided by the number of patients who reached the time point.

[0084] Figure 8 shows the proportion of patients who discontinued maintenance daily OCS. Data are presented as the number of patients who discontinued OCS divided by the number of patients who reached the time point.

[0085] Figure 9A shows post-BD FEV₁ over time in tezepelumab treated subjects. Figure 9B shows the change from baseline in ACQ-6 score over time in tezepelumab treated patients.

DETAILED DESCRIPTION

[0086] Use of an anti-TSLP antibody addresses an unmet need in corticosteroid-dependent asthma patients in which other medications may not control moderate to severe symptoms. It is provided that treatment with anti-TSLP antibodies such as tezepelumab could eliminate regular disease activity and make more patients steroid-free or reduce the need for use of steroids in the treatment of corticosteroid-dependent asthma.

Definitions

[0087] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below.

[0088] As used in the specification and the appended claims, the indefinite articles “a” and “an” and the definite article “the” include plural as well as singular referents unless the context clearly dictates otherwise.

[0089] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the present disclosure belongs. The following references provide one of skill with a general definition of many of the terms used in this disclosure include, but are not limited to: Singleton *et al.*, DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY (2d Ed. 1994); THE CAMBRIDGE DICTIONARY OF SCIENCE AND TECHNOLOGY (Walker Ed., 1988); THE GLOSSARY OF GENETICS, 5th Ed., R. Rieger *et al.* (Eds.), Springer Verlag (1991); and Hale & Marham, THE HARPER COLLINS DICTIONARY OF BIOLOGY (1991).

[0090] The term “about” or “approximately” means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term “about” or “approximately” means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term “about” or “approximately” means within 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range. Whenever the term “about” or “approximately” precedes the first numerical value in a series of two or more numerical values, it is understood that the term “about” or “approximately” applies to each one of the numerical values in that series.

[0091] The term “corticosteroid-dependent asthma” as used herein refers to a subject with severe asthma who require long-term maintenance OCS therapy in addition to high dose ICS plus LABA, with or without other asthma controllers.

[0092] The term “corticosteroid-dependent asthma exacerbation” as used herein refers to a worsening of corticosteroid-dependent asthma that leads to any of the following: required treatment with a burst of systemic corticosteroids for at least 3 consecutive days or a single depot- injectable corticosteroid dose OR resulted in an emergency department visit (defined as evaluation and treatment for < 24 hours in an ER or urgent care center) which required systemic corticosteroids (as per above) OR an inpatient hospitalization due to asthma (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours).

[0093] The term “worsening of corticosteroid-dependent asthma” refers to new or increased symptoms and/or signs (examination) that can be either concerning to the subject having corticosteroid-dependent asthma (subject-driven) or related to a Patient Daily Diary alert (diary-driven).

[0094] The term “cytokine” as used herein refers to one or more small (5-20 kD) proteins released by cells that have a specific effect on interactions and communications between cells or on the behavior of cells, such as immune cell proliferation and differentiation. Functions of cytokines in the immune system include, promoting influx of circulating leukocytes and lymphocytes into the site of immunological encounter; stimulating the development and proliferation of B cells, T cells, peripheral blood mononuclear cells (PBMCs) and other immune cells; and providing antimicrobial activity. Exemplary immune cytokines, include but are not limited to, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-12, IL-13, IL-15, IL17A, IL-17F, IL-18, IL-21, IL-22, IL-23, IL-31, IL-33, interferon (including IFN alpha, beta, and gamma), tumor necrosis factor (including TNF alpha, beta), transforming growth factor (including TGF alpha, beta), granulocyte colony stimulating factor (GCSF), granulocyte macrophage colony stimulating factor (GMCSF) and thymic stromal lymphopoietin (TSLP).

[0095] A “T helper (Th) 1 cytokine” or “Th1-specific cytokine” refers to cytokines that are expressed (intracellularly and/or secreted) by Th1 T cells, and include IFN-g, TNF-a, and IL-12. A “Th2 cytokine” or “Th2-specific cytokine” refers to cytokines that are expressed (intracellularly and/or secreted) by Th2 T cells, including IL-4, IL-5, IL-13, and IL-10. A “Th17 cytokine” or “Th17-specific cytokine” refers to cytokines that are expressed (intracellularly and/or secreted) by Th17 T cells, including IL-17A, IL-17F, IL-22 and IL-21. Certain

populations of Th17 cells express IFN-g and/or IL-2 in addition to the Th17 cytokines listed herein. A polyfunctional CTL cytokine includes IFN-g, TNF-a, IL-2 and IL-17.

[0096] The term “specifically binds” is “antigen specific”, is “specific for”, “selective binding agent”, “specific binding agent”, “antigen target” or is “immunoreactive” with an antigen refers to an antibody or polypeptide that binds a target antigen with greater affinity than other antigens of similar sequence. It is provided herein that the agent specifically binds target proteins useful in identifying immune cell types, for example, a surface antigen (e.g., T cell receptor, CD3), a cytokine (e.g., TSLP, IL-4, IL-5, IL-13, IL-17, IFN-g, TNF-a) and the like. In various embodiments, the antibody specifically binds the target antigen, but can cross-react with an ortholog of a closely related species, e.g., an antibody may bind human protein and also bind a closely related primate protein.

[0097] The term “antibody” or “immunoglobulin” refers to a tetrameric glycoprotein that consists of two heavy chains and two light chains, each comprising a variable region and a constant region. “Heavy Chains” and “Light Chains” refer to substantially full-length canonical immunoglobulin light and heavy chains (see e.g., Immunobiology, 5th Edition (Janeway and Travers et al., Eds., 2001). Antigen-binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. The term “antibody” includes monoclonal antibodies, polyclonal antibodies, chimeric antibodies, human antibodies, and humanized antibodies. For the purposes of the claims of the present invention, the term “antibody” and “anti-TSLP antibody” refer to a tetrameric glycoprotein that consists of two heavy chains and two light chains, each comprising a variable region and a constant region and having an IgG1, IgG2, IgG3 or IgG4 Fc region.

[0098] Antibody variants include antibody fragments and antibody like proteins with changes to structure of canonical tetrameric antibodies. Typically, antibody variants include V regions with a change to the constant regions, or, alternatively, adding V regions to constant regions, optionally in a non-canonical way. Examples include antibody fragments that can bind an antigen (e.g., Fab', F'(ab)2, Fv,), biparatopic and recombinant peptides comprising the foregoing as long as they exhibit the desired biological activity. Variants may comprise an Fc region from an IgG antibody, e.g., an IgG1, IgG2, IgG3 or IgG4 Fc region.

[0099] An antibody variant provided herein also includes antibody derivatives having the CDRs set out in SEQ ID NO: 3-8, but may have an amino acid change or chemical modification (e.g., oxidation, methylation) in a variable region amino acid of SEQ ID NO: 10 or 12, or a Fc region amino acid set out in SEQ ID NO: 13 or 14, as a result of manufacturing or purification procedures, or due to improvement in manufacturing or purification procedures. Antibody variants/derivatives of tezepelumab are described in

PCT/US22/25994 (International Publication WO 2022/226339) and PCT/US22/25999 (International Publication WO 2022/226342), incorporated herein by reference in their entireties.

[0100] Antibody fragments include antigen-binding portions of the antibody including, inter alia, Fab, Fab', F(ab')₂, Fv, domain antibody (dAb), complementarity determining region (CDR) fragments, CDR-grafted antibodies, or a variant or a derivative thereof, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide, such as one, two, three, four, five or six CDR sequences, as long as the antibody retains the desired biological activity.

[0101] "Valency" refers to the number of antigen binding sites on each antibody or antibody fragment that targets an epitope. A typical full length IgG molecule, or F(ab)₂ is "bivalent" in that it has two identical target binding sites. A "monovalent" antibody fragment such as a F(ab)' or scFv with a single antigen binding site. Trivalent or tetravalent antigen binding proteins can also be engineered to be multivalent.

[0102] "Monoclonal antibody" refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts.

[0103] The term "inhibits TSLP activity" includes inhibiting any one or more of the following: binding of TSLP to its receptor; proliferation, activation, or differentiation of cells expressing TSLPR in the presence of TSLP; inhibition of Th2 cytokine production in a polarization assay in the presence of TSLP; dendritic cell activation or maturation in the presence of TSLP; and mast cell cytokine release in the presence of TSLP. See, e.g., US Patent 7982016 B2, column 6 and example 8 and US 2012/0020988 A1, examples 7-10.

[0104] The term "sample" or "biological sample" refers to a specimen obtained from a subject for use in the present methods, and includes urine, whole blood, plasma, serum, saliva, sputum, skin or tissue biopsies, cerebrospinal fluid, peripheral blood mononuclear cells with in vitro stimulation, peripheral blood mononuclear cells without in vitro stimulation, gut lymphoid tissues with in vitro stimulation, gut lymphoid tissues without in vitro stimulation, gut lavage, bronchioalveolar lavage, nasal lavage, and induced sputum.

[0105] The terms "treat", "treating" and "treatment" refer to eliminating, reducing, suppressing or ameliorating, either temporarily or permanently, either partially or completely, a clinical symptom, manifestation or progression of an event, disease or condition associated with an inflammatory disorder described herein. As is recognized in the pertinent

field, drugs employed as therapeutic agents may reduce the severity of a given disease state, but need not abolish every manifestation of the disease to be regarded as useful therapeutic agents. Similarly, a prophylactically administered treatment need not be completely effective in preventing the onset of a condition in order to constitute a viable prophylactic agent. Simply reducing the impact of a disease (for example, by reducing the number or severity of its symptoms, or by increasing the effectiveness of another treatment, or by producing another beneficial effect), or reducing the likelihood that the disease will occur or worsen in a subject, is sufficient. One embodiment of the disclosure is directed to a method for determining the efficacy of treatment comprising administering to a patient the therapeutic agent in an amount and for a time sufficient to induce a sustained improvement over baseline of an indicator that reflects the severity of the particular disorder.

[0106] The term “therapeutically effective amount” refers to an amount of therapeutic agent that is effective to ameliorate or lessen symptoms or signs of disease associated with a disease or disorder.

Severe Asthma

[0107] Participants with uncontrolled severe asthma may require long-term daily maintenance treatment with OCS. However, OCS are associated with multiple and potentially debilitating adverse outcomes when given for extended periods of time. These include, but are not limited to, metabolic disorders such as glucose intolerance and dyslipidaemia (Gounarides et al 2008, de Oliveira et al 2011), osteoporosis (Sambrook et al 1990), adrenal axis insufficiency and excessive and abnormal fat deposition (Gounarides et al 2008). The odds for developing OCS associated side effects are dose dependently associated with long-term (≥ 6 months) OCS use starting at doses of 5 mg or even lower per day of prednisone (Dalal et al 2016). Chronic OCS dosing in patients with severe asthma is also associated with increased direct healthcare costs and resource utilization. As such, a reduction in OCS dose in severe asthma patients requiring chronic maintenance OCS use would be of clinical relevance.

[0108] Previous randomized, controlled trials of monoclonal antibodies targeting type 2 (T2) cytokines, specifically interleukin [IL]-4/IL-13 and IL-5, or their respective receptors, have demonstrated tapering or discontinuation of the daily OCS doses in severe asthma patients requiring maintenance therapy with OCS (Bel et al 2014, Nair et al 2017, Rabe et al 2018), particularly in those with eosinophilic asthma.

[0109] Although OCS therapy can be effective at treating several inflammatory diseases, it adversely affects health-related quality of life (Swedin et al, 2017; Sweeney et al, 2016)

and is associated with several side-effects, including osteoporosis, hypertension, and depression (Dinsen et al, 2013). Long-term use of OCS suppresses the hypothalamic-pituitary-adrenal (HPA) axis and prevents cortisol production (Neogi et al, 2010; Nicholas et al, 2018). Upon withdrawal of OCS, restoration of the HPA axis may take a longer time, thus leading to adrenal insufficiency (AI) in approximately 50% of patients (Dinsen et al, 2013). Symptoms and signs of AI are often nonspecific and can include fatigue and nausea; moreover, impairment of the cortisol-induced stress response can be life-threatening (adrenal crisis) in physiologically traumatic situations such as during surgery, bodily injury, or severe systemic infections (Alves et al, 2008; Dinsen et al, 2013; Johnson et al, 2014; Joseph et al, 2016). It is therefore important to screen and monitor patients for AI while down-titrating their OCS dose, especially once the patient has reached a physiological dose, which is defined as approximately 5 mg per day of oral prednisone (Alves et al, 2008).

[0110] In the OCS-sparing phase 3 study SOURCE (NCT03406078), tezepelumab numerically reduced OCS use in participants with OCS-dependent asthma compared to placebo, but the difference was not statistically significant. A numerically higher proportion of tezepelumab treated participants reduced their daily OCS dose by 90–100% compared to placebo-treated participants. Post hoc analysis of the SOURCE data suggests that the lack of significance in the effect of tezepelumab on OCS dose reduction may have been due in part to study design features (Wechsler et al 2022). In addition, tezepelumab-treated participants with a baseline blood eosinophil count < 150 cells/ μ L had less of an OCS-sparing effect than placebo-treated participants.

[0111] It is provided that the administration improves one or more measures of corticosteroid-dependent asthma selected from the group consisting of forced expiratory volume (FEV), FEV₁ reversibility, forced vital capacity (FVC), FeNO, Asthma Control Questionnaire-6 score and AQLQ(S)+12 score, change from baseline in pre-BD FEV₁, reduction from baseline in daily maintenance OCS dose, daily maintenance OCS dose $\leq$ 5 mg, and $\geq$ 50% reduction from baseline in daily maintenance OCS dose, asthma exacerbations, as measured by AAER and time to first asthma exacerbation, rate of asthma exacerbations associated with emergency room (ER) visit, urgent care visit or hospitalization, and proportion of participants who did not experience an asthma exacerbation, weekly mean home PEF (morning and evening), and/or St George's Respiratory Questionnaire (SGRQ) score. It is further provided that the administration reduces the incidence of adrenal insufficiency in a subject.

[0112] Methods for scoring and determining a reduction therein for the various measures are described herein and known in the art.

[0113] Global asthma symptom is an assessment of asthma symptoms (0 to 3) each morning and evening. The sum of evening and subsequent morning single global item scores (0 to 6) will be used for the alerts system.

[0114] The Asthma Control Questionnaire (ACQ-6) is an assessment of asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and short acting beta-agonist use). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and < 1.5 indicate partly controlled asthma, and a score ≥ 1.5 indicates not well controlled asthma. Individual changes of at least 0.5 are considered to be clinically meaningful, and a decrease of at least 0.5 is the responder definition for ACQ-6.

[0115] The AQLQ(S)+12 is a questionnaire that measures the health-related quality of life experienced by asthma participants. The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli). Participants are asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The responder definition for AQLQ(s)+12 is 0.5-point improvement from baseline.

[0116] The St George's Respiratory Questionnaire SGRQ is a 50-item PRO instrument developed to measure the health status of participants with airway obstruction diseases. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Based on empirical data and interviews with patients, a mean change score of 4 units is associated with a minimum clinically important difference (MCID).

[0117] The EQ-5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty. The questionnaire also includes a visual analogue scale (VAS), where the participant will be asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state

[0118] The EuroQOL quality of life 5-dimensions 3-level version (EQ-5D-3L) is a standardized instrument for use as a measure of health-related quality of life (HRQoL) and was developed by EuroQol (Brooks, 1996). It defines health in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. And 3 ordinal levels of severity: 1, no problem; 2, some problems; and 3, severe problems. Overall health

state is defined as a 5-digit number. The questionnaire also includes a VAS, where the participant will be asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state.

TSLP

[0119] Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine that is produced in response to pro-inflammatory stimuli and drives allergic inflammatory responses primarily through its activity on dendritic cells (Gilliet, *J Exp Med.* 197:1059-1067, 2003; Soumelis, *Nat Immunol.* 3:673-680, 2002; Reche, *J Immunol.* 167:336-343, 2001), mast cells (Allakhverdi, *J Exp Med.* 204:253-258, 2007) and CD34+ progenitor cells. TSLP signals through a heterodimeric receptor consisting of the interleukin (IL)-7 receptor alpha (IL-7R α) chain and a common γ chain-like receptor (TSLPR) (Pandey, *Nat Immunol.* 1:59-64, 2000; Park, *J Exp Med.* 192:659-669, 2000).

[0120] Data from other studies suggest that TSLP may promote airway inflammation through Th2 independent pathways such as the crosstalk between airway smooth muscle and mast cells (Allakhverdi et al, *J Allergy Clin Immunol.* 123(4):958-60, 2009; Shikotra et al, *supra*). TSLP can also promote induction of T cells to differentiate into Th-17-cytokine producing cells with a resultant increase in neutrophilic inflammation commonly seen in more severe asthma (Tanaka et al, *Clin Exp Allergy.* 39(1):89-100, 2009). These data and other emerging evidence suggest that blocking TSLP may serve to suppress multiple biologic pathways including but not limited to those involving Th2 cytokines (IL-4/13/5).

[0121] In the PATHWAY phase 2b study (NCT02054130) of anti-TSLP antibody tezepelumab, tezepelumab significantly reduced exacerbations by up to 71% in adults with severe, uncontrolled asthma, irrespective of baseline disease phenotype (Corren et al 2017). In the NAVIGATOR (NCT03347279) phase 3 study tezepelumab reduced exacerbations in patients with severe, uncontrolled asthma, irrespective of baseline levels of T2 inflammatory biomarkers (blood eosinophil counts, FeNO, and serum total IgE), allergic status, and baseline maintenance OCS use (Menzies Gow et al 2021). In these studies, tezepelumab also improved lung function, asthma control, and patient health-related quality of life in the overall population.

[0122] Tezepelumab was well tolerated in the OCS-dependent asthma population in the SOURCE (NCT03406078) phase 3 study. In this study, 71.6 % (53/74) of tezepelumab-treated participants and 85.5% (65/76) of placebo-treated participants reported an adverse event (AE), and 14.9% (11/74) and 21.1% (16/76) reported a serious adverse event (SAE),

respectively. There were no meaningful differences in the frequency and type of AEs between the tezepelumab and placebo groups.

[0123] In the NAVIGATOR phase 3 study, a total of 77.1% (407/528) of the participants in the tezepelumab group and 79.5% (422/531) of those in the placebo group reported an ontreatment AE, and 8.7% (46/528) and 13.2 (70/531) reported a SAE, respectively. At or after baseline, 4.9% (26/527) of the participants in the tezepelumab group and 8.3% (44/530) of those in the placebo group were positive for anti-drug antibodies. Neutralizing antibodies were detected in 1 (0.2%) participant in each group (Menzies-Gow et al 2021).

Antibodies

[0124] It is provided that antibodies or antibody variants specific for TSLP are useful in the treatment of corticosteroid-dependent asthma, including severe asthma not controlled by use of corticosteroids or other treatments.

[0125] Specific binding agents such as antibodies and antibody variants or fragments that bind to their target antigen, e.g., TSLP, are useful in the methods of the disclosure. In one embodiment, the specific binding agent is an antibody. The antibodies may be monoclonal (MAbs); recombinant; chimeric; humanized, such as complementarity-determining region (CDR)-grafted; human; antibody variants, including single chain; and/or bispecific; as well as fragments; variants; or derivatives thereof. Antibody fragments include those portions of the antibody that bind to an epitope on the polypeptide of interest. Examples of such fragments include Fab and F(ab') fragments generated by enzymatic cleavage of full-length antibodies. Other binding fragments include those generated by recombinant DNA techniques, such as the expression of recombinant plasmids containing nucleic acid sequences encoding antibody variable regions.

[0126] Monoclonal antibodies may be modified for use as therapeutics or diagnostics. One embodiment is a "chimeric" antibody in which a portion of the heavy (H) and/or light (L) chain is identical with or homologous to a corresponding sequence in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with or homologous to a corresponding sequence in antibodies derived from another species or belonging to another antibody class or subclass. Also included are fragments of such antibodies, so long as they exhibit the desired biological activity. See U.S. Pat. No. 4,816,567; Morrison et al., 1985, Proc. Natl. Acad. Sci. 81:6851-55.

[0127] In another embodiment, a monoclonal antibody is a "humanized" antibody. Methods for humanizing non-human antibodies are well known in the art. See U.S. Pat. Nos.

5,585,089 and 5,693,762. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source that is non-human. Humanization can be performed, for example, using methods described in the art (Jones et al., 1986, Nature 321:522-25; Riechmann et al., 1998, Nature 332:323-27; Verhoeyen et al., 1988, Science 239:1534-36), by substituting at least a portion of a rodent complementarity-determining region for the corresponding regions of a human antibody. For example, with CDR-grafting, non-human CDR sequences are inserted into human framework regions (Lu et al. Journal of Biomedical Science (2020) 27:1).

[0128] Also encompassed by the disclosure are human antibodies and antibody variants (including antibody fragments) that bind TSLP. Human antibody refers to an antibody generated from human immunoglobulin sequences and comprising human variable and constant regions. Using transgenic animals (e.g., mice) that are capable of producing a repertoire of human antibodies in the absence of endogenous immunoglobulin production such antibodies are produced by immunization with a polypeptide antigen (i.e., having at least 6 contiguous amino acids), optionally conjugated to a carrier. See, e.g., Jakobovits et al., 1993, Proc. Natl. Acad. Sci. 90:2551-55; Jakobovits et al., 1993, Nature 362:255-58; Bruggermann et al., 1993, Year in Immuno. 7:33. See also PCT App. Nos. PCT/US96/05928 and PCT/US93/06926. Additional methods are described in U.S. Pat. No. 5,545,807, PCT App. Nos. PCT/US91/245 and PCT/GB89/01207, and in European Patent Nos. 546073B1 and 546073A1. Human antibodies can also be produced by the expression of recombinant DNA in host cells or by expression in hybridoma cells, using phage display libraries, or by single B cell cloning (Lu et al. Journal of Biomedical Science (2020) 27:1).

[0129] Chimeric, CDR grafted, and humanized antibodies and/or antibody variants are typically produced by recombinant methods. Nucleic acids encoding the antibodies are introduced into host cells and expressed using materials and procedures described herein. In a preferred embodiment, the antibodies are produced in mammalian host cells, such as CHO cells. Monoclonal (e.g., human) antibodies may be produced by the expression of recombinant DNA in host cells or by expression in hybridoma cells as described herein.

[0130] Antibodies and antibody variants (including antibody fragments) useful in the present methods comprise an anti-TSLP antibody comprising: a. a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and, b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID

NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody or antibody variant specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0131] Also provided is an antibody or antibody variant comprising a. a light chain variable domain selected from the group consisting of: i. a sequence of amino acids at least 80% identical to SEQ ID NO:12; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and, b. a heavy chain variable domain selected from the group consisting of: i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody or antibody variant specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0132] Tezepelumab is an exemplary anti-TSLP antibody having: a. i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8.

[0133] Tezepelumab also comprises a light chain variable domain having the amino acid sequence set out in SEQ ID NO:12; encoded by a polynucleotide sequence set out in SEQ ID NO:11; and a heavy chain variable domain having the amino acid sequence set out in SEQ ID NO:10, encoded by a polynucleotide sequence set out in SEQ ID NO:9.

[0134] Tezepelumab is an IgG2 antibody. The sequence of the full-length heavy chain and light chain of tezepelumab, including the IgG2 chain, is set out in SEQ ID NOs: 13 and 14, respectively.

[0135] Exemplary sequences of tezepelumab are also set out in US Patent 7,982,016 SEQ ID NOs: 13, 60, 105, 145, 173, 212; SEQ ID NOs: 361 and 363; and a light chain comprising a light chain variable domain comprising the amino acid sequence as set forth in SEQ ID NO:363 and a lambda light chain constant domain comprising the amino acid sequence as set forth in SEQ ID NO:369; and a heavy chain comprising a heavy chain variable domain comprising the amino acid sequence as set forth in SEQ ID NO:361 and an IgG2 heavy constant domain comprising the amino acid sequence as set forth in SEQ ID NO:365, herein incorporated by reference.

[0136] In various embodiments, anti-TSLP antibody derivatives are described in International Patent Publications WO 2022/226342 and WO 2022/226339, incorporated herein by reference in their entireties. Exemplary derivatives include tezepelumab antibodies that may have modifications after purification of antibody or after long term storage, including but not limited to, an isomerization derivative, a deamidation derivative, an oxidation derivative, a glycosylation derivative, disulfide isoform derivatives, and/or high molecular weight (HMW) species or antibody fragments. Exemplary derivatives may also be variants that have the amino acid sequences set out in SEQ ID NOs: 13-36 of WO2022/226342 as well as variants therein of SEQ ID NO: 3-8, e.g., including residues identified as possible sources of reduced stability in anti-TSLP antibody tezepelumab CDRs (SEQ ID NOs: 3-8) or in the variable region (SEQ ID NOs: 10 and 12), which include CDRH1 M34, CDRH2 W52, CDRH2 D54, CDRH2 N57, CDRH2 D62, CDRH3 W102, FRH1 N25, FRH1 N26, CDRL2 D49, CDRL2 D50, FRL2 N65, CDRL3 W90, CDRL3 D91, CDRL3 S92, S93, S94, and/or CDRL3 D95.

[0137] In various embodiments, the anti-TSLP antibody or antibody variant thereof is bivalent and selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a monoclonal antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a monomeric antibody, a diabody, a triabody, a tetrabody, a Fab fragment, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody.

[0138] In various embodiments, the anti-TSLP antibody is bivalent and selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a monoclonal antibody, a recombinant antibody, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody.

[0139] It is provided that the antibody or antibody variant is an IgG2 antibody. Exemplary sequences for a human IgG2 constant region are available from the Uniprot database as Uniprot number P01859, incorporated herein by reference. Information, including sequence

information for other antibody heavy and light chain constant regions is also publicly available through the Uniprot database as well as other databases well-known to those in the field of antibody engineering and production.

[0140] It is provided that the anti-TSLP antibody variant or anti-TSLP derivative has substantially similar pK characteristics as tezepelumab-ekko in humans.

[0141] In certain embodiments, derivatives of antibodies include tetrameric glycosylated antibodies wherein the number and/or type of glycosylation site has been altered compared to the amino acid sequences of a parent polypeptide. In certain embodiments, variants comprise a greater or a lesser number of N-linked glycosylation sites than the native protein. Alternatively, substitutions which eliminate this sequence will remove an existing N-linked carbohydrate chain. Also provided is a rearrangement of N-linked carbohydrate chains wherein one or more N-linked glycosylation sites (typically those that are naturally occurring) are eliminated and one or more new N-linked sites are created. Additional preferred antibody variants include cysteine variants wherein one or more cysteine residues are deleted from or substituted for another amino acid (e.g., serine) as compared to the parent amino acid sequence. Cysteine variants may be useful when antibodies must be refolded into a biologically active conformation such as after the isolation of insoluble inclusion bodies. Cysteine variants generally have fewer cysteine residues than the native protein, and typically have an even number to minimize interactions resulting from unpaired cysteines.

[0142] Desired amino acid substitutions (whether conservative or non-conservative) can be determined by those skilled in the art at the time such substitutions are desired. In certain embodiments, amino acid substitutions can be used to identify important residues of antibodies to human TSLP, or to increase or decrease the affinity of the antibodies to human TSLP described herein.

[0143] According to certain embodiments, preferred amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and/or (4) confer or modify other physiochemical or functional properties on such polypeptides. According to certain embodiments, single or multiple amino acid substitutions (in certain embodiments, conservative amino acid substitutions) may be made in the naturally-occurring sequence (in certain embodiments, in the portion of the polypeptide outside the domain(s) forming intermolecular contacts). In certain embodiments, a conservative amino acid substitution typically may not substantially change the structural characteristics of the parent sequence (e.g., a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent

sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described in *Proteins, Structures and Molecular Principles* (Creighton, Ed., W. H. Freeman and Company, New York (1984)); *Introduction to Protein Structure* (C. Branden and J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton et al. *Nature* 354:105 (1991), which are each incorporated herein by reference.

Methods of Administration

[0144] In one aspect, methods of the present disclosure include a step of administering a therapeutic anti-TSLP antibody or antibody variant described herein, optionally in a pharmaceutically acceptable carrier or excipient. In certain embodiments, the pharmaceutical composition is a sterile composition.

[0145] Provided herein are methods for treating corticosteroid dependent asthma in a subject, including severe asthma. In various embodiments, the method comprises selecting a subject in need of treatment for oral corticosteroid-dependent asthma, and administering an anti-TSLP antibody as described herein.

[0146] It is provided that anti-TSLP antibodies useful to treat corticosteroid dependent asthma as described herein also include those described in the publications set out in Table A and described in WO2023098491A1, WO2021155634A1, WO2022166072A1, WO2021043221A1, WO2022184074A1, WO2021104053A1, WO2023116925A1, WO2021155861A1, WO2022116858A1, WO2022117079A1, WO2020244544A1, WO2021152488A1, WO2022253147A1, WO2023070948A1, WO2023142309A1, WO2022095689A1, WO2021115240A1, WO2022166739A1, WO2019100111A1, in WO 2017/042701, WO 2016/142426, US20170066823, US20120020988 and US8637019, the disclosure of each of which is incorporated by reference.

TABLE A

WO2017/042701	An anti-TSLP antibody comprising a heavy chain (HC) CDR1 comprising the sequence of SEQ ID NO: 13, a HC CDR2 comprising the sequence of SEQ ID NO: 14, and a HC CDR3 comprising the sequence of SEQ ID NO: 15; An anti-TSLP antibody comprising a light chain (LC) CDR1 comprising the sequence of SEQ ID NO: 16, a LC CDR2 comprising the sequence of SEQ ID NO: 17, a LC CDR3 comprising the sequence of SEQ ID NO: 18; An anti-TSLP antibody comprising a heavy chain (HC) CDR1 comprising the sequence of SEQ ID NO: 19, a HC CDR2 comprising the sequence
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	of SEQ ID NO: 20, a HC CDR3 comprising the sequence of SEQ ID NO:15; An anti-TSLP antibody comprising a light chain (LC) CDR1 comprising the sequence of SEQ ID NO: 21, a LC CDR2 comprising the sequence of SEQ ID NO: 22, a LC CDR3 comprising the sequence of SEQ ID NO: 23; An anti-TSLP antibody comprising a HC variable region comprising the sequence of SEQ ID NO: 26 and/or a LC variable region comprising the sequence of SEQ ID NO: 27; An anti-TSLP antibody comprising a HC variable region comprising the sequence of SEQ ID NO: 28 and/or a LC variable region comprising the sequence of SEQ ID NO: 29; An anti-TSLP antibody that comprises a paratope comprising at least one of the following residues: Thr28, Asp31, Tyr32, Trp33, Asp56, Glu101, Ile102, Tyr103, Tyr104, Tyr105 of a heavy chain sequence of SEQ ID NO: 26 or Gly28, Ser29, Lys30, Tyr31, Tyr48, Asp50, Asn51, Glu52, Asn65, and Trp92 of a light chain sequence of SEQ ID NO:27; An anti-TSLP antibody that specifically binds an epitope in human TSLP, wherein the epitope comprises at least one of the following residues: Lys38, Ala41, Leu44, Ser45, Thr46, Ser48, Lys49, Ile52, Thr53, Ser56, Gly57, Thr58, Lys59, Lys101, Gln145, and Arg149 of SEQ ID NO: 30;
WO2016/142426	An anti-TSLP antibody comprising the amino acid sequence of SEQ ID NO: 31; An anti-TSLP antibody comprising a CDR1 comprising the sequence of SEQ ID NO: 32; a CDR2 comprising the sequence of SEQ ID NO: 33, and a CDR3 comprising the sequence of SEQ ID NO: 34; An anti-TSLP antibody comprising a CDR1 comprising the sequence of SEQ ID NO: 32; a CDR2 comprising the sequence of SEQ ID NO: 35, and a CDR3 comprising the sequence of SEQ ID NO: 34; An anti-TSLP antibody comprising a variant of the CDR1 of SEQ ID NO: 31 wherein the residue corresponding to residue 28 in SEQ ID NO:31 is Pro, the residue corresponding to residue 30 in SEQ ID NO:31 is Arg, the residue corresponding to residue 31 in SEQ ID NO:31 is Asn, the residue corresponding to residue 32 in SEQ ID NO: 31 is Trp and the residue corresponding to residue 34 in SEQ ID NO: 31 is Asp;

	An anti-TSLP antibody comprising a variant of the CDR2 of SEQ ID NO: 31 wherein the residue corresponding to residue 50 in SEQ ID NO:31 is Gly, the residue corresponding to residue 53 in SEQ ID NO:31 is His and the residue corresponding to residue 55 in SEQ ID NO:31 is Gln; An anti-TSLP antibody comprising a variant of the CDR3 of SEQ ID NO: 31 wherein the residue corresponding to residue 91 in SEQ ID NO:31 is He, Leu, Val or Phe, the residue corresponding to residue 92 in SEQ ID NO:31 is Gly or Ala, the residue corresponding to residue 93 in SEQ ID NO:31 is Glu, Phe, Asp or Ser and the residue corresponding to residue 94 in SEQ ID NO:31 is Asp.
WO2010/017468	An anti-TSLP antibody (9B7) comprising a HC CDR3 comprising the sequence of SEQ ID NO:38, wherein the other CDRs of the HC and LC comprise the sequences of SEQ ID NOs: 36, 37, and 39-41; An anti-TSLP antibody (6C5) comprising a HC CDR3 comprising the sequence of SEQ ID NO:44, wherein the other CDRs of the HC and LC comprise the sequences of SEQ ID NOs: 42, 43, and 45-47; An anti-TSLP antibody (6A3) comprising a HC CDR3 comprising the sequence of SEQ ID NO:50, wherein the other CDRs of the HC and LC comprise the sequences of SEQ ID NOs: 48, 49, and 51-53; An anti-TSLP antibody (1A11) comprising a HC CDR3 comprising the sequence of SEQ ID NO:56, wherein the other CDRs of the HC and LC comprise the sequences of SEQ ID NOs: 54, 55, and 57-59; An anti-TSLP antibody comprising (i) heavy chain variable region of SEQ ID NO:60 and/or the light chain variable region of SEQ ID NO:61; An anti-TSLP antibody comprising (i) heavy chain variable region of SEQ ID NO: 62 and/or the light chain variable region of SEQ ID NO:63; An anti-TSLP antibody comprising (i) heavy chain variable region of SEQ ID NO: 64 and/or the light chain variable region of SEQ ID NO:65; An anti-TSLP antibody comprising (i) heavy chain variable region of SEQ ID NO:66 and/or the light chain variable region of SEQ ID NO: 67; An anti-TSLP antibody comprising (i) heavy chain variable region of SEQ ID NO: 68 and/or the light chain variable region of SEQ ID NO: 69; An anti-TSLP antibody comprising a HC CDR selected from the group consisting of SEQ ID NO:38, SEQ ID NO:44, SEQ ID NO:50 and SEQ ID NO:56, and analogs thereof;

	An anti-TSLP antibody comprising a heavy chain comprising the following CDRs or analogs thereof CDRH1 : RYNVH (SEQ ID NO:36), CDRH2: MIWDGGSTDYNSALKS (SEQ ID NO:37), CDRH3: NRYESG (SEQ ID NO:38), and a light chain comprising the following CDRs or analogs thereof CDRL1 : KSSQSLNLSGNRKNYLT (SEQ ID NO:39), CDRL2: WASTRES (SEQ ID NO:40), and CDRL3: QNDYTYPFTFGS (SEQ ID NO:41); or An anti-TSLP antibody comprising a heavy chain comprising the following CDRs or analogs thereof CRDH1 : AYWMS (SEQ ID NO:42),CDRH2: EINPDSSTINCTPSLKD (SEQ ID NO:43), CDRH3: RLRPFWYFDVW (SEQ ID NO:44), and a light chain comprising the following CDRs or analogs thereof CDRL1 : RSSQSIVQSNNGNTYLE (SEQ ID NO:45), CDRL2: KVSNRFS (SEQ ID NO:46), and CDRL3: FQGSHVPRT (SEQ ID NO:47); An anti-TSLP antibody comprising a heavy chain comprising the following CDRs or analogs thereof CRDH1 : TDYAWN (SEQ ID NO:48), CDRH2: YIFYSGSTTYTPSLKS (SEQ ID NO:49), CDRH3: GGYDVNYF (SEQ ID NO:50), and a light chain comprising the following CDRs or analogs thereof CDRL1 : LASQTIGAWLA (SEQ ID NO:51), CDRL2: AATRLAD (SEQ ID NO:52), and CDRL3: QQFFSTPWT (SEQ ID NO:53); An anti-TSLP antibody comprising a heavy chain comprising the following CDRs or analogs thereof CDRH1 : GYTMN (SEQ ID NO:54), CDRH2: LINPYNGVTSYNQKFK (SEQ ID NO:55), CDRH3: GDGNYWYF (SEQ ID NO:56), and a light chain comprising the following CDRs or analogs thereof CDRL1 : SASSSVTYMHW (SEQ ID NO:57), CDRL2: EISKLAS (SEQ ID NO:58), and CDRL3: QEWNYPYTF (SEQ ID NO:59); An anti-TSLP antibody comprising a HC CDR1 comprising the sequence of SEQ ID NO: 70; a CDR2 comprising the sequence of SEQ ID NO: 71, and a CDR3 comprising the sequence of SEQ ID NO: 72; An anti-TSLP antibody comprising a LC CDR1 comprising the sequence of SEQ ID NO: 73; a CDR2 comprising the sequence of SEQ ID NO: 74, and a CDR3 comprising the sequence of SEQ ID NO: 75;
US2012/0020988	An anti-TSLP antibody comprising a heavy chain variable domain comprising a CDR1 region of SEQ ID NO: 76, a CDR2 region of SEQ ID NO:77, and CDR3 region of SEQ ID NO:78, and a light chain variable

	domain comprising a CDR1 region of SEQ ID NO: 79, a CDR2 region of SEQ ID NO:80, and a CDR3 region of SEQ ID NO:81. An anti-TSLP antibody comprising a heavy chain variable domain comprising SEQ ID NO:82 and a light chain variable domain comprising SEQ ID NO:83; An anti-TSLP antibody comprising a heavy chain variable domain comprising a CDR1 region of SEQ ID NO: 76 or 84, a CDR2 region of SEQ ID NO: 77 or 85, and CDR3 region of SEQ ID NO: 78, and a light chain variable domain comprising a CDR1 region of SEQ ID NO: 79 or 86, a CDR2 region of SEQ ID NO: 80, 87, or 88, and a CDR3 region of SEQ ID NO: 81. An anti-TSLP antibody comprising a heavy chain variable domain comprising a CDR1 region of SEQ ID NO: 76, a CDR2 region of SEQ ID NO:85, and CDR3 region of SEQ ID NO: 78, and a light chain variable domain comprising a CDR1 region of SEQ ID NO: 86, a CDR2 region of SEQ ID NO:87 and a CDR3 region of SEQ ID NO:81; An anti-TSLP antibody comprising a heavy chain variable domain comprising a CDR1 region of SEQ ID NO: 76, a CDR2 region of SEQ ID NO:85, and CDR3 region of SEQ ID NO: 78, and a light chain variable domain comprising a CDR1 region of SEQ ID NO: 86, a CDR2 region of SEQ ID NO:88 and a CDR3 region of SEQ ID NO:81; An anti-TSLP antibody comprising a heavy chain variable domain comprising a CDR1 region of SEQ ID NO: 84, a CDR2 region of SEQ ID NO:85, and CDR3 region of SEQ ID NO: 78, and a light chain variable domain comprising a CDR1 region of SEQ ID NO: 86, a CDR2 region of SEQ ID NO:88 and a CDR3 region of SEQ ID NO:81; or An anti-TSLP antibody comprising a heavy chain variable domain comprising a CDR1 region of SEQ ID NO: 76, a CDR2 region of SEQ ID NO:85, and CDR3 region of SEQ ID NO: 78, and a light chain variable domain comprising a CDR1 region of SEQ ID NO: 86, a CDR2 region of SEQ ID NO: 80 and a CDR3 region of SEQ ID NO:81. An anti-TSLP antibody comprising a heavy chain variable domain comprises SEQ ID NO:89 and a light chain variable domain comprises SEQ ID NO:90;
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	An anti-TSLP antibody comprising a heavy chain variable domain comprises SEQ ID NO:89 and a light chain variable domain comprises SEQ ID NO:91; An anti-TSLP antibody comprising a heavy chain variable domain comprises SEQ ID NO:92 and a light chain variable domain comprises SEQ ID NO:93; An anti-TSLP antibody comprising a heavy chain variable domain comprises SEQ ID NO:89 and a light chain variable domain comprises SEQ ID NO:94,
US8637019	An anti-TSLP antibody comprising heavy chain variable region comprising: a CDR-H1 sequence comprising SEQ ID NO:95, a CDR-H2 sequence comprising SEQ ID NO:96, and a CDR-H3 sequence comprising SEQ ID NO:97; and/or an antibody light chain variable region or a TSLP-binding fragment thereof, said light chain variable region comprising: a CDR-L1 sequence comprising SEQ ID NO: 98, a CDR-L2 sequence comprising SEQ ID NO: 99, and a CDR-L3 sequence comprising SEQ ID NO: 100. An anti-TSLP antibody comprising a heavy chain variable region comprises the amino acid sequence of SEQ ID NO:101 and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 102. An anti-TSLP antibody comprising SEQ ID NO:103 and SEQ ID NO:104.

[0147] In various embodiments, the antibody is tezepelumab or a tezepelumab variant or tezepelumab derivative.

[0148] It is provided that the subject to be treated is human. The subject may be an adult, an adolescent, or a child.

[0149] Therapeutic antibody (or antibody variant) compositions may be delivered to the patient at multiple sites. The multiple administrations may be rendered simultaneously or may be administered over a period of time. In certain cases it is beneficial to provide a continuous flow of the therapeutic composition. Additional therapy may be administered on a period basis, for example, hourly, daily, weekly, every 2 weeks, every 3 weeks, monthly, bimonthly, or at a longer interval.

[0150] In various embodiments, the amounts of therapeutic agent, such as a bivalent antibody having two TSLP binding sites, in a given dosage may vary according to the size of the individual to whom the therapy is being administered as well as the characteristics of the disorder being treated.

[0151] In exemplary treatments, the anti-TSLP antibody or antibody variant is administered in a dose range of about 140 mg to about 420 mg per dose. In various embodiments, the dose may be given in about 140 mg, 210 mg, 280 mg or 420 mg. In various embodiments, the anti-TSLP antibody or antibody variant may be administered at a dose of about 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410 or 420 mg per dose. These concentrations may be administered as a single dosage form or as multiple doses. The above doses are given every two weeks or every four weeks. In various embodiments, the anti-TSLP antibody or antibody variant is administered at a single dose of 210 mg every two weeks or every four weeks. In various embodiments, the anti-TSLP antibody or antibody variant is administered at a single dose of 210 mg every four weeks.

[0152] For antibody variants, the amount of antibody variant should be such that the number of TSLP binding sites that are in the dose have an equimolar number of TSLP binding sites to canonical bivalent antibody described above.

[0153] It is provided that the anti-TSLP antibody or antibody variant is administered every 2 weeks or every 4 weeks for a period of at least 4 months, 6 months, 9 months, 1 year, 2 years or more. In various embodiments, the administration is subcutaneous or intravenous. In various embodiments, the administration is subcutaneous.

[0154] Treatment with the anti-TSLP antibody or antibody variant is provided to improve one or more measures of corticosteroid-dependent asthma including forced expiratory volume (FEV), FEV₁ reversibility, forced vital capacity (FVC), FeNO, Asthma Control Questionnaire (ACQ)-6 score and AQLQ(S)+12 score, change from baseline in pre-BD FEV₁, reduction from baseline in daily maintenance OCS dose, daily maintenance OCS dose $\leq$ 5 mg, and $\geq$ 50% reduction from baseline in daily maintenance OCS dose, asthma exacerbations, as measured by AAER and time to first asthma exacerbation, rate of asthma exacerbations associated with emergency room (ER) visit, urgent care visit or hospitalization, and proportion of participants who did not experience an asthma exacerbation, weekly mean home PEF (morning and evening), and/or St George's Respiratory Questionnaire (SGRQ) score. It is further provided that the administration reduces the incidence of adrenal insufficiency in a subject.

[0155] In one embodiment, the administration improves one or more symptoms of corticosteroid-dependent asthma including, but not limited to, lung function, such as pre-bronchodilator forced expiratory volume in 1 second (pre-BD FEV₁), and/or daily maintenance OCS dose in a subject while maintaining asthma control. In various embodiments, the administration results in discontinued OCS without loss of asthma control.

[0156] In various embodiments, treatment with anti-TSLP modulates the levels of one or more biomarkers of chronic rhinosinusitis, including, cytokines, IgE, CCL17, CCL18, CCL22, and RNA transcriptional changes in nasal epithelium. In various embodiments, treatment with anti-TSLP reduces the level of Th2 cytokines. In various embodiments, the treatment modulates levels of or activity of IL-4, IL-5, IL-13, IL-17, IL-22, IL-23, IL-31, and/or IL-33, or combinations thereof.

[0157] In various embodiments, treatment with the anti-TSLP antibody delays the time to an asthma exacerbation or flare up compared to a subject not receiving the anti-TSLP antibody.

[0158] Also provided in the present disclosure is the administration of multiple agents, such as an antibody composition in conjunction with a second agent as described herein, including but not limited to an anti-inflammatory agent or asthma therapy.

[0159] However, it is provided that, in various embodiments, the administration reduces frequency of or levels of co-administered therapy in the subject, e.g., compared to baseline frequency/levels of the subject or compared to a control. Exemplary co-administered therapies include, but are not limited to, systemic corticosteroids, dupilumab, immunosuppressive or immunomodulating drugs (e.g., cyclosporine, mycophenolate-mofetil, interferon (IFN)-gamma, Janus kinase inhibitors, azathioprine, methotrexate), anti-IL-13 antibodies, anti-IL-5 pathway antibodies (benralizumab, mepolizumab, reslizumab), or combinations thereof. In various embodiments, the administration eliminates the need for corticosteroid therapy or other adjunct therapy.

[0160] In various embodiments, the subject is also receiving treatment with corticosteroids. In various embodiments the corticosteroids are oral corticosteroids selected from the group consisting of one or more of prednisone, prednisolone, cortisone, hydrocortisone, methylprednisolone, triamcinolone, betamethasone, dexamethasone, and deflazacort.

[0161] In various embodiments, the method comprises administering anti-TSLP antibody or antibody variant in conjunction with an oral corticosteroid, wherein the subject goes

through an optimization phase of OCS therapy, a reduction phase of OCS therapy and a maintenance phase of OCS therapy.

[0162] In various embodiments, the method comprises reducing the dose of corticosteroids when the subject receives a reduction phase of treatment. In various embodiments, the dose of corticosteroid is reduced every 4 weeks for approximately 20 weeks. In various embodiments, the dose of corticosteroid is reduced by 5 mg/day or 2.5 mg/day.

[0163] In various embodiments, the optimization phase comprises a dose of OCS of 30 mg/day, 25 mg/day, 20 mg/day, 15 mg/day, 10 mg/day, 7.5 mg/day or 5 mg/day. In various embodiments, the reduction phase comprises a dose of OCS of 25 mg/day, 20 mg/day, 15 mg/day, 10 mg/day, 7.5 mg/day, 5 mg/day, 2.5 mg/day or 0 mg/day. In various embodiments, the maintenance phase comprises a dose of OCS of 15 mg/day, 10 mg/day, 7.5 mg/day, 5 mg/day, 2.5 mg/day or 0 mg/day.

[0164] It is provided that the dose of oral corticosteroid administered is adjusted for the therapeutic being administered, e.g., as set out in Figure 2B, to provide the equivalent dose amount. For example, a higher dose of cortisone may be needed to provide what is equivalent to a dose of prednisone, or a lower dose of dexamethasone may be needed to provide an equivalent dose to prednisone. One of skill would understand how to adjust the dose as needed.

[0165] In various embodiments, the administration eliminates the need for oral corticosteroid therapy for an extended period of time, e.g., 6 months, 1 year, 2 years, 3 years or indefinitely.

Formulations

[0166] In some embodiments, the disclosure provides use of pharmaceutical compositions comprising a therapeutically effective amount of an anti-TSLP antibody or antibody variant together with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative, and/or adjuvant. In addition, the disclosure provides methods of treating a subject by administering such pharmaceutical composition.

[0167] In certain embodiments, acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed. In certain embodiments, the pharmaceutical composition may contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolality, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In such embodiments, suitable formulation materials include, but are not limited to, amino acids

(such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, sucrose, mannose or dextrans); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. See, REMINGTON'S PHARMACEUTICAL SCIENCES, 18th Edition, (A. R. Genrmo, ed.), 1990, Mack Publishing Company.

[0168] A suitable vehicle or carrier may be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In specific embodiments, pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, and may further include sorbitol or a suitable substitute therefor.

[0169] The formulation components are present preferably in concentrations that are acceptable to the site of administration. In certain embodiments, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 4.5 to about 8. Including about 4.5, about 4.6, about 4.7, about 4.8, about 4.9., about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, and about 8.0.

[0170] In various embodiments, the anti-TSLP antibody or antibody variant is in a formulation containing one or more basic amino acids (e.g., arginine, histidine or lysine) or salt thereof, or a calcium or magnesium salt, and a surfactant. In various embodiments, the formulation comprises 0.005% (w/v) to about 0.015% (w/v) polysorbate 20 or polysorbate 80. In various embodiments, the formulation is at pH between 4.5 and 6.8. In various embodiments, the antibody or antibody fragment in the formulation is at a concentration of greater than 110 mg/ml, e.g., from about 110 mg/ml to about 250 mg/ml, e.g., from about 140 mg/ml to about 250 mg/ml, from about 160 mg/mL to about 250 mg/mL, or from about 140 mg/mL to about 210 mg/mL, or about 180 mg/ml or about 210 mg/ml. The formulation may be stored at 2° to 8° C or -20° to -70° C. Exemplary formulations are described in co-owned application PCT/US2021/17880, incorporated herein by reference.

[0171] In various embodiments, the anti-TSLP antibody or antibody variant is in a formulation containing comprising greater than about 100 mg/mL of an anti-TSLP antibody, a surfactant, proline, and a buffer. In exemplary instances, the surfactant, e.g., polysorbate 80, is present in the composition at a concentration about 0.005% (w/v), 0.010% (w/v), or 0.015% (w/v). In exemplary aspects, the composition comprises equal to or less than about 3.0% (w/v) proline, e.g., about 2.4% (w/v) to about 2.8% (w/v) proline or about 2.5% (w/v) to about 2.8% (w/v) proline. In exemplary instances, the proline is L-proline. In certain aspects, proline is the only amino acid present in the composition. In exemplary aspects, the buffer is selected from the group consisting of: succinate, glutamate, histidine, and acetate. In some embodiments, the buffer is acetate. In exemplary aspects, the composition comprises about 1 mM to about 50 mM buffer, e.g., about 10 mM to about 30 mM buffer, optionally, about 15 mM to about 30 mM buffer, about 20 mM to about 30 mM buffer, or about 10 mM to about 25 mM buffer. Exemplary formulations are described in co-owned application PCT/US2021/018561, incorporated herein by reference.

[0172] In various embodiments, the anti-TSLP antibody is administered in a dose of 110 mg/mL in 10 mM acetate, 3.0% (w/v) L-proline, 0.01 % (w/v) polysorbate 80, at pH 5.2.

[0173] When parenteral administration is provided, the therapeutic compositions for use may be provided in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired anti-TSLP antibody in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which the antibody is formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, the preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads or liposomes, that may provide controlled or

sustained release of the product which can be delivered via depot injection. In certain embodiments, hyaluronic acid may also be used, having the effect of promoting sustained duration in the circulation. In certain embodiments, implantable drug delivery devices may be used to introduce the antibody. In various embodiments, the administration may be via pre-filled syringe or autoinjector. In various embodiments, the auto-injector is an Ypsomed YpsoMate®. In various embodiments, the auto-injector is disclosed in WO 2018/226565, WO 2019/094138, WO 2019/178151, WO 20120/072577, WO2020/081479, WO 2020/081480, PCT/US20/70590, PCT/US20/70591, PCT/US20/53180, PCT/US20/53179, PCT/US20/53178, or PCT/US20/53176.

Kits

[0174] As an additional aspect, the disclosure includes kits which comprise one or more compounds or compositions packaged in a manner which facilitates their use to practice methods of the disclosure. In one embodiment, such a kit includes a compound or composition described herein, packaged in a container such as a sealed bottle or vessel, with a label affixed to the container or included in the package that describes use of the compound or composition in practicing the method. Preferably, the compound or composition is packaged in a unit dosage form for administration as described herein. The kit may further include a device suitable for administering the composition according to a specific route of administration or for practicing a screening assay. Preferably, the kit contains a label that describes use of the antibody composition.

[0175] Additional aspects and details of the disclosure will be apparent from the following examples, which are intended to be illustrative rather than limiting.

EXAMPLES

Example 1—A Phase 3 Study to Evaluate the Effect of Tezepelumab in Oral Corticosteroid-Dependent Asthma

[0176] In the previous phase 2b study, PATHWAY (NCT02054130) and phase 3 NAVIGATOR (NCT03347279) study, tezepelumab treatment reduced the annualized asthma exacerbation rate (AAER) over 52 weeks and improved lung function, asthma control and health-related quality of life (HRQoL) in patients with severe, uncontrolled asthma, including those receiving maintenance OCS (Corren J et al. N Engl J Med 2017;377:936–46; Menzies-Gow A et al. N Engl J Med 2021;384:1800–9).

[0177] The aim of the present study is to investigate the efficacy and safety of tezepelumab in participants with severe oral corticosteroid (OCS)-dependent asthma receiving medium- or high-dose inhaled corticosteroids (ICS) for ≥ 12 months, a LABA and high-dose ICS for ≥ 3 months, OCS for ≥ 6 months and a stable dose of 7.5 mg to ≤ 30 mg OCS daily for ≥ 1 month to achieve asthma control.

[0178] Approximately 207 patients from global study sites are randomized 2:1 to receive tezepelumab 210 mg or placebo every 4 weeks. The participants are evaluated to ensure that a maximum of 20% of participants have a baseline blood eosinophil count (BEC) of < 150 cells/ μL at screening; these patients must have a history of a BEC of ≥ 300 cells/ μL in the 12 months before study entry. Approximately 40% of participants have a BEC of ≥ 300 cells/ μL at screening.

[0179] Treatment allocation is stratified by region and BEC at screening (< 150 cells/ μL ; $150 - < 300$ cells/ μL ; ≥ 300 cells/ μL), to ensure that treatment assignment across regions and blood eosinophil subgroup is balanced. Participants are adults with severe asthma who require daily or daily equivalent maintenance OCS therapy in addition to high dose ICS plus LABA, with or without other asthma controllers, and who have had at least 1 asthma exacerbation in the previous 2 years and have received at least one dose of study intervention.

[0180] Inclusion criteria for the study:

[0181] 1. Participant must be 18 to 80 years of age inclusive, at the time of signing the informed consent form.

[0182] 2. Documented physician-diagnosed asthma for at least 12 months prior to Visit 1.

[0183] 3. Participants must have received a physician-prescribed medium- or high-dose ICS (medium dose ICS corresponds to 500 μg and high dose ICS corresponds to > 500 μg fluticasone propionate dry powder formulation or equivalents) as per GINA guideline (GINA 2022) for at least 12 months prior to Visit 1.

[0184] 4. Participants must have received physician-prescribed LABA and high dose ICS (total daily dose > 500 μg fluticasone propionate dry powder formulation or equivalent) for at least 3 months prior to Visit 1. The ICS and LABA can be parts of a combination product or given by separate inhalers. (a) Equivalent ICS doses as detailed in Appendix G

[0185] 5. Additional maintenance asthma controller medications are allowed according to standard practice of care i.e., leukotriene receptor antagonists (LTRAs), theophylline, long-

acting muscarinic antagonists (LAMAs), and chromones. The use of these medications must be documented for at least 3 months prior to Visit 1.

[0186] 6. Participants must have received OCS for the treatment of asthma for at least 6 months prior to Visit 1 and on a stable dose of between ≥ 7.5 to ≤ 30 mg (prednisone or prednisolone) daily or daily equivalent for at least one month prior to Visit 1. The OCS dose may be administered every other day (or different doses every other day); Average dose over 2 days = The daily dose.

[0187] 7. Morning pre-BD FEV₁ must be $< 80\%$ predicted normal at Visit 1 or Visit 2.

[0188] 8. Evidence of asthma as documented by either: (a) Post-BD (albuterol/salbutamol) responsiveness test result: FEV₁ $\geq 12\%$ and ≥ 200 mL (15-30 min after administration of 4 puffs of albuterol/salbutamol), documented either in the previous 60 months prior to or at Visit 1 or at Visit 2 or at Visit 3; OR (b) Airway hyperresponsiveness (methacholine: provocative concentration that causes a positive reaction [PC20] of < 8 mg/mL) documented in the 60 months prior to Visit 1.

[0189] 9. Blood eosinophils at Visit 1 ≥ 150 cells/ μ L ($\geq 0.15 \times 10^9$ /L or $\geq 0.15 \times 10^3$ / μ l) or documented EOS ≥ 300 cells/ μ L ($\geq 0.3 \times 10^9$ /L or $\geq 0.3 \times 10^3$ / μ l) within 12 months prior to Visit 1.

[0190] 10. Participants must have a history of at least one asthma exacerbation event within 24 months prior to Visit 1. For the purpose of this study an asthma exacerbation is defined as a worsening of asthma that either: (a) required treatment with a burst of systemic corticosteroids for at least 3 consecutive days or a single depot- injectable corticosteroid dose OR (b) resulted in an emergency department visit (defined as evaluation and treatment for < 24 hours in an ER or urgent care center) which required systemic corticosteroids (as per above) OR (c) an inpatient hospitalization due to asthma (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours).

[0191] 11. Body weight ≥ 40 kg at Visit 1.

[0192] 12. Male or female.

[0193] 13. All women of childbearing potential must have a negative serum pregnancy test results at Visit 1 and a negative urine pregnancy test at randomization.

[0194] 14. Female participants of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrolment throughout the study and until at least 16 weeks after last dose of study intervention. Cessation of contraception after this point should be discussed

with a responsible physician. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea.

[0195] Exclusion criteria include:

[0196] 1. Any clinically important pulmonary disease other than asthma (e.g., active lung infection, Chronic Obstructive Pulmonary Disease (COPD), bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (e.g., allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome).

[0197] 2. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that is not stable in the opinion of the investigator and could: (a) Affect the safety of the participant throughout the study (b) Influence the findings of the study or the interpretation (c) Impede the participant's ability to complete the entire duration of study

[0198] 3. History of cancer: (a) Participants who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible to participate in the study provided that curative therapy was completed at least 12 months prior to Visit 1. (b) Participants who have had other malignancies are eligible provided that curative therapy was completed at least 5 years prior to Visit 1.

[0199] 4. Asthma exacerbation, requiring use of systemic corticosteroids or increase in the maintenance dose of OCS finalized within 30 days prior to Visit 1.

[0200] 5. Clinically significant infection, including upper or lower respiratory tract infection (URTI and LRTI, respectively), requiring treatment with systemic antibiotics or antiviral medications finalized < 2 weeks before Visit 1 or during the run-in period.

[0201] 6. Participants with evidence of active COVID-19 infection during run-in period and optimization. Evaluation will be based on local standard of care as determined by current local guidelines.

[0202] 7. A helminth infection diagnosed within 6 months prior to Visit 1 that has not been treated with, or has failed to respond to, standard of care therapy.

[0203] 8. A participant who is on short-acting beta agonists (SABA) maintenance treatment within 30 days prior to Visit 1.

- [0204]** 9. Current smokers or participants with smoking history ≥ 10 pack-years and participants using vaping products, including electronic cigarettes. Former smokers with a smoking history of < 10 pack-years and users of vaping or e-cigarette products must have stopped for at least 6 months prior to Visit 1 to be eligible.
- [0205]** 10. Chronic alcohol or drug abuse within 12 months prior to Visit 1.
- [0206]** 11. Tuberculosis requiring treatment within the 12 months prior to Visit 1.
- [0207]** 12. A positive human immunodeficiency virus (HIV) test at Visit 1 or participant taking antiretroviral medications or history of any known immunodeficiency disorder, as determined by medical history and/or participant's verbal report.
- [0208]** 13. Major surgery within 8 weeks prior to Visit 1 or planned surgical procedures requiring general anesthesia or hospitalization for > 1 day during the conduct of the study.
- [0209]** 14. Receipt of any marketed or investigational biologic agent within 4 months or 5 half-lives (whichever is longer) prior to Visit 1 or receipt of any investigational non-biologic agent within 30 days or 5 half-lives (whichever is longer) prior to Visit 1.
- [0210]** 15. Treatment with the following medications within the last 12 weeks or 5 half-lives (whichever is longer) prior to Visit 1: systemic immunosuppressive/immunomodulating drugs (e.g., methotrexate, cyclosporine, oral/parenteral/intra-articular corticosteroids for other use than treatment of asthma)
- [0211]** 16. Receipt of immunoglobulin or blood products within 30 days prior to Visit 1.
- [0212]** 17. Receipt of the T2 cytokine inhibitor Suplatast tosilate within 15 days prior to Visit 1.
- [0213]** 18. Receipt of live attenuated vaccines 30 days prior to the date of randomization and during the study including the follow-up period.
- [0214]** 19. COVID-19 vaccination within 28 days prior to randomization.
- [0215]** 20. Participants who have been treated with bronchial thermoplasty within 36 months prior to Visit 1.
- [0216]** 21. Sensitivity to any component of the study intervention formulation or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation.
- [0217]** 22. History of anaphylaxis or documented immune complex disease (Type III hypersensitivity reactions) following any biologic therapy.

- [0218] 23. Concurrent enrollment in another IP-related interventional clinical trial.
- [0219] 24. Participant randomized in other ongoing or previous tezepelumab studies.
- [0220] 25. Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff and/or site staff), or participants employed by or relatives of the employees of the site or sponsor.
- [0221] 26. Any clinically meaningful abnormal findings in physical examination, vital signs, electrocardiogram (ECG), haematology, clinical chemistry, or urinalysis during the run-in period, which in the opinion of the investigator, may put the participant at risk because of his/her participation in the study, or may influence the results of the study, or the participant's ability to complete entire duration of the study.
- [0222] 27. Evidence of active liver disease, including jaundice or aspartate transaminase, alanine transaminase, or alkaline phosphatase beyond twice the upper limit of normal (ULN), at Visit 1.
- [0223] 28. Positive hepatitis B surface antigen, or hepatitis C virus antibody serology at Visit 1, or a positive medical history for hepatitis B or C. Participants with a history of hepatitis B vaccination without a history of hepatitis B are allowed to participate.
- [0224] 29. Women who are currently pregnant (confirmed with positive pregnancy test) or breastfeeding or lactating.
- [0225] 30. Unwillingness or inability to follow the study procedures, or restrictions, in the opinion of the investigator
- [0226] 31. Previous allogeneic bone marrow transplant.
- [0227] 32. Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.
- [0228] 33. During the optimization period, asthma control reached at an OCS dose of < 7.5 mg or > 30 mg and/or 3 consecutive dose reductions after which asthma control was still obtained.
- [0229] 34. Evidence of clinically significant infection (including COVID-19) or participant receiving treatment with systemic antibiotics or antiviral medications.
- [0230] 35. Despite screening of the participant, enrolment/randomization is stopped at the study level.
- [0231] **Regimen:** The study comprises a 2-week run-in period followed by an up to 8-week OCS optimization phase, a 28-week treatment period and a 12-week follow-up period.

The aim of the OCS optimization phase is to identify the lowest OCS dose at which asthma control is maintained. During this phase, the entry OCS dose will be reduced every 2 weeks as per the titration schema shown in Figure 1, providing that all the criteria for OCS dose reduction are met (Table 1). There are three phases in the treatment period: Induction phase: a 4-week period (Week 0 to Week 4) during which participants remain on their optimized OCS dose; OCS reduction phase: a 20-week period (Week 4 to Week 24) during which the OCS dose will be reduced at the start of the phase and then every 4 weeks, providing that all the criteria for OCS reduction are met (Table 1); Maintenance phase: a 4-week period (Week 24 to Week 28) during which participants remain on the stable maintenance OCS dose reached during the reduction phase or continue without OCS if the dose was reduced to 0 mg.

Table 1. OCS dose reduction schedule during the optimization phase

Regimen	Starting dose of OCS (mg/day) at each visit of optimization phase	Change by (mg/day) ^a
Daily regimen	>10-30	5.0
	7.5-10	2.5

^a During the Optimization phase the reductions should occur at 2-week intervals

Table 2. Exemplary OCS Dose Reduction Schedule During the Reduction Phase

Optimized dose a Wk0	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24
30 ^a	25	20	15	10	7.5	5
25	20	15	10	7.5	5	2.5
20	15	10	7.5	5	2.5	0
15	10	7.5	5	2.5	0	0
12.5	7.5	5	2.5	0	0	0
10	7.5	5	2.5	0	0	0
7.5	5	2.5	0	0	0	0

^a All doses expressed in mg/day of Prednisone/Prednisolone.

The OCS dose may be administered every other day (or different doses every other day). Average dose over 2 days = The daily dose

[0232] Tezepelumab is administered at a 110 mg/mL in 10 mM acetate, 3.0% (w/v) L-proline, 0.01 % (w/v) polysorbate 80, pH 5.2. Placebo is 0.7% (w/v) sodium carboxy methyl cellulose in 10 mM acetate, 250 mM L-proline, 0.01% (w/v) polysorbate 80, pH 5.0.

[0233] Medium dose ICS corresponds to 500 µg and high dose ICS corresponds to > 500 µg fluticasone propionate dry powder formulation or equivalents as outlined in Figure 2. Participants may also receive other physician-prescribed asthma controller medications.

[0234] ENDPOINTS AND ASSESSMENTS

[0235] Primary endpoints include assessing the effect of tezepelumab compared with placebo in reducing the prescribed maintenance OCS dose while maintaining asthma control as set out in Table 3. Efficacy will be determined by the percentage reduction from baseline in the daily maintenance OCS dose at week 28 while maintaining asthma control.

Table 3. Asthma control criteria for oral corticosteroid dose reduction

Criterion ^a	Definition of Asthma Control
1	Mean morning PEF ≥ 80% of baseline
2	An increase of no more than two nights with asthma-related awakenings (requiring rescue medication) over a 7-day period compared with baseline
3	Mean use of SABA rescue medication: no more than four inhalations/day above baseline
4	Pre-BD FEV ₁ ≥ 80% of baseline
5	No requirement to increase dose of systemic corticosteroids for asthma symptoms/exacerbations since last visit
6	Non-asthma criterion: no signs or symptoms of adrenal insufficiency

^a If the participant does not meet at least one of the asthma control criteria listed for OCS dose reduction, the OCS dose will be returned to the last effective dose and further OCS dose reductions will not take place.

OCS, oral corticosteroids; PEF, peak expiratory flow; Pre-BD FEV₁, pre-bronchodilator forced expiratory volume in 1 second; SABA, short-actingβ₂-agonist.

[0236] The categories for percent change from baseline in daily OCS dose are defined as: 1. ≥ 90% to ≤ 100% reduction; 2. ≥ 75% to < 90% reduction; 3. ≥ 50% to < 75% reduction; 4. > 0% to < 50% reduction; 5. no change or any increase. A secondary objective of the study is change from baseline in pre-bronchodilator forced expiratory volume in 1 second (pre-BD FEV₁) at Week 28.

[0237] Secondary endpoints include the ability of tezepelumab to improve lung function, asthma control and HRQoL and reduce asthma exacerbations, while reducing OCS dose, for example as measured by change from baseline in pre-BD FEV₁ at week 28.

[0238] Additional outcome metrics include the following:

[0239] Evaluation of the effect of tezepelumab compared with placebo on the daily dose of maintenance OCS Proportion of participants at week 28 with 100% reduction from baseline in daily maintenance OCS dose, daily maintenance OCS dose ≤ 5 mg, and $\geq 50\%$ reduction from baseline in daily maintenance OCS dose at week 28;

[0240] Evaluation of the effect of tezepelumab compared with placebo on asthma exacerbations, as measured by AAER over 28 weeks and time to first asthma exacerbation, with supportive outcome variables including rate of asthma exacerbations associated with emergency room (ER) visit, urgent care visit or hospitalization over 28 weeks, and proportion of participants who did not experience an asthma exacerbation over 28 weeks;

[0241] Assessment of the effect of tezepelumab compared with placebo on asthma control and other asthma control metrics such as change from baseline in ACQ-6 score at week 28, and/or weekly mean home PEF (morning and evening) at week 28'

[0242] Assessment of the effect of tezepelumab compared with placebo on asthma-related quality of life as measured by change from baseline in AQLQ(s)+12 total score at week 28, and/or St George's Respiratory Questionnaire (SGRQ) score at week 28;

[0243] Assessment of the effect of tezepelumab on biomarkers such as change from baseline in FeNO, peripheral blood eosinophils and total serum IgE at week 28;

[0244] Evaluation of the pharmacokinetics of tezepelumab, such as tezepelumab serum trough concentrations at weeks 0, 12 and 28;

[0245] Evaluation of the immunogenicity of tezepelumab, as measured by incidence of anti-drug antibodies at weeks 0, 12, 28 and 40.

[0246] Further assessments include assessing the effect of tezepelumab compared with placebo on other pre-BD lung function measures, as measured by the change from baseline in pre-BD forced vital capacity (FVC) at Week 28, forced expiratory flow over 25- 75% of the vital capacity (FEF25-75%) at Week 28; assessments of the effect of tezepelumab compared with placebo on post-BD lung function as measured by the change from baseline in post-BD forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC) at Week 28, and forced expiratory flow over 25- 75% of the vital capacity (FEF25-75%) at Week 28; assessing the effect of tezepelumab compared with placebo on general health-related quality of life, as measured by change from baseline in European Quality of Life - 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L) score at Week 28; assess the effect of tezepelumab compared with placebo on health status of participants with airway obstruction disease as measured by change from baseline in weekly mean daily Asthma Symptom Diary (ASD) at Week 28; and assessment of efficacy of tezepelumab compared with placebo on

health resource utilization as measured by efficacy of tezepelumab compared with placebo on health resource utilization.

Table 4. Asthma Worsening Alert Criteria

Criteria ^{a,b}	Definition
1	Decrease in morning peak expiratory flow $\geq 20\%$ on at least 2 consecutive days compared with the average at baseline
2	An increase in rescue medication use of ≥ 5 puffs/day on at least 2 consecutive days compared with the average use during baseline
3	An additional nebulized β_2 agonist use on at least 2 consecutive days compared with the average use during baseline
4	An increase of 3 or more nights with awakenings due to asthma requiring rescue medication over a 7-day period compared with baseline
5	An increase in global asthma symptom score of at least 2 units above the baseline average or the highest possible score (daily score of 6), on at least 2 consecutive days

a An alert in itself will not qualify as a clinically significant exacerbation and the site should follow up with the participant as appropriate.

b Baseline values for alerts will be calculated from the most recent 7 days of available data prior to Visit 2 for the optimization phase and prior to randomization Visit 6 for the treatment period.

[0247] *Spirometry*: Lung function (FEV₁; FEF 25 to 75% and forced vital capacity [FVC]) will be measured by spirometry at the study site using equipment provided by a central vendor. Spirometry is performed by the investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Graham et al 2019). The Global Lung Function Initiative (GLI) equations is used to determine the predicted normal values (PNV) and are pre-programmed into the spirometer (Quanjer et al 2012). FEV₁, expressed as percent of the PNV, is calculated as follows:

$$\text{FEV}_1\% \text{ of PNV} = (\text{FEV}_1 \text{ measured} / \text{FEV}_1 \text{ PNV}) \times 100$$

[0248] *Post-BD spirometry and bronchodilator responsiveness test*: Post-BD spirometry is performed. Bronchodilatation can be induced using albuterol (90 µg metered dose) or salbutamol (100 µg metered dose) up to a maximum of 4 inhalations. In rare cases where a participant has an adverse or allergic reaction to albuterol/salbutamol, levalbuterol (45 µg metered dose; up to a maximum of 4 inhalations) can be used. The highest pre- and post-BD FEV₁ is used to determine bronchodilator responsiveness. Bronchodilator responsiveness is calculated as follows:

$$\% \text{ Bronchodilator responsiveness} = (\text{post-BD FEV}_1 - \text{pre-BD FEV}_1) \times 100 / \text{pre-BD FEV}_1$$

[0249] *Home PEF testing*: An electronic, handheld spirometer to measure PEF (ePEF meter) is provided to the participant at Visit 1. Participants are trained on at-home use of the

ePEF meter at Visit 1. Home PEF testing is performed by the participant in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller).

[0250] *Fractional exhaled nitric oxide:* Airway inflammation is evaluated using a standardized single-breath FeNO test. The single exhalation technique recommended by the manufacturer will be followed (Alving et al 2017). Participants are asked whether they have had a respiratory infection in the 2 weeks prior to measurement. The FeNO measurements are not performed within 2 weeks of a respiratory infection. The FeNO test is performed prior to spirometry. Participants should not eat or drink one hour prior to having the FeNO test. Participants should not use their rescue SABA medication (e.g., albuterol/salbutamol) within 6 hours of the measurement. Inhaled BDs (including ICS-LABA) should be withheld for the effect duration specific to the BD spirometry requirements. NIOX VERO® Airway Inflammation Monitor will be used to measure FeNO.

[0251] *Hypothalamic-pituitary-adrenal Axis Evaluation.* For all participants, HPA axis integrity will be evaluated after 4 weeks on 5 mg/day and prior to tapering down the OCS dose (for participants with baseline OCS doses equal to 5 mg/day, this will be assessed 4 weeks after the first dose of tezepelumab administration and before initiation of the OCS reduction phase). The morning cortisol test will be done in all participants 4 weeks after reaching the 5 mg dose of OCS, and before further dose reductions. AI readouts include: normal AI >350 nmol/L SI, indeterminate results 100-350 nmol/L SI; complete AI <100 nmol/L SI, for participants not taking estrogen-containing contraceptives and for participants taking estrogen-containing contraceptives: normal >700 nmol/L, indeterminate results 200 - 700 nmol/L, complete AI <200 nmol/L.

[0252] *Adrenocorticotrophic Hormone Stimulation Test.* The tetracosactide (also known as Synacthen, Cortrosyn, or cosyntropin) ACTH stimulation test will be performed when morning cortisol levels are in the indeterminate range. The normal, indeterminate and complete AI ranges are the same as for the HPA axis test.

[0253] Patient reported outcomes are also collected.

[0254] *Asthma Daily Diary:* The daily diary is completed each day from the evening of Visit 1 to the morning of Visit 13. The morning diary includes: Asthma Symptom Diary (ASD) morning items, global asthma symptom item, questions about rescue medication, night-time awakening, and use of maintenance medications. The evening diary includes: ASD evening items, global asthma symptom item, questions about rescue medications, and OCS use.

Upon completion of the morning and evening questions, the participant will complete the peak expiratory flow assessment.

[0255] *Asthma Symptom Diary:* Asthma symptoms is recorded using the ASD (Globe et al 2015). The ASD comprises 10 items (5 items in the morning; 5 items in the evening). The morning items assess night-time symptom severity in relation to wheezing, shortness of breath, cough, and chest tightness, and the frequency of night-time awakening. The evening items assess symptom severity in relation to wheezing, shortness of breath, cough, and chest tightness, and activity limitation since waking. Items are scored from “0” (no symptom, no night-time awakening, or no activity limitation) to “4” (very severe symptom, unable to sleep, or extreme activity limitation). A daily ASD score is the mean of the 10 items. Responses for all 10 items are required to calculate the daily ASD score; otherwise, it is treated as missing. Calculation of a daily ASD score requires data from the evening diary assessment and the subsequent morning diary assessment. For the 7-day average asthma symptom score, scoring is done with no imputation using the mean of at least 4 of the 7 daily ASD scores as a mean weekly item score. The 7-day average ASD score ranges from 0 to 4.

[0256] *Global asthma symptom items:* In addition to the ASD, participants will complete a single-item global assessment of asthma symptoms (0 to 3) each morning and evening. The sum of evening and subsequent morning single global item scores (0 to 6) will be used for the alerts system.

[0257] *Asthma Control Questionnaire:* The Asthma Control Questionnaire (ACQ-6) is an assessment of asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and short acting beta-agonist use). Participants are asked to recall their level of asthma control during the previous week by responding to one bronchodilator use question and 5 symptom questions. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and < 1.5 indicate partly controlled asthma, and a score ≥ 1.5 indicates not well controlled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered to be clinically meaningful, and a decrease of at least 0.5 is the responder definition for ACQ-6.

[0258] *Standardized asthma quality of life questionnaire for 12 years and older (AQLQ(S)+12):* The AQLQ(S)+12 is a questionnaire that measures the health-related quality of life experienced by asthma participants. The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli). Participants are asked to recall their experiences during the previous 2 weeks and to score each of the

questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The 4 individual domain scores (symptoms, activity limitations, emotional function, and environmental stimuli) are the means of the responses to the questions in each of the domains. The responder definition for AQLQ(s)+12 is 0.5-point improvement from baseline.

[0259] *St George's Respiratory Questionnaire (SGRQ)*: The SGRQ is a 50-item PRO instrument developed to measure the health status of participants with airway obstruction diseases (Jones et al 1991). The questionnaire is divided into 2 parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and 3 component scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Likewise, the component scores range from 0 to 100, with higher scores indicative of greater impairment. Based on empirical data and interviews with patients, a mean change score of 4 units is associated with a minimum clinically important difference (MCID). Specific details on the scoring algorithms are provided by the developer in a user manual (Jones et al 2009).

[0260] *European quality of life-5 dimensions-5 levels (EQ-5D-5L)*: The EQ-5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty. The participant will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the participant will be asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state.

[0261] *Asthma exacerbations*: During the study, an asthma exacerbation is defined as a worsening of asthma that leads to any of the following:

[0262] • A temporary bolus/burst of systemic corticosteroids (or a temporary increase in stable OCS background dose) for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day burst of systemic corticosteroids.

[0263] • An emergency room or urgent care visit (defined as evaluation and treatment for < 24 hours in an emergency department or urgent care center) due to asthma that required systemic corticosteroids (as per the above), and/or

[0264] • An inpatient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours) due to asthma.

[0265] Participants are required to report any of the following in the eDiary:

[0266] • An increase in rescue medication use of 4 or more puffs on at least 2 consecutive days compared with the average use during baseline or use of 12 puffs/day on any one day, and/or;

[0267] • An additional nebulized β 2 agonist use on at least 2 consecutive days compared with the average use during baseline, and/or;

[0268] • An increase of 2 or more nights with awakenings due to asthma requiring rescue medication over a 7-day period compared with the average during baseline, and/or ≥ 6 out of previous 7 nights with awakenings due to asthma requiring rescue medication (this criterion should be met on 2 consecutive days).

[0269] If an exacerbation event is not associated with deterioration in at least 1 of the pre-specified objective measurements, the Investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF. Events that are not supported by any objective assessment will be deemed not to be a protocol-defined exacerbation.

[0270] The start of an exacerbation is defined as the start date of systemic corticosteroids or of a temporary increase in a stable OCS background dose, date of ER or urgent care visits requiring systemic corticosteroids, or date of hospital admission due to asthma, whichever occurs earlier. The end date of an exacerbation is defined as the last date of systemic corticosteroids or of a temporary increase in a stable OCS background dose, date of ER or urgent care visit, or date of hospital discharge, whichever occurs later.

[0271] If less than 7 days have elapsed since the end date of an asthma exacerbation and the start date of a new asthma exacerbation, the second event will be considered a relapse of the prior asthma exacerbation

[0272] *EQ-5D-3L*. The EuroQOL quality of life 5-dimensions 3-level version (EQ-5D-3L) is a standardized instrument for use as a measure of health-related quality of life (HRQoL) and was developed by EuroQol (Brooks, 1996). It defines health in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension

has 3 ordinal levels of severity: 1, no problem; 2, some problems; and 3, severe problems. Overall health state is defined as a 5-digit number. The participant will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a VAS, where the participant will be asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state.

[0273] *Patient Global Impression of Severity.* The PGI-S is a single item designed to capture the subject's perception of overall symptom severity at the time of completion on a 5-point categorical response scale (no symptoms to very severe symptoms).

[0274] *Adverse Events:* All adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product through the end of study/safety follow-up visit or 20 weeks after the last administration of investigational product are to be collected/reported.

[0275] BIOMARKERS

[0276] *Serum Immunoglobulins.* The levels of total immunoglobulin E (IgE) and an assessment for the presence of allergen-specific IgE (IgE FEIA) will be collected at the pre-specified scheduled visits prior to IP administration (pre-dose) according to the SoA and evaluated by a central laboratory.

[0277] *Pharmacokinetic Assessments:* Whole blood samples of approximately 5 mL are collected for measurement of serum concentrations of tezepelumab.

[0278] STATISTICAL ANALYSIS

[0279] For the primary endpoints, the treatment effect will be tested using a logistic regression model adjusting for covariates. From this model, odd ratios and 95% CIs will be reported comparing each tezepelumab dose group to placebo. In addition, the percentage of subjects in each treatment group with a response and the difference in the percentage of subjects responding between each tezepelumab dose group and placebo will be summarized with a 95% confidence interval.

Example 2-Long term administration of tezepelumab reduces need for oral corticosteroids

[0280] In a phase 3 study of tezepelumab in asthma patients, NAVIGATOR (NCT03347279), tezepelumab treatment significantly reduced the annualized asthma exacerbation rate compared with placebo in patients with severe, uncontrolled asthma

(Menzies-Gow et al. N Engl J Med 2021;384:1800–9). A separate phase 3 study, SOURCE (NCT03406078), evaluated the OCS-sparing effect of tezepelumab in adults with OCS-dependent asthma. The primary endpoint was not met in SOURCE (NCT03406078); however, 54% and 46% of tezepelumab- and placebo-treated patients discontinued daily OCS use, respectively (Wechsler ME et al. Lancet Respir Med 2022;10:650–60).

[0281] This example describes a phase 3, multicenter, randomized, placebo-controlled, double-blind, extension study of patients (12–80 years old) (DESTINATION) who completed the parent study NAVIGATOR (52 weeks) or SOURCE (48 weeks). Patients randomized to tezepelumab (210 mg subcutaneously every 4 weeks) in the parent study continued receiving tezepelumab in DESTINATION. Those randomized to placebo in the parent study were re-randomized 1:1 to tezepelumab or placebo in DESTINATION.

[0282] The proportion of patients with a 100% reduction in the daily OCS dose from baseline to week 104 who maintained asthma control was assessed in patients enrolled in DESTINATION. These patients were receiving maintenance OCS at week 0 in previous studies. Changes from baseline to week 104 in mean OCS doses were assessed in patients enrolled in the present study. OCS dose titration was at the discretion of investigators as per usual clinical practice and was not mandated by the protocol.

[0283] Within each parent study, baseline demographics and clinical characteristics were well balanced between the participants in each treatment group; however, there were important baseline differences in patients between the two parent studies. Overall, 42 patients originally from NAVIGATOR and 92 patients originally from SOURCE were receiving maintenance OCS at baseline.

[0284] Among patients from NAVIGATOR, a numerically higher proportion in the tezepelumab group than in the placebo group discontinued OCS by week 104 (37.9% vs 7.7%; Figure 4A). Among patients from SOURCE, a numerically higher proportion in the tezepelumab group than in the placebo group discontinued OCS by week 48 (61.7% vs 53.1%) and by week 104 (66.7% vs 46.9%; Table 1).

[0285] The mean daily OCS dose in the tezepelumab group decreased from 12.67 mg at baseline to 4.76 mg at week 104 in patients from NAVIGATOR (Figure 4A) and from 11.21 mg at baseline to 2.80 mg at week 104 in patients from SOURCE (Figure 4B) (OCS dose titration was at the discretion of investigators and was not mandated). The mean daily OCS dose in the placebo group decreased from 16.35 mg at baseline to 10.73 mg at week 104 in patients from NAVIGATOR (Figure 4A) and from 11.95 mg at baseline to 3.16 mg at week 104 in patients from SOURCE (Figure 4B) (OCS dose reduction was mandated during the

dose reduction phase (weeks 4–40) and was then discretionary from week 48 to week 104). In patients from SOURCE, a numerically higher proportion of tezepelumab recipients than placebo recipients had their daily OCS dose reduced to 5 mg or lower at week 104 (80.0% vs 71.9%).

[0286] Compared with patients treated with placebo, numerically more patients treated with tezepelumab discontinued OCS treatment completely over 104 weeks without losing asthma control or reduced their daily OCS dose from baseline to week 104. These findings suggest that tezepelumab may be effective in reducing the daily dose of maintenance OCS over time in patients with severe, OCS-dependent asthma.

Example 3- Efficacy and Safety Study of Tezepelumab to Reduce Oral Corticosteroid Use in Severe Asthma

[0287] A related Phase IIIb study, WAYFINDER, was conducted at different enrollment sites. The purpose of WAYFINDER is, in oral corticosteroid (OCS)-dependent participants with severe asthma on high-dose inhaled corticosteroids (ICS) plus long-acting β_2 agonist (LABA) and long-term OCS therapy, to assess the proportion of participants that are able to discontinue OCS completely or reduce to ≤ 5 mg/day. Participants received tezepelumab 210 mg on an open-label basis every 4 weeks (Q4W). Tapering of the OCS dose will begin while maintaining asthma control and testing for adrenal insufficiency (AI). A similar titration schedule as that set out in Example 2 was used in the WAYFINDER study. Exemplary titration schedules are shown in Table 5 and Figure 6.

Table 5. Oral Corticosteroid Titration Schema Until Reaching 5 mg/day weeks.

Baseline OCS dose	OCS down-titration schema until reaching 5 mg/day (without worsening of asthma)
> 20 mg/day	Reductions of 5 mg of the daily dose every 1 week until reaching a dose of 20 mg/day; followed by reductions of 5 mg every 2 weeks (Q2W) until a dose of 10 mg/day is reached; followed by reductions of 2.5 mg Q2W until reaching a dose of 7.5 mg/day; and then reductions of 2.5 mg Q4W until reaching a dose of 5 mg/day
> 10 to ≤ 20 mg/day	Reductions of 5 mg of the daily dose Q2W until reaching a dose of 10 mg/day; followed by reductions of 2.5 mg Q2W until reaching a dose of 7.5 mg/day; and then reductions of 2.5 mg Q4W until reaching a dose of 5 mg/day
> 7.5 to ≤ 10 mg/day	Reductions of 2.5 mg of the daily dose Q2W until reaching a dose of 7.5 mg/day followed by reductions of 2.5 mg Q4W until reaching a dose of 5 mg/day
> 5 to ≤ 7.5 mg/day	Reductions of 2.5 mg of the daily dose Q4W until reaching a dose of 5 mg/day

Abbreviations: OCS = oral corticosteroids; Q2W = every two weeks; Q4W = every four weeks.

[0288] Primary endpoints for this study include assessment of the proportion of participants who discontinue OCS without loss of asthma control and the proportion of participants who reduce OCS dose to ≤ 5 mg/day without loss of asthma control. For all participants, hypothalamic-pituitary-adrenal axis integrity will be evaluated when they have been on 5 mg/day for 4 weeks and prior to any further tapering down the OCS dose (for participants with baseline OCS doses equal to 5 mg/day, this will be assessed 4 weeks after the first dose of tezepelumab administration and before initiation of the OCS reduction phase). A screening method with morning serum cortisol will be done (8 to 9 am morning cortisol level) for all participants, to determinate whether the participants have normal cortisol levels, complete AI, or indeterminate results. Participants with normal morning cortisol levels will continue down-titration. Participants with complete AI will delay titration and repeat the test 3 months later. For participants showing indeterminate results, an ACTH stimulation test will be performed and decisions regarding how to continue OCS down-titration will be based on results of this test (see Table 6).

Table 6. Adrenocorticotrophic Hormone Stimulation Testing

	ACTH stimulation test results		
	Normal (> 450 nmol/L^a)	Partial AI (250-450 nmol/L^b)	Complete AI (< 250 nmol/L^c)
OCS down-titration	Reduction of 2.5 mg Q4W	Reduction of 1 mg Q4W	Continue on same OCS dose
Repeat morning cortisol test for further OCS down-titration	No need	2 months later	3 months later

Abbreviations: OCS = oral corticosteroids; Q2W = every two weeks; Q4W = every four weeks.

^a. > 675 nmol/L for participants taking oestrogen-containing contraceptives

^b. 375-675 nmol/L for participants taking oestrogen-containing contraceptives

^c. < 375 nmol/L for participants taking oestrogen-containing contraceptives

[0289] The study shows that the proportion of patients receiving a maintenance OCS dose of ≤ 5 mg/day increased over time (Figures 7A) and the proportion of patients with $\geq 50\%$ reduction in OCS dose also increased over time (Figure 7B). The proportion of patients who discontinued maintenance daily OCS generally increased over time in subjects receiving tezepelumab (Figure 8).

[0290] From the same study, post bronchial FED and patient score on the ACQ-6 was also determined. Figures 9A and 9B show that post-BD FEV₁ was generally stable over time and mean ACQ-6 score decreased by the end of 28 weeks.

[0291] It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but is intended to cover all modifications which are within the spirit and scope of the invention as defined by the appended claims; the above description; the following numbered paragraphs, and/or shown in the attached drawings.

[0292] Examples of the Embodiments:

[0293] Paragraph 1. A method for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises

a. a light chain variable domain comprising:

i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;

ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;

iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and

b. a heavy chain variable domain comprising:

i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;

ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and

iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2, wherein the antibody is an IgG2 antibody.

[0294] Paragraph 2. A method for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises

a. a light chain variable domain selected from the group consisting of:

i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and

b. a heavy chain variable domain selected from the group consisting of:

i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0295] Paragraph 3. The method of paragraph 1 or 2, wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0296] Paragraph 4. The method of any one of paragraphs 1 to 3, wherein the antibody or antibody variant is administered every 2 weeks or every 4 weeks.

[0297] Paragraph 5. The method of any one of paragraphs 1 to 4, wherein the antibody is an IgG2 antibody.

[0298] Paragraph 6. The method of any one of paragraphs 1 to 5, wherein the antibody or antibody variant is administered at a dose of 210 mg.

[0299] Paragraph 7. The method of any one of paragraphs 1 to 6, wherein the antibody is tezepelumab.

[0300] Paragraph 8. A method for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg at an interval of every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises

a. a light chain variable domain comprising:

i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;

ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;

iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and

b. a heavy chain variable domain comprising:

i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;

ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and

iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0301] Paragraph 9. A method for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg at an interval of every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises

- a. a light chain variable domain selected from the group consisting of:
 - i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and
- b. a heavy chain variable domain selected from the group consisting of:
 - i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0302] Paragraph 10. The method of paragraph 8 or 9, wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0303] Paragraph 11. The method of any one of paragraphs 1 to 10, wherein the antibody or antibody variant is administered for a period of at least 4 months, 6 months, 9 months, 1 year, 2 years or more.

[0304] Paragraph 12. The method of any one of paragraphs 1 to 11, wherein said anti-TSLP antibody or antibody variant thereof is bivalent and selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a monoclonal antibody, a recombinant antibody, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody.

- [0305]** Paragraph 13. The method of any one of paragraphs 8 to 13, wherein the antibody is an IgG2 antibody.
- [0306]** Paragraph 14. The method of any one of paragraphs 6 to 11, wherein the antibody is tezepelumab.
- [0307]** Paragraph 15. The method of any one of paragraphs 1 to 14, wherein the antibody or antibody variant is a human antibody.
- [0308]** Paragraph 16. The method of any one of paragraphs 1 to 15, wherein, the antibody or antibody variant is administered to the subject in a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient.
- [0309]** Paragraph 17. The method of any one of paragraphs 1 to 16, wherein the corticosteroid-dependent asthma is severe or asthma.
- [0310]** Paragraph 18. The method of any one of paragraphs 1 to 17, wherein the corticosteroid-dependent asthma is oral corticosteroid-dependent asthma.
- [0311]** Paragraph 19. The method of any one of paragraphs 1 to 18, wherein the subject is an adult.
- [0312]** Paragraph 20. The method of any one of paragraphs 1 to 19, wherein the subject is a child or adolescent.
- [0313]** Paragraph 21. The method of any one of paragraphs 1 to 20, wherein the administration improves one or more measures of corticosteroid-dependent asthma selected from the group consisting of forced expiratory volume (FEV), FEV₁ reversibility, forced vital capacity (FVC), FeNO, Asthma Control Questionnaire (ACQ)-6 score and AQLQ(S)+12 score, change from baseline in pre-BD FEV₁, reduction from baseline in daily maintenance OCS dose, daily maintenance OCS dose $\leq$ 5 mg, and $\geq$ 50% reduction from baseline in daily maintenance OCS dose, asthma exacerbations, as measured by AAER and time to first asthma exacerbation, rate of asthma exacerbations associated with emergency room (ER) visit, urgent care visit or hospitalization, and proportion of participants who did not experience an asthma exacerbation, weekly mean home PEF (morning and evening), adrenal insufficiency, and/or St George's Respiratory Questionnaire (SGRQ) score.
- [0314]** Paragraph 22. The method of any one of paragraphs 1 to 21, wherein the administration improves one or more symptoms of corticosteroid dependent asthma as measured by a patient symptom diary.
- [0315]** Paragraph 23. The method of any one of paragraphs 1 to 22, wherein the antibody is administered every 4 weeks.

[0316] Paragraph 24. The method of any one of paragraphs 1 to 23, wherein the antibody is tezepelumab.

[0317] Paragraph 25. The method of paragraph 24, wherein the antibody is an IgG2 antibody, and has the full length heavy and light chain sequences set out in SEQ ID NOs: 13 and 14, respectively.

[0318] Paragraph 26. The method of any one of paragraphs 1 to 25, wherein the antibody variant has substantially similar pK characteristics as tezepelumab-ekko in humans.

[0319] Paragraph 27. A method of reducing the frequency of asthma exacerbation in a subject having corticosteroid-dependent asthma comprising, administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant to the subject in a dose of 140 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises

a. a light chain variable domain comprising:

i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;

ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;

iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and

b. a heavy chain variable domain comprising:

i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;

ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and

iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0320] Paragraph 28. A method of reducing the frequency of asthma exacerbation in a subject having corticosteroid-dependent asthma comprising, administering a therapeutically effective amount of an anti-TSLP antibody or antibody variant to the subject in a dose of 140 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein

both binding sites of the antibody have identical binding to TSLP, and the antibody comprises

- a. a light chain variable domain selected from the group consisting of:
 - i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and
- b. a heavy chain variable domain selected from the group consisting of:
 - i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b).

[0321] Paragraph 29. The method of paragraph 27 or 28, wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0322] Paragraph 30. The method of any one of paragraphs 27 to 29, wherein the antibody or antibody variant is administered every 4 weeks.

[0323] Paragraph 31. The method of any one of paragraphs 27 to 30, wherein the antibody or antibody variant is administered at a dose of 210 mg.

[0324] Paragraph 32. The method of any one of paragraphs 27 to 31, wherein the antibody or antibody variant is administered for a period of at least 4 months, 6 months, 9 months, 1 year, 2 years or more.

[0325] Paragraph 33. The method of any one of paragraphs 27 to 32, wherein said anti-TSLP antibody or antibody variant is selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a monoclonal antibody, a recombinant antibody, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody.

- [0326]** Paragraph 34. The method of any one of paragraphs 27 to 33, wherein the antibody or antibody variant is an IgG2 antibody.
- [0327]** Paragraph 35. The method of any one of paragraphs 27 to 34, wherein the antibody or antibody variant is a human antibody.
- [0328]** Paragraph 36. The method of any one of paragraphs 27 to 35, wherein the antibody is tezepelumab.
- [0329]** Paragraph 37. The method of any one of paragraphs 27 to 36, wherein the antibody or antibody variant is administered to the subject in a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient.
- [0330]** Paragraph 38. The method of any one of paragraphs 27 to 37, wherein the administration delays the time to an asthma exacerbation compared to a subject not receiving the anti-TSLP antibody.
- [0331]** Paragraph 39. The method of any one of paragraphs 27 to 38, wherein the administration reduces frequency of or levels of co-administered therapy in the subject.
- [0332]** Paragraph 40. The method of paragraph 39, wherein the administration eliminates the need for oral corticosteroid therapy or inhaled corticosteroid therapy.
- [0333]** Paragraph 41. The method of any one of paragraphs 27 to 40, wherein the method comprises reducing the dose of corticosteroids the subject receives during a reduction phase of treatment and keeping the subject on a maintenance dose of corticosteroids.
- [0334]** Paragraph 42. The method of paragraph 41, wherein the dose of corticosteroid is reduced every 4 weeks for approximately 20 weeks.
- [0335]** Paragraph 43. The method of paragraph 41 or 42, wherein the dose of corticosteroid is reduced by 5 mg/day or 2.5 mg/day.
- [0336]** Paragraph 44. A method for eliminating the need for oral corticosteroids in a subject with asthma comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody or antibody variant for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises
- a. a light chain variable domain comprising:
 - i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;

- ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;
- iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and
- b. a heavy chain variable domain comprising:
 - i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;
 - ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and
 - iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0337] Paragraph 45. A method for eliminating the need for oral corticosteroids in a subject with asthma comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody or antibody variant for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises

- a. a light chain variable domain selected from the group consisting of:
 - i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and
- b. a heavy chain variable domain selected from the group consisting of:
 - i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of

SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b).

[0338] Paragraph 46. A method for reducing the amount of daily maintenance oral corticosteroids in a subject with asthma to ≤ 5 mg/day comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody or antibody variant for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises

- a. a light chain variable domain comprising:
 - i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;
 - ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;
 - iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and
- b. a heavy chain variable domain comprising:
 - i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;
 - ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and
 - iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0339] Paragraph 47. A method for reducing the amount of daily maintenance oral corticosteroids in a subject with asthma to ≤ 5 mg/day comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody or antibody variant for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises

- a. a light chain variable domain selected from the group consisting of:
 - i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and

b. a heavy chain variable domain selected from the group consisting of:

i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b).

[0340] Paragraph 48. The method of any one of paragraphs 44 to 47 wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0341] Paragraph 49. The method of any one of paragraph 27 to 48, wherein the anti-TSLP antibody is tezepelumab.

[0342] Paragraph 50. The method of paragraph 49, wherein the antibody is an IgG2 antibody, and has the full length heavy and light chain sequences set out in SEQ ID NOs: 13 and 14, respectively.

[0343] Paragraph 51. The method of any one of paragraphs 27 to 50, wherein the subject has oral corticosteroid-dependent asthma.

[0344] Paragraph 52. The method of any one of paragraphs 1 to 51, wherein the administration is subcutaneous or intravenous.

[0345] Paragraph 53. An anti-TSLP antibody or antibody variant for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of the anti-TSLP antibody or antibody variant to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises

a. a light chain variable domain comprising:

i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;

ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;

iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and

b. a heavy chain variable domain comprising:

i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;

ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and

iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2, wherein the antibody is an IgG2 antibody.

[0346] Paragraph 54. An anti-TSLP antibody or antibody variant for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of the anti-TSLP antibody or antibody variant to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises

a. a light chain variable domain selected from the group consisting of:

i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and

b. a heavy chain variable domain selected from the group consisting of:

i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0347] Paragraph 55. Use of an anti-TSLP antibody or antibody variant for the manufacture of a medicament for use in treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of the anti-TSLP antibody or antibody variant to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises

a. a light chain variable domain comprising:

i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;

ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;

iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and

b. a heavy chain variable domain comprising:

i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;

ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and

iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2, wherein the antibody is an IgG2 antibody.

[0348] Paragraph 56. Use of an anti-TSLP antibody or antibody variant for the manufacture of a medicament for use in treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of the anti-TSLP antibody or antibody variant to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein both binding sites of the antibody have identical binding to TSLP, and the antibody comprises

a. a light chain variable domain selected from the group consisting of:

i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and

b. a heavy chain variable domain selected from the group consisting of:

i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0349] Paragraph 57. The antibody or antibody variant for use or the use of any one of paragraphs 53 to 56, wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0350] Paragraph 58. The antibody or antibody variant for use or the use of any one of paragraphs 53 to 57, wherein the antibody or antibody variant is administered every 2 weeks or every 4 weeks.

[0351] Paragraph 59. The antibody or antibody variant for use or the use of any one of paragraphs 53 to 58, wherein the antibody is an IgG2 antibody.

[0352] Paragraph 60. The antibody or antibody variant for use or the use of any one of paragraphs 53 to 59, wherein the antibody or antibody variant is administered at a dose of 210 mg.

[0353] Paragraph 61. The antibody or antibody variant for use or the use of any one of paragraphs 53 to 60, wherein the antibody is tezepelumab.

[0354] Paragraph 62. The antibody or antibody variant for use or the use of any one of paragraphs 53 to 61, wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0355] Paragraph 63. The antibody or antibody variant for use or the use of any one of paragraphs 53 to 62, wherein the antibody or antibody variant is administered every 2 weeks or every 4 weeks.

[0356] Paragraph 64. The antibody or antibody variant for use or the use of any one of paragraphs 53 to 63, wherein the antibody is an IgG2 antibody.

[0357] Paragraph 65. The antibody or antibody variant for use or the use of any one of paragraphs 53 to 64, wherein the antibody or antibody variant is administered at a dose of 210 mg.

[0358] Paragraph 66. The antibody or antibody variant for use or the use of any one of paragraphs 53 to 65, wherein the antibody is tezepelumab.

[0359] Paragraph 67. A method for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of an anti-TSLP to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein the antibody comprises

a. a light chain variable domain comprising:

i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;

ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;

iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and

b. a heavy chain variable domain comprising:

i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;

ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and

iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2, wherein the antibody is an IgG2 antibody.

[0360] Paragraph 68. A method for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of an anti-TSLP antibody to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein the antibody comprises

a. a light chain variable domain selected from the group consisting of:

- i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and
- b. a heavy chain variable domain selected from the group consisting of:
 - i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or
 - c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0361] Paragraph 69. The method of paragraph 67 or 68, wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0362] Paragraph 70. The method of any one of paragraphs 67 to 69, wherein the antibody is administered every 2 weeks or every 4 weeks.

[0363] Paragraph 71. The method of any one of paragraphs 67 to 70, wherein the antibody is an IgG2 antibody.

[0364] Paragraph 72. The method of any one of paragraphs 67 to 71, wherein the antibody is administered at a dose of 210 mg.

[0365] Paragraph 73. The method of any one of paragraphs 67 to 72, wherein the antibody is tezepelumab.

[0366] Paragraph 74. A method for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of an anti-TSLP antibody to the subject in a dose of 210 mg at an interval of every 4 weeks, wherein the antibody comprises

- a. a light chain variable domain comprising:

i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;

ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;

iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and

b. a heavy chain variable domain comprising:

i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;

ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and

iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0367] Paragraph 75. A method for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of an anti-TSLP antibody to the subject in a dose of 210 mg at an interval of every 4 weeks, wherein the antibody comprises

a. a light chain variable domain selected from the group consisting of:

i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and

b. a heavy chain variable domain selected from the group consisting of:

i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID

NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0368] Paragraph 76. The method of paragraph 74 or 75, wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0369] Paragraph 77. The method of any one of paragraphs 67 to 76, wherein the antibody is administered for a period of at least 4 months, 6 months, 9 months, 1 year, 2 years or more.

[0370] Paragraph 78. The method of any one of paragraphs 67 to 77, wherein said anti-TSLP antibody is bivalent and selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a monoclonal antibody, a recombinant antibody, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody.

[0371] Paragraph 79. The method of any one of paragraphs 74 to 78, wherein the antibody is an IgG2 antibody.

[0372] Paragraph 80. The method of any one of paragraphs 74 to 79, wherein the antibody is tezepelumab.

[0373] Paragraph 81. The method of any one of paragraphs 67 to 80, wherein the antibody is a human antibody.

[0374] Paragraph 82. The method of any one of paragraphs 67 to 81, wherein the antibody is administered to the subject in a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient.

[0375] Paragraph 83. The method of any one of paragraphs 67 to 82, wherein the corticosteroid-dependent asthma is severe or asthma.

[0376] Paragraph 84. The method of any one of paragraphs 67 to 83, wherein the corticosteroid-dependent asthma is oral corticosteroid-dependent asthma.

[0377] Paragraph 85. The method of any one of paragraphs 67 to 84, wherein the subject is an adult.

[0378] Paragraph 86. The method of any one of paragraphs 67 to 85, wherein the subject is a child or adolescent.

[0379] Paragraph 87. The method of any one of paragraphs 67 to 86, wherein the administration improves one or more measures of corticosteroid-dependent asthma selected

from the group consisting of forced expiratory volume (FEV), FEV₁ reversibility, forced vital capacity (FVC), FeNO, Asthma Control Questionnaire (ACQ)-6 score and AQLQ(S)+12 score, change from baseline in pre-BD FEV₁, reduction from baseline in daily maintenance OCS dose, daily maintenance OCS dose $\leq$ 5 mg, and $\geq$ 50% reduction from baseline in daily maintenance OCS dose, asthma exacerbations, as measured by AAER and time to first asthma exacerbation, rate of asthma exacerbations associated with emergency room (ER) visit, urgent care visit or hospitalization, and proportion of participants who did not experience an asthma exacerbation, weekly mean home PEF (morning and evening), adrenal insufficiency, and/or St George's Respiratory Questionnaire (SGRQ) score.

[0380] Paragraph 88. The method of any one of paragraphs 67 to 87, wherein the administration improves one or more symptoms of corticosteroid dependent asthma as measured by a patient symptom diary.

[0381] Paragraph 89. The method of any one of paragraphs 67 to 88, wherein the antibody is administered every 4 weeks.

[0382] Paragraph 90. The method of any one of paragraphs 67 to 89, wherein the antibody is tezepelumab.

[0383] Paragraph 91. The method of paragraph 90, wherein the antibody is an IgG2 antibody, and has the full length heavy and light chain sequences set out in SEQ ID NOs: 13 and 14, respectively.

[0384] Paragraph 92. The method of any one of paragraphs 67 to 91, wherein the antibody variant has substantially similar pK characteristics as tezepelumab-ekko in humans.

[0385] Paragraph 93. A method of reducing the frequency of asthma exacerbation in a subject having corticosteroid-dependent asthma comprising, administering a therapeutically effective amount of an anti-TSLP antibody to the subject in a dose of 140 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein the antibody comprises

a. a light chain variable domain comprising:

i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;

ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;

iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and

- b. a heavy chain variable domain comprising:
 - i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;
 - ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and
 - iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0386] Paragraph 94. A method of reducing the frequency of asthma exacerbation in a subject having corticosteroid-dependent asthma comprising, administering a therapeutically effective amount of an anti-TSLP antibody to the subject in a dose of 140 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein the antibody comprises

- a. a light chain variable domain selected from the group consisting of:
 - i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and
- b. a heavy chain variable domain selected from the group consisting of:
 - i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b).

[0387] Paragraph 95. The method of paragraph 93 or 94, wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0388] Paragraph 96. The method of any one of paragraphs 93 to 95, wherein the antibody is administered every 4 weeks.

- [0389]** Paragraph 97. The method of any one of paragraphs 93 to 96, wherein the antibody is administered at a dose of 210 mg.
- [0390]** Paragraph 98. The method of any one of paragraphs 93 to 97, wherein the is administered for a period of at least 4 months, 6 months, 9 months, 1 year, 2 years or more.
- [0391]** Paragraph 99. The method of any one of paragraphs 93 to 98, wherein said anti-TSLP antibody is selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a monoclonal antibody, a recombinant antibody, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody.
- [0392]** Paragraph 100. The method of any one of paragraphs 93 to 99, wherein the antibody is an IgG2 antibody.
- [0393]** Paragraph 101. The method of any one of paragraphs 93 to 100, wherein the antibody is a human antibody.
- [0394]** Paragraph 102. The method of any one of paragraphs 93 to 101, wherein the antibody is tezepelumab.
- [0395]** Paragraph 103. The method of any one of paragraphs 93 to 102, wherein the antibody is administered to the subject in a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient.
- [0396]** Paragraph 104. The method of any one of paragraphs 93 to 103, wherein the administration delays the time to asthma exacerbation compared to a subject not receiving the anti-TSLP antibody.
- [0397]** Paragraph 105. The method any one of paragraphs 93 to 104, wherein the administration reduces frequency of or levels of co-administered therapy in the subject.
- [0398]** Paragraph 106. The method of paragraph 105, wherein the administration eliminates the need for oral corticosteroid therapy or inhaled corticosteroid therapy.
- [0399]** Paragraph 107. The method of any one of paragraphs 93 to 106, wherein the method comprises reducing the dose of corticosteroids the subject receives during a reduction phase of treatment and keeping the subject on a maintenance dose of corticosteroids.
- [0400]** Paragraph 108. The method of paragraph 107, wherein the dose of corticosteroid is reduced every 4 weeks for approximately 20 weeks.
- [0401]** Paragraph 109. The method of paragraph 107 or 108, wherein the dose of corticosteroid is reduced by 5 mg/day or 2.5 mg/day.

[0402] Paragraph 110. A method for eliminating the need for oral corticosteroids in a subject with asthma comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, wherein the antibody comprises

- a. a light chain variable domain comprising:
 - i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;
 - ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;
 - iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and
- b. a heavy chain variable domain comprising:
 - i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;
 - ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and
 - iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0403] Paragraph 111. A method for eliminating the need for oral corticosteroids in a subject with asthma comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, wherein the antibody comprises

- a. a light chain variable domain selected from the group consisting of:
 - i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and
- b. a heavy chain variable domain selected from the group consisting of:

- i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;
- ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;
- iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b).

[0404] Paragraph 112. A method for reducing the amount of daily maintenance oral corticosteroids in a subject with asthma to ≤ 5 mg/day comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, wherein the antibody comprises

- a. a light chain variable domain comprising:
 - i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;
 - ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;
 - iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and
- b. a heavy chain variable domain comprising:
 - i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;
 - ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and
 - iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0405] Paragraph 113. A method for reducing the amount of daily maintenance oral corticosteroids in a subject with asthma to ≤ 5 mg/day comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, the antibody comprises a light chain variable domain selected from the group consisting of:

- a. a light chain variable domain comprising:

- i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and
- b. a heavy chain variable domain selected from the group consisting of:
 - i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b).

[0406] Paragraph 114. The method of any one of paragraphs 110 to 113 wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0407] Paragraph 115. The method of any one of paragraphs 110 to 114, wherein the anti-TSLP antibody is tezepelumab.

[0408] Paragraph 116. The method of paragraph 115, wherein the antibody is an IgG2 antibody, and has the full length heavy and light chain sequences set out in SEQ ID NOs: 13 and 14, respectively.

[0409] Paragraph 117. The method of any one of paragraphs 110 to 116, wherein the subject has oral corticosteroid-dependent asthma.

[0410] Paragraph 118. The method of any one of paragraphs 110 to 117, wherein the administration is subcutaneous or intravenous.

[0411] Paragraph 119. An anti-TSLP antibody for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of the anti-TSLP antibody or antibody variant to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein the antibody comprises

- a. a light chain variable domain comprising:

i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;

ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;

iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and

b. a heavy chain variable domain comprising:

i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;

ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and

iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2, wherein the antibody is an IgG2 antibody.

[0412] Paragraph 120. An anti-TSLP antibody for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of the anti-TSLP antibody or antibody variant to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein the antibody comprises

a. a light chain variable domain selected from the group consisting of:

i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and

b. a heavy chain variable domain selected from the group consisting of:

i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID

NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0413] Paragraph 121. Use of an anti-TSLP antibody for the manufacture of a medicament for use in treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of the anti-TSLP antibody to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein the antibody comprises

- a. a light chain variable domain comprising:
 - i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;
 - ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;
 - iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and
- b. a heavy chain variable domain comprising:
 - i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;
 - ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and
 - iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2, wherein the antibody is an IgG2 antibody.

[0414] Paragraph 122. Use of an anti-TSLP antibody for the manufacture of a medicament for use in treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of the anti-TSLP antibody to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein the antibody comprises

- a. a light chain variable domain selected from the group consisting of:
 - i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and

b. a heavy chain variable domain selected from the group consisting of:

i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0415] Paragraph 123. The antibody for use or the use of any one of paragraphs 119 to 122, wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0416] Paragraph 124. The antibody for use or the use of any one of paragraphs 119 to 123, wherein the antibody is administered every 2 weeks or every 4 weeks.

[0417] Paragraph 125. The antibody for use or the use of any one of paragraphs 119 to 124, wherein the antibody is an IgG2 antibody.

[0418] Paragraph 126. The antibody for use or the use of any one of paragraphs 119 to 125, wherein the antibody is administered at a dose of 210 mg.

[0419] Paragraph 127. The antibody for use or the use of any one of paragraphs 119 to 126, wherein the antibody is tezepelumab.

[0420] Paragraph 128. The antibody for use or the use of any one of paragraphs 119 to 127, wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

[0421] Paragraph 129. The antibody for use or the use of any one of paragraphs 119 to 128, wherein the antibody is administered every 2 weeks or every 4 weeks.

[0422] Paragraph 130. The antibody for use or the use of any one of paragraphs 119 to 129, wherein the antibody is an IgG2 antibody.

[0423] Paragraph 131. The antibody for use or the use of any one of paragraphs 119 to 130, wherein the antibody is administered at a dose of 210 mg.

[0424] Paragraph 132. The antibody for use or the use of any one of paragraphs 119 to 131, wherein the antibody is tezepelumab.

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What is Claimed:

1. A method for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of an anti-TSLP to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein the antibody comprises

a. a light chain variable domain comprising:

i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;

ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;

iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and

b. a heavy chain variable domain comprising:

i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;

ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and

iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2, wherein the antibody is an IgG2 antibody.

2. A method for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of an anti-TSLP antibody to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein the antibody comprises

a. a light chain variable domain selected from the group consisting of:

i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and

- b. a heavy chain variable domain selected from the group consisting of:
 - i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.
- 3. The method of claim 1 or 2, wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.
- 4. The method of any one of claims 1 to 3, wherein the antibody is administered every 2 weeks or every 4 weeks.
- 5. The method of any one of claims 1 to 4, wherein the antibody is an IgG2 antibody.
- 6. The method of any one of claims 1 to 5, wherein the antibody is administered at a dose of 210 mg.
- 7. The method of any one of claims 1 to 6, wherein the antibody is tezepelumab.
- 8. A method for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of an anti-TSLP antibody to the subject in a dose of 210 mg at an interval of every 4 weeks, wherein the antibody comprises
 - a. a light chain variable domain comprising:
 - i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;
 - ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;
 - iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and
 - b. a heavy chain variable domain comprising:
 - i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;

ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and

iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

9. A method for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of an anti-TSLP antibody to the subject in a dose of 210 mg at an interval of every 4 weeks, wherein the antibody comprises

a. a light chain variable domain selected from the group consisting of:

i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and

b. a heavy chain variable domain selected from the group consisting of:

i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

10. The method of claim 8 or 9, wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

11. The method of any one of the preceding claims, wherein the antibody is administered for a period of at least 4 months, 6 months, 9 months, 1 year, 2 years or more.

12. The method of any one of the preceding claims, wherein said anti-TSLP antibody is bivalent and selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a monoclonal antibody, a recombinant antibody, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody.

13. The method of any one of claims 8 to 13, wherein the antibody is an IgG2 antibody.
14. The method of any one of claims 6 to 11, wherein the antibody is tezepelumab.
15. The method of any one of the preceding claims, wherein the antibody is a human antibody.
16. The method of any one of the preceding claims wherein, the antibody is administered to the subject in a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient.
17. The method of any one of the preceding claims, wherein the corticosteroid-dependent asthma is severe or asthma.
18. The method of any one of the preceding claims, wherein the corticosteroid-dependent asthma is oral corticosteroid-dependent asthma.
19. The method of any one of the preceding claims, wherein the subject is an adult.
20. The method of any one of the preceding claims, wherein the subject is a child or adolescent.
21. The method of any one of the preceding claims, wherein the administration improves one or more measures of corticosteroid-dependent asthma selected from the group consisting of forced expiratory volume (FEV), FEV₁ reversibility, forced vital capacity (FVC), FeNO, Asthma Control Questionnaire (ACQ)-6 score and AQLQ(S)+12 score, change from baseline in pre-BD FEV₁, reduction from baseline in daily maintenance OCS dose, daily maintenance OCS dose $\leq$ 5 mg, and $\geq$ 50% reduction from baseline in daily maintenance OCS dose, asthma exacerbations, as measured by AAER and time to first asthma exacerbation, rate of asthma exacerbations associated with emergency room (ER) visit, urgent care visit or hospitalization, and proportion of participants who did not experience an asthma exacerbation, weekly mean home PEF (morning and evening), adrenal insufficiency, and/or St George's Respiratory Questionnaire (SGRQ) score.
22. The method of any one of the preceding claims, wherein the administration improves one or more symptoms of corticosteroid dependent asthma as measured by a patient symptom diary.
23. The method of any one of the preceding claims, wherein the antibody is administered every 4 weeks.

24. The method of any one of the preceding claims, wherein the antibody is tezepelumab.

25. The method of claim 24, wherein the antibody is an IgG2 antibody, and has the full length heavy and light chain sequences set out in SEQ ID NOs: 13 and 14, respectively.

26. The method of any one of the preceding claims, wherein the antibody variant has substantially similar pK characteristics as tezepelumab-ekko in humans.

27. A method of reducing the frequency of asthma exacerbation in a subject having corticosteroid-dependent asthma comprising, administering a therapeutically effective amount of an anti-TSLP antibody to the subject in a dose of 140 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein the antibody comprises

a. a light chain variable domain comprising:

i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;

ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;

iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and

b. a heavy chain variable domain comprising:

i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;

ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and

iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

28. A method of reducing the frequency of asthma exacerbation in a subject having corticosteroid-dependent asthma comprising, administering a therapeutically effective amount of an anti-TSLP antibody to the subject in a dose of 140 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein the antibody comprises

a. a light chain variable domain selected from the group consisting of:

- i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and
 - b. a heavy chain variable domain selected from the group consisting of:
 - i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;
 - ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;
 - iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b).
29. The method of claim 27 or 28, wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.
30. The method of any one of claims 27 to 29, wherein the antibody is administered every 4 weeks.
31. The method of any one of claims 27 to 30, wherein the antibody is administered at a dose of 210 mg.
32. The method of any one of claims 27 to 31, wherein the is administered for a period of at least 4 months, 6 months, 9 months, 1 year, 2 years or more.
33. The method of any one of claims 27 to 32, wherein said anti-TSLP antibody is selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a monoclonal antibody, a recombinant antibody, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody.
34. The method of any one of claims 27 to 33, wherein the antibody is an IgG2 antibody.
35. The method of any one of claims 27 to 34, wherein the antibody is a human antibody.
36. The method of any one of claims 27 to 35, wherein the antibody is tezepelumab.

37. The method of any one of claims 27 to 36, wherein the antibody is administered to the subject in a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient.

38. The method of any one of claims 27 to 37, wherein the administration delays the time to asthma exacerbation compared to a subject not receiving the anti-TSLP antibody.

39. The method any one of claims 27 to 38, wherein the administration reduces frequency of or levels of co-administered therapy in the subject.

40. The method of claim 39, wherein the administration eliminates the need for oral corticosteroid therapy or inhaled corticosteroid therapy.

41. The method of any one of claims 27 to 40, wherein the method comprises reducing the dose of corticosteroids the subject receives during a reduction phase of treatment and keeping the subject on a maintenance dose of corticosteroids.

42. The method of claim 41, wherein the dose of corticosteroid is reduced every 4 weeks for approximately 20 weeks.

43. The method of claim 41 or 42, wherein the dose of corticosteroid is reduced by 5 mg/day or 2.5 mg/day.

44. A method for eliminating the need for oral corticosteroids in a subject with asthma comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, wherein the antibody comprises a. a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

45. A method for eliminating the need for oral corticosteroids in a subject with asthma comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, wherein the antibody comprises a. a light chain variable domain selected from the group

consisting of: i. a sequence of amino acids at least 80% identical to SEQ ID NO:12; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and b. a heavy chain variable domain selected from the group consisting of: i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b).

46. A method for reducing the amount of daily maintenance oral corticosteroids in a subject with asthma to ≤ 5 mg/day comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, wherein the antibody comprises a. a light chain variable domain comprising: i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

47. A method for reducing the amount of daily maintenance oral corticosteroids in a subject with asthma to ≤ 5 mg/day comprising administering to the subject a therapeutically effective amount of an anti-TSLP antibody for at least 2 years at a dose of 210 mg at an interval of every 4 weeks, the antibody comprises a. a light chain variable domain selected from the group consisting of: i. a sequence of amino acids at least 80% identical to SEQ ID NO:12; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and b. a heavy chain variable domain selected from the group consisting of: i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10; ii. a sequence of amino acids encoded by a polynucleotide

sequence that is at least 80% identical to SEQ ID NO:9; iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b).

48. The method of any one of claims 44 to 47 wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

49. The method of any one of claims 27 to 48, wherein the anti-TSLP antibody is tezepelumab.

50. The method of claim 49, wherein the antibody is an IgG2 antibody, and has the full length heavy and light chain sequences set out in SEQ ID NOs: 13 and 14, respectively.

51. The method of any one of claims 27 to 50, wherein the subject has oral corticosteroid-dependent asthma.

52. The method of any one of the preceding claims, wherein the administration is subcutaneous or intravenous.

53. An anti-TSLP antibody for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of the anti-TSLP antibody or antibody variant to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein the antibody comprises

a. a light chain variable domain comprising:

i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;

ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;

iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and

b. a heavy chain variable domain comprising:

i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;

ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and

iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2, wherein the antibody is an IgG2 antibody.

54. An anti-TSLP antibody for treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of the anti-TSLP antibody or antibody variant to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein the antibody comprises

a. a light chain variable domain selected from the group consisting of:

i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and

b. a heavy chain variable domain selected from the group consisting of:

i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

55. Use of an anti-TSLP antibody for the manufacture of a medicament for use in treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of the anti-TSLP antibody to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein the antibody comprises

a. a light chain variable domain comprising:

i. a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;

ii. a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4;

iii. a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and

b. a heavy chain variable domain comprising:

i. a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;

ii. a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:7, and

iii. a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2, wherein the antibody is an IgG2 antibody.

56. Use of an anti-TSLP antibody for the manufacture of a medicament for use in treating corticosteroid-dependent asthma in a subject comprising, administering a therapeutically effective amount of the anti-TSLP antibody to the subject in a dose of 140 to 420 mg at an interval of every 2 weeks or 4 weeks, wherein the antibody comprises

a. a light chain variable domain selected from the group consisting of:

i. a sequence of amino acids at least 80% identical to SEQ ID NO:12;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; and

b. a heavy chain variable domain selected from the group consisting of:

i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9;

iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or c. a light chain variable domain of (a) and a heavy chain variable domain of (b), wherein the antibody specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

57. The antibody for use or the use of any one of claims 53 to 56, wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

58. The antibody for use or the use of any one of claims 53 to 57, wherein the antibody is administered every 2 weeks or every 4 weeks.

59. The antibody for use or the use of any one of claims 53 to 58, wherein the antibody is an IgG2 antibody.

60. The antibody for use or the use of any one of claims 53 to 59, wherein the antibody is administered at a dose of 210 mg.

61. The antibody for use or the use of any one of claims 53 to 60, wherein the antibody is tezepelumab.

62. The antibody for use or the use of any one of claims 53 to 61, wherein the light chain variable domain is set out in SEQ ID NO:12 and the heavy chain variable domain is set out in SEQ ID NO:10.

63. The antibody for use or the use of any one of claims 53 to 62, wherein the antibody is administered every 2 weeks or every 4 weeks.

64. The antibody for use or the use of any one of claims 53 to 63, wherein the antibody is an IgG2 antibody.

65. The antibody for use or the use of any one of claims 53 to 64, wherein the antibody is administered at a dose of 210 mg.

66. The antibody for use or the use of any one of claims 53 to 65, wherein the antibody is tezepelumab.