

TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH ANTI-TSLP ANTIBODY**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] The present application claims the priority benefit of U.S. Provisional Application No. 63/618,273, filed January 5, 2024, hereby incorporated by reference in its entirety.

INCORPORATION BY REFERENCE OF SEQUENCE DISCLOSURE

[0002] The Sequence Listing, which is a part of the present disclosure, is submitted concurrently with the specification as a computer readable file. The name of the file containing the Sequence Listing is "59123_SeqListing.xml", which was created on December 13, 2024, and is 15,648 bytes in size. The subject matter of the Sequence Listing is incorporated herein in its entirety by reference.

FIELD OF THE DISCLOSURE

[0003] The present disclosure relates, in general, to methods of treating chronic obstructive pulmonary disease, using an antibody specific for thymic stromal lymphopoietin (TSLP).

BACKGROUND

[0004] Chronic obstructive pulmonary disease (COPD) is a progressive disease and a significant cause of morbidity and mortality worldwide. In contrast to other chronic diseases, COPD is increasing in prevalence and is projected to be the third leading cause of death and disability worldwide by 2020 (Global Initiative for Chronic Obstructive Lung Disease (Gold 2019)).

[0005] Acute exacerbations of COPD (AECOPD) are responsible for a large portion of the economic burden of COPD. In addition to a substantial economic burden, AECOPDs are also responsible for much of the morbidity and mortality from COPD. Patients with frequent AECOPD show associated increased airway inflammation and accelerated decline in lung function compared with patients with infrequent exacerbations (Donaldson et al 2002).

[0006] Thymic stromal lymphopoietin (TSLP) is an upstream pleiotropic cytokine which is released by airway epithelial cells in response to either allergens or non-specific stimuli such as viruses, bacteria, and cigarette smoke, all of which are known to be associated with COPD exacerbations (Ziegler et al 2013). In response to an allergen or non-specific stimuli, TSLP activates dendritic cells, which stimulate Type 2 helper T (Th2) cells to differentiate and produce the Type 2 cytokines interleukin (IL)-4, IL-5, and IL-13 (Watson and Gauvreau

2014). TSLP can also drive Th17 cell expansion through activation of dendritic cells, which will increase neutrophil recruitment (Ziegler et al 2013).

[0007] TSLP, along with the other epithelial “alarmins”, IL-25 and IL-33, activates Type 2 innate lymphoid cells (ILC2) and other inflammatory cell (including mast cells, basophils, and macrophages), thus promoting T2 inflammation by up-regulating Type 2 cytokines in response to an epithelial insult (e.g., pollutants, microbes, cigarette smoke, bacterial and viral infections, mechanical injury, trauma and pro-inflammatory cytokines etc.) (Camelo et al 2017).

[0008] TSLP protein is released from COPD epithelium following toll-like receptor (TLR) viral (Calvern et al 2012) and pro-inflammatory cytokine stimulation (Kato et al 2007, Lee and Ziegler 2007). TSLP protein has been detected in nasal secretions from healthy subjects undergoing natural rhinovirus infection (Perez et al 2014) as well as in the bronchoalveolar lavage (BAL) fluid and sputum of non-exacerbating COPD subjects (Ying et al 2008), and significantly higher in induced sputum from COPD subjects compared to healthy smokers and healthy control (Anzalone et al 2018). TSLP mRNA expression is seen in airway epithelial cells in patients with COPD (Ying et al 2008).

[0009] Tezepelumab (also known as AMG 157) (Gilliet, et al., J Exp Med 2003; 197:1059-63) is a fully human monoclonal antibody (immunoglobulin G2λ) that targets TSLP, which 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

[0010] The anti-TSLP antibody described herein addresses an unmet need in patients with chronic obstructive pulmonary disease, in which other medications may not control symptoms.

[0011] In one aspect, the disclosure provides a method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering an anti-TSLP antibody to the subject in a dose of 210 mg 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.

[0012] Also provided is a method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering an anti-TSLP antibody to the subject in a dose of 210 mg 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.

[0013] In various embodiments, the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

[0014] In various embodiments, the antibody is administered every 2 weeks. In various embodiments, the antibody is administered every 4 weeks. In various embodiments, the antibody is administered at a dose of 210 mg. In various embodiments, the antibody is administered at a dose of 420 mg. In various embodiments, the antibody is an IgG2 antibody. In various embodiments, the antibody is a human IgG2 antibody.

[0015] The disclosure also provides a method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising administering anti-TSLP antibody or antibody variant in a dose of 210 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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;

[0016] The disclosure provides a method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising administering an anti-TSLP antibody or antibody variant in a dose of 210 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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.

[0017] The disclosure further provides a method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD) and administering an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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.

[0018] Also contemplated is a method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD), administering an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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.

[0019] In various embodiments, the sequence of amino acids is at least about 80%, 85%, 90% 95%, 96%, 97%, 98%, 99% or more identical to the heavy chain variable domain comprising the amino acid sequence set forth in SEQ ID NO: 10 or at least about 80%, 85%, 90% 95%, 96%, 97%, 98%, 99% or more identical to the light chain variable region domain comprising the amino acid sequence set forth in SEQ ID NO: 12. It is contemplated that heavy chain variable region sequences less than 100% identical to SEQ ID NO: 10 retain the CDR amino acid sequences set forth in SEQ ID NOs: 6-8, and light chain variable region sequences less than 100% identical to SEQ ID NO: 12 retain the CDR amino acid sequences set forth in SEQ ID NOs: 3-5.

[0020] In various embodiments, the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

[0021] In various embodiments, the antibody or antibody variant is administered every 4 weeks.

[0022] In various embodiments, the antibody or antibody variant is administered at a dose of 420 mg every 2 weeks. In various embodiments, the antibody or antibody variant is administered at a dose of 420 mg 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.

[0023] In various embodiments, the antibody is administered at a dose of 420 mg every 2 weeks. In various embodiments, the antibody is administered at a dose of 420 mg every 4 weeks. In various embodiments, the antibody is administered at a dose of 210 mg every 2 weeks. In various embodiments, the antibody is administered at a dose of 210 mg every 4 weeks. In various embodiments, the antibody is an IgG2 antibody. In various embodiments, the antibody is a human IgG2 antibody.

[0024] In various embodiments, the disclosure provides a method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering an anti-TSLP antibody to the subject in a dose of 210 mg at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14. Also contemplated is a method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering an anti-TSLP antibody to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

[0025] In various embodiments, the subject is also receiving treatment with bronchodilators and/or corticosteroids, oral steroids, phosphodiesterase-4 inhibitors, theophylline, or combinations thereof.

[0026] In various embodiments the bronchodilators are short-acting or long-acting β 2 agonist. In various embodiments, short-acting β 2 agonists include albuterol (PROAIR® HFA, VENTOLIN HFA®), ipratropium (ATROVENT® HFA®), levalbuterol (XOPENEX®). In various embodiments, the long-acting β 2 agonist includes aclidinium (TUDORZA®).

PRESSAIR®), arformoterol (BROVANA®), formoterol (PERFOROMIST®), Indacaterol (ARCAPTA® NEOINHALER®), tiotropium (SPIRIVA®), salmeterol (SEREVENT®), or umeclidinium (INCRUSE® ELLIPTA®), or combinations thereof.

[0027] In various embodiments the corticosteroids are oral corticosteroids (OCS) or inhaled corticosteroids (ICS). In various embodiments, the oral corticosteroids are one or more of prednisone, prednisolone, cortisone, hydrocortisone, methylprednisolone, triamcinolone, betamethasone, dexamethasone, deflazacort, fluticasone or budesonide. In various embodiments, the inhaled corticosteroids include fluticasone, budesonide, mometasone, ciclesonide, and beclomethasone.

[0028] In various embodiments, the subject may be receiving a combination treatment such as luticasone and vilanterol (BREEO® ELLIPTA®); fluticasone, umeclidinium and vilanterol (TRELEGY® ELLIPTA®); formoterol and budesonide (SYMBICORT®); salmeterol and fluticasone (ADVAIR® HFA, AIRDUO® DIGIHALER®, others); aclidinium and formoterol (DUAKLIR® PRESSAIR®); albuterol and ipratropium (COMBIVENT® RESPIMAT®); formoterol and glycopyrrolate (BEVESPI® AEROSPHERE®); glycopyrrolate and indacaterol (UTIBRON®); olodaterol and tiotropium (STIOLTO® RESPIMAT®); or umeclidinium and vilanterol (ANORO® ELLIPTA®).

[0029] In various embodiments, the co-administered therapy is triple inhaled maintenance therapy (inhaled corticosteroid/long-acting β 2 agonist and long acting muscarinic antagonist [ICS/LABA/LAMA]).

[0030] In various embodiments, the method comprises administering an anti-TSLP antibody or antibody variant in conjunction with bronchodilators, corticosteroids, oral steroids, phosphodiesterase-4 inhibitors, theophylline, or combinations thereof.

[0031] In various embodiments, the anti-TSLP antibody variant has substantially similar pK characteristics as tezepelumab-ekko in humans.

[0032] 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.

[0033] 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.

[0034] In one embodiment, the anti-TSLP antibody variant is selected from the group consisting of 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.

[0035] In various embodiments, the anti-TSLP antibody is an anti-TSLP antibody derivative.

[0036] In various embodiments, the antibody is an IgG2 antibody.

[0037] In one embodiment, the antibody or antibody variant is a human antibody.

[0038] In various embodiments, the antibody is tezepelumab. In various embodiments, tezepelumab is an IgG2 antibody. In various embodiments, tezepelumab has the full length heavy and light chain amino acid sequences set out in SEQ ID NOs: 13 and 14, respectively. In various embodiments, the tezepelumab is tezepelumab-ekko.

[0039] In various embodiments, the antibody or antibody variant further is administered to the subject in a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient.

[0040] In various embodiments, the chronic obstructive pulmonary disease (COPD) is moderate to very severe COPD.

[0041] In various embodiments, the subject is an adult.

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

[0043] In various embodiments, the method improves one or more measures of COPD in a subject selected from the group consisting of moderate or severe COPD exacerbation, time to first COPD exacerbation, rate of COPD exacerbations associated with emergency room (ER) visit, urgent care visit or hospitalization, proportion of participants who did not experience an COPD exacerbation, FeNO, COPD Assessment Test (CAT) score, Clinically Important Deterioration (CID) score, Exacerbations of Chronic Pulmonary Disease Tool–Patient-reported Outcome (EXACT-PRO) score, EXACT PRO Respiratory Score (E-RS), composite endpoint for exacerbations (moderate or severe) in COPD (COPDCompEx) score, change from baseline in pre- and post-BD FEV₁, St George's Respiratory Questionnaire (SGRQ) score, E-RS or CAT score, BOD Index, mMRC dyspnoea scale score, 5-level EuroQoL-5 Dimension score, and/or reporting of a worsening event, e.g., dyspnea, sputum volume, and sputum color, blood IgE, eosinophil-derived neurotoxin (EDN), IL-5, CT imaging biomarkers (mucous plugging, airway lumen dimensions, air trapping, emphysema progression, airway remodeling).

[0044] In one embodiment, the administration improves one or more symptoms of COPD as measured by patient diary. Examples of a patient diary include, but are not limited to, Exacerbations of Chronic Pulmonary Disease Tool– Patient-reported Outcome (EXACT-PRO) score, E-RS, St George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT): composite endpoint for exacerbations (moderate or severe) in COPD (COPDCommpEx).

[0045] In various embodiments, treatment with anti-TSLP antibody or antibody variant modulates the levels of one or more biomarkers of COPD, 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] Also provided herein is a method for reducing CAT score in a subject having COPD comprising administering an anti-TSLP antibody or antibody variant in a dose of 210 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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 for reducing CAT score in a subject having COPD comprising administering an anti-TSLP antibody or antibody variant in a dose of 210 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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] Provided herein is a method a method of reducing the frequency of COPD exacerbation in a subject having COPD comprising selecting a subject in need of treatment for COPD, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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.

[0049] Further contemplated is a method of reducing the frequency of moderate or severe COPD exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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] Also contemplated is a method of reducing the frequency of moderate or severe COPD exacerbation in a subject comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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.

[0051] Also provided is a method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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).

[0052] Also contemplated is a method of reducing the frequency of moderate or severe COPD exacerbation in a subject comprising, administering 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 are identical binding sites that bind 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.

[0053] Also provided is a method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering 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 are identical binding sites that bind 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).

[0054] In various embodiments, the disclosure provides a method of treating chronic obstructive pulmonary disease (COPD) in a subject in need thereof comprising administering to an anti-TSLP antibody to the subject in a dose of 210 mg or 420 mg as described herein administered every 2 weeks to every 4 weeks. In various embodiments, the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14. In various embodiments, the antibody is tezepelumab.

[0055] In various embodiments, the disclosure provides a method of treating chronic obstructive pulmonary disease (COPD) in a subject in need thereof comprising administering to the subject between 210 mg and 420 mg of anti-TSLP antibody as described herein

administered over a period of two to four weeks. In various embodiments, the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14. In various embodiments, the antibody is tezepelumab.

[0056] In various embodiments, the subject has a baseline eosinophil count of 300 cells/ μ L or greater. In various embodiments, the subject has a baseline eosinophil count of 100-300 cells/ μ L or greater. In various embodiments, the subject has a baseline eosinophil count of 100-300 cells/ μ L. In various embodiments, the subject has a baseline eosinophil count of 150-300 cells/ μ L or greater. In various embodiments, the subject has a baseline eosinophil count of 150-300 cells/ μ L. In various embodiments, the subject has a baseline eosinophil count of 100 cells/ μ L or greater. In various embodiments, the subject has a baseline eosinophil count of 150 cells/ μ L or greater. In various embodiments, the subject has FeNO levels greater than or equal to 25 ppb. In various embodiments, the subject is between 40 and 65 years of age. In various embodiments, the subject is 65 years of age or older. In various embodiments, the subject has improvement in pre-BD FEV1 levels, SGRQ score, E-RS and/or CAT score compared to baseline at Week 52. It is contemplated that the improvement in score is related to the minimal clinically important differences (MCID) for the test being measured or to the least square mean difference compared to placebo group. For example, a clinically relevant improvement in E-RSTM includes a reduction in score by 2 or more compared to baseline levels. A clinically relevant improvement in CAT score includes a reduction in score by 2 or more compared to baseline levels. A clinically relevant improvement in SGRQ includes a reduction in score by 4 or more compared to baseline levels.

[0057] Also contemplated is a method of treating COPD in a subject having COPD and a baseline eosinophil count of 100 cells/ μ L or greater comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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.

[0058] Also provided is a method of treating COPD in a subject having COPD and a baseline eosinophil count of 100 cells/ μ L or greater comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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).

[0059] Also contemplated is a method of treating COPD in a subject having COPD and has FeNO levels greater than or equal to 25 ppb comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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] Also provided is a method of treating COPD in a subject having COPD and has FeNO levels greater than or equal to 25 ppb comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 420 mg at an interval of every 4

weeks, wherein both binding sites of the antibody are identical binding sites that bind 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).

[0061] Further contemplated is a method of treating COPD in a subject having COPD and is between 40 and 65 years of age comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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] Also provided is a method of treating COPD in a subject having COPD and is between 40 and 65 years of age comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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).

[0063] Also contemplated is a method of treating COPD in a subject having COPD and a baseline eosinophil count of 100 cells/ μ L or greater comprising, administering 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 are identical binding sites that bind 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.

[0064] Also provided is a method of treating COPD in a subject having COPD and a baseline eosinophil count of 100 cells/ μ L or greater comprising, administering a 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 are identical binding sites that bind 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).

[0065] Also contemplated is a method of treating COPD in a subject having COPD and has FeNO levels greater than or equal to 25 ppb comprising, 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 are identical binding sites that bind 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.

[0066] Also provided is a method of treating COPD in a subject having COPD and has FeNO levels greater than or equal to 25 ppb comprising, administering 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 are identical binding sites that bind 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).

[0067] Further contemplated is a method of treating COPD in a subject having COPD and is between 40 and 65 years of age comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein

both binding sites of the antibody are identical binding sites that bind 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.

[0068] Also provided is a method of treating COPD in a subject having COPD and is between 40 and 65 years of age comprising, administering 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 are identical binding sites that bind 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).

[0069] In various embodiments, the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

[0070] In various embodiments, the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14. In various embodiments, the antibody is tezepelumab.

[0071] In another aspect, the disclosure contemplates a composition comprising an anti-TSLP antibody or antibody variant for treating chronic obstructive pulmonary disease (COPD) in a subject, wherein the composition is administered in a dose of 210 mg to 420 mg

at an interval of every 2 weeks or 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind TSLP, the 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 specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0072] Also provided is a composition comprising an anti-TSLP antibody or antibody variant for treating chronic obstructive pulmonary disease (COPD) in a subject, wherein the composition is administered in a dose of 210 mg to 420 mg at an interval of every 2 weeks or 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind TSLP, the antibody 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.

[0073] Further contemplated is use of a composition comprising an anti-TSLP antibody or antibody variant in the manufacture of a medicament for treating chronic obstructive pulmonary disease (COPD) in a subject, wherein the composition is in a dose of 210 mg to 420 mg for administration at an interval of every 2 weeks or 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind TSLP, the 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 specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

[0074] Also provided is use of a composition comprising an anti-TSLP antibody or antibody variant in the preparation of a medicament for treating chronic obstructive pulmonary disease (COPD), wherein the composition is in a dose of 210 mg to 420 mg for administration at an interval of every 2 weeks or 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind TSLP, the antibody 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.

[0075] In various embodiments, the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

[0076] In various embodiments, the composition for treating chronic obstructive pulmonary disease (COPD) in a subject comprises an anti-TSLP antibody, wherein the antibody is administered in a dose of 210 mg at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14. In another embodiment, a composition for treating chronic obstructive pulmonary disease (COPD) in a subject comprises an anti-TSLP antibody, wherein the antibody is administered in a dose of 420 mg at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain

amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

[0077] Also contemplated herein is use of a composition comprising an anti-TSLP antibody in the preparation of a medicament for treating chronic obstructive pulmonary disease (COPD), wherein the composition is in a dose of 210 mg for administration at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14. In another embodiment, disclosed is use of a composition comprising an anti-TSLP antibody in the preparation of a medicament for treating chronic obstructive pulmonary disease (COPD), wherein the composition is in a dose of 420 mg for administration at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

[0078] In various embodiments, the composition is a pharmaceutical composition comprising an anti-TSLP antibody or variant thereof and one or more pharmaceutically acceptable carriers or excipients. In various embodiments, the composition comprises an anti-TSLP antibody and a surfactant, proline, and a buffer. In some embodiments, the surfactant is polysorbate 80. In various embodiments, the buffer is selected from the group consisting of: succinate, glutamate, histidine, and acetate. In various embodiments, the formulation is at pH between 4.5 and 6.8.

[0079] In various embodiments, the composition comprises anti-TSLP antibody and one or more basic amino acids (e.g., arginine, histidine or lysine) or salt thereof, or a calcium or magnesium salt, and a surfactant (e.g., polysorbate 20 or polysorbate 80). In various embodiments, the formulation is at pH between 4.5 and 6.8.

[0080] 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 420 mg.

[0081] In various embodiments, the antibody is an IgG2 antibody. In various embodiments the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14. In various embodiments, the antibody is tezepelumab.

[0082] 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 420 mg every 2 weeks. In various embodiments, the antibody or antibody variant is

administered at a dose of 420 mg every 4 weeks. In various embodiments, the antibody or antibody variant is administered at a dose of 210 mg every 4 weeks.

[0083] It is contemplated that the dosing and antibody and antibody variant types referenced above apply to each method, composition or use contemplated herein.

[0084] In various embodiments, the antibody or antibody variant is administered to the subject in a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient.

[0085] In various embodiments, the administration delays the time to a COPD exacerbation compared to a subject not receiving the anti-TSLP antibody. In various embodiments, the administration reduces the severity of a COPD exacerbation compared to a subject not receiving the anti-TSLP antibody.

[0086] In various embodiments, the administration is subcutaneous. In various embodiments, the administration is intravenous.

[0087] Syringes, e.g., single use or pre-filled syringes, sterile sealed containers, e.g. vials, bottle, vessel, and/or kits or packages comprising any of the foregoing antibodies or compositions, optionally with suitable instructions for use, are also contemplated for use in the methods. In various embodiments, the administration is via pre-filled syringe or autoinjector. In various embodiments, the auto-injector is an Ypsomed YpsoMate® device.

[0088] 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 contemplated as possible endpoints of a range, any and all numeric values between such endpoints are contemplated, and any and all combinations of upper and lower endpoints are envisioned.

[0089] 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

- [0090] Figure 1. List of COPD medications.
- [0091] Figure 2. Sequences of anti-TSLP antibody tezepelumab.
- [0092] Figure 3. Subject characteristics at baseline.
- [0093] Figure 4. Primary Endpoint: Rate of Moderate or Severe COPD Exacerbations (FAS) – by subgroups, Forest Plot.
- [0094] Figure 5. Secondary endpoint: Rate of Severe COPD Exacerbations (FAS) – primary estimand, Negative Binomial Model.
- [0095] Figure 6. Additional secondary endpoints: Change from Baseline to Week 52, Repeated Measures Analysis (FAS).
- [0096] Figure 7. Additional secondary endpoints: Change from Baseline to Week 52, Repeated Measures Analysis (FAS) By Baseline EoS
- [0097] Figure 8. Biomarker Analysis: Blood EOS, FeNO and Neutrophils.

DETAILED DESCRIPTION

[0098] Use of an anti-TSLP antibody addresses an unmet need in chronic obstructive pulmonary disease (COPD) in which other medications may not control moderate to severe symptoms. It is contemplated 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 COPD.

[0099] The hypothesis for the mechanism of action of tezepelumab in COPD is two-fold. First, because TSLP is one of the earliest responses to airway damage caused by a range of stimuli, inhibition of TSLP is expected to prevent the acute response to epithelial damage and prevent COPD exacerbations. Secondly, given that TSLP is an upstream and pleiotropic cytokine, the blockade of TSLP is anticipated to have broad impact on the spectrum of acute and chronic airway inflammatory responses seen in COPD. Both effects are expected to reduce COPD exacerbations and improve COPD symptoms (Camelo et al 2017).

[00100] Thus, it is hypothesized that inhibition of upstream TSLP by tezepelumab will be effective in reducing airway inflammation in patients with COPD and reducing annualized moderate to severe COPD exacerbation rates. The purpose of the present study is to investigate the ability of tezepelumab versus placebo to enable reduction of the annualized

moderate to severe COPD exacerbation rate in subjects with moderate to very severe COPD receiving standard maintenance therapy.

Definitions

[00101] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below.

[0100] 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.

[0101] 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).

[0102] 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.

[0103] The term “chronic obstructive pulmonary disease” “COPD” as used herein refers to a chronic inflammatory lung disease that results in obstructed airflow in the lungs and breathing difficulty in patients with COPD. Emphysema and chronic bronchitis are contributors to COPD. COPD can be diagnosed by post-bronchodilator FEV₁/FVC <0.70 according to the outlined GOLD standards set out by the Global Initiative for Chronic Obstructive Lung Disease: GOLD 1 - mild: FEV₁ ≥80% predicted; GOLD 2 - moderate: 50% ≤ FEV₁ <80% predicted; GOLD 3 - severe: 30% ≤ FEV₁ <50% predicted; GOLD 4 - very severe: FEV₁ <30% predicted.

[0104] The term “COPD exacerbation” as used herein refers to moderate to severe COPD exacerbation is defined as a change in the subject's usual COPD symptoms that is beyond normal day-to-day variation, is acute in onset, lasts 2 or more days (or less if the worsening is so rapid and profound that the treating physician judges that intensification of treatment cannot be delayed), and may warrant a change in regular medication and leads to any of the following: Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids; Use of antibiotics for at least 3 days; An inpatient hospitalization due to COPD (defined as an inpatient admission ≥ 24 hours in the hospital, in an observation area, the emergency department or other equivalent healthcare facility depending on the country and healthcare system); Results in death.

[0105] A COPD exacerbation will be considered severe if it results in at least 1 of the following: Hospitalization defined as inpatient admission for ≥ 24 hours to an observation area, the emergency department, or other equivalent healthcare facility (depending on the country and healthcare system) for the COPD exacerbation; Death related to COPD or COPD exacerbation.

[0106] A COPD exacerbation that does not meet the requirements to be classified as severe will be considered moderate if it results in at least 1 of the following: Use of systemic corticosteroids and/or antibiotics for at least 3 days; A single depot injectable dose of corticosteroids, which will be considered equivalent to at least 3-day course of systemic corticosteroids.

[0107] Symptoms in the GOLD diagnosis are assessed using the Modified British Medical Research Council (mMRC) or COPD assessment test (CAT) scale. GOLD considers exacerbations as follows, assessed independently of symptoms to highlight their clinical relevance: Group A: low risk (0-1 exacerbations per year, not requiring hospitalization) and fewer symptoms (mMRC 0-1 or CAT < 10); Group B: low risk (0-1 exacerbations per year, not requiring hospitalization) and more symptoms (mMRC ≥ 2 or CAT ≥ 10); Group E: high risk (≥ 2 exacerbations per year, or ≥ 1 requiring hospitalization) and any level of symptoms.

[0108] The term “worsening of COPD” refers to new or increased symptoms and/or signs (examination) that can be either concerning to the subject having COPD (subject-driven) or related to a Patient Daily Diary alert (diary-driven).

[0109] 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, IL-17A, 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).

[0110] 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.

[0111] 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 contemplated 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.

[0112] 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.

[0113] 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.

[0114] An antibody variant contemplated 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.

[0115] 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.

[0116] “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.

[0117] “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.

[0118] 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.

[0119] 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.

[0120] 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 invention is directed to a method for determining the efficacy of treatment comprising administering to a patient 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.

[0121] 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.

Chronic Obstructive Pulmonary Disease

[0122] The recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition of COPD describes COPD as “a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration, exacerbations) due to

abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction.” Risk factors for COPD include environmental factors, such as indoor and outdoor air pollution, lung development and aging, smoking, socioeconomic status, and asthma and airway hyper-reactivity.

[0123] It is contemplated that the administration improves one or more measures of COPD selected from the group consisting of COPD exacerbation, time to first COPD exacerbation, rate of COPD exacerbations associated with emergency room (ER) visit, urgent care visit or hospitalization, and proportion of participants who did not experience an COPD exacerbation, FeNO, COPD Assessment Test (CAT) score, Clinically Important Deterioration (CID) score, Exacerbations of Chronic Pulmonary Disease Tool– Patient-reported Outcome (EXACT-PRO) score, E-RS, composite endpoint for exacerbations (moderate or severe) in COPD (COPDCompEx) score, change from baseline in pre- and post-BD FEV₁, St George's Respiratory Questionnaire (SGRQ) score, E-RS or CAT score, and/or reporting of a worsening event, e.g., dyspnea, sputum volume, and sputum color.

[0124] It is contemplated that the administration improves one or more measures of COPD selected from the group consisting of COPD exacerbation, time to first COPD exacerbation, rate of COPD exacerbations associated with emergency room (ER) visit, urgent care visit or hospitalization, proportion of participants who did not experience an COPD exacerbation, FeNO, COPD Assessment Test (CAT) score, Clinically Important Deterioration (CID) score, Exacerbations of Chronic Pulmonary Disease Tool– Patient-reported Outcome (EXACT-PRO) score, E-RS, composite endpoint for exacerbations (moderate or severe) in COPD (COPDCompEx) score, change from baseline in pre- and post-BD FEV₁, St George's Respiratory Questionnaire (SGRQ) score, E-RS or CAT score, BOD Index, mMRC dyspnoea scale score, 5-level EuroQoL-5 Dimension, and/or reporting of a worsening event, e.g., dyspnea, sputum volume, and sputum color, blood IgE, eosinophil-derived neurotoxin (EDN), IL-5, CT imaging biomarkers (mucous plugging, airway lumen dimensions, air trapping, emphysema progression, airway remodeling).

[0125] Methods for scoring and determining a reduction therein for the various measures are described herein and known in the art. The assessments include, but are not limited to, the following.

[0126] *COPD Assessment Test (CAT)*: The CAT is an 8-item PRO developed to measure the impact of COPD on health status (Jones et al 2009). The instrument uses semantic differential six-point response scales which are defined by contrasting adjectives to capture the impact of COPD. Content includes items related to cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home,

sleep and energy. A CAT total score is the sum of item responses. Scores range from 0-40 with higher scores indicative of greater COPD impact on health status.

[0127] *Spirometry*: Lung function (FEV₁; forced vital capacity [FVC]) is measured by spirometry. 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:

[0128] $FEV_1\% \text{ of PNV} = (FEV_1 \text{ measured} / FEV_1 \text{ PNV}) \times 100$

[0129] *COPDCompEx*: COPDCompEx is a composite endpoint for exacerbations (moderate or severe) in COPD. COPDCompEx combines exacerbations with events defined from patient daily diaries. The definitions for both types of exacerbation are as follows: Exacerbations: episodes leading to one or more of the following: hospitalization, emergency room visit, treatment with systemic corticosteroids, or treatment with antibiotics. Diary events: defined by threshold and slope criteria using the following diary variables: individual domains of the breathlessness, cough, sputum scale, sleep, chest tightness and rescue medication use.

[0130] 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).

[0131] BMI, Airflow Obstruction, Dyspnoea Index

[0132] The BOD Index is a composite index calculated based on BMI, airflow obstruction as measured by pre-BD FEV₁ (Section 8.2.3) and dyspnoea assessed by the mMRC Dyspnoea Scale. The BOD Index is used to predict mortality in COPD (Ansari et al 2016, Puhan et al 2013).

[0133] The mMRC dyspnoea scale assesses signs and symptoms of breathlessness and is a single item measure of patient's level of dyspnoea as rated by the physician. It has 5 grades rated 1 to 5, where 1 is the least severe and 5 is the most severe. The scale measures physician-perceived effect of breathlessness on daily activities (Primary Care Respiratory Society 2024).

TSLP

[0134] 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).

[0135] 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).

[0136] 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.

[0137] 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.

[0138] 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

[0139] It is contemplated that antibodies or antibody variants specific for TSLP are useful in the treatment of COPD, including moderate to severe or very severe COPD.

[0140] 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.

[0141] 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.

[0142] 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 (CDR) or framework 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).

[0143] 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).

[0144] 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.

[0145] 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.

[0146] Also contemplated 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.

[0147] 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.

[0148] 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.

[0149] 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.

[0150] 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.

[0151] 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.

[0152] 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.

[0153] 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.

[0154] It is contemplated 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.

[0155] It is contemplated that the anti-TSLP antibody variant or anti-TSLP derivative has substantially similar pK characteristics as tezepelumab-ekko in humans.

[0156] 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.

[0157] 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.

[0158] 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.

[0159] It is contemplated that anti-TSLP antibodies useful to treat COPD as described herein, e.g., at 210 mg or 420 mg every 2 weeks or every 4 weeks, also include those described in the publications set out in Table 1 and described in WO2023098491A1, WO2021155634A1, WO2022166072A1, WO2021043221A1, WO2022184074A1, WO2021104053A1, WO2023116925A1, WO2021155861A1, WO2022116858A1, WO2022117079A1, WO2020244544A1, WO2021152488A1, WO2022253147A1, WO2023070948A1, WO2023142309A1, WO2022095689A1, WO2021115240A1, WO2022166739A1 and WO2019100111A1, the disclosure of each of which is incorporated by reference herein.

Table 1

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 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
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	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 : KSSQSLLNSG NRKNYLT (SEQ ID NO:39), CDRL2: WASTRES (SEQ ID NO:40), and CDRL3: QNDYTPFTFGS (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 : RSSQSIVQSNGNTYLE
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	(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 CDRH1 : 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; 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.
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Methods of Administration

[0160] 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.

[0161] Contemplated herein are methods for treating COPD in a subject, including moderate or severe COPD. In various embodiments, the method comprises selecting a subject in need of treatment for COPD, and administering an anti-TSLP antibody as described herein.

[0162] In various embodiments, the antibody is tezepelumab or tezepelumab variant or tezepelumab derivative.

[0163] It is contemplated that the subject to be treated is human. The subject may be an adult.

[0164] 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.

[0165] 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.

[0166] In exemplary treatments, the anti-TSLP antibody or antibody variant is administered in a dose range of about 280 mg to about 420 mg per dose. In various embodiments, the anti-TSLP antibody or antibody variant may be administered at a dose of about 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 420 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 420 mg 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. In various embodiments, the disclosure provides methods of treating chronic obstructive pulmonary disease (COPD) in a subject in need thereof comprising administering to the subject between 210 mg and 420 mg of anti-TSLP antibody as described herein administered over a period of two to four weeks.

[0167] 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.

[0168] It is contemplated 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.

[0169] Treatment with the anti-TSLP antibody or antibody variant is contemplated to improve one or more measures of COPD including COPD exacerbation, time to first COPD exacerbation, rate of COPD exacerbations associated with emergency room (ER) visit, urgent care visit or hospitalization, severity of exacerbation, proportion of participants who did not experience an COPD exacerbation, FeNO, COPD Assessment Test (CAT) score, Clinically Important Deterioration (CID) score, Exacerbations of Chronic Pulmonary Disease Tool– Patient-reported Outcome (EXACT-PRO) score, E-RS, composite endpoint for exacerbations (moderate or severe) in COPD (COPDCompEx) score, change from baseline in pre- and post-BD FEV₁, St George's Respiratory Questionnaire (SGRQ) score, E-RS or CAT score, and/or reporting of a worsening event, e.g., dyspnea, sputum volume, and sputum color.

[0170] Treatment with the anti-TSLP antibody or antibody variant is contemplated to improve one or more measures of COPD including COPD exacerbation, time to first COPD exacerbation, rate of COPD exacerbations associated with emergency room (ER) visit, urgent care visit or hospitalization, severity of exacerbation, proportion of participants who did not experience an COPD exacerbation, FeNO, COPD Assessment Test (CAT) score, Clinically Important Deterioration (CID) score, Exacerbations of Chronic Pulmonary Disease Tool– Patient-reported Outcome (EXACT-PRO) score, E-RS, composite endpoint for exacerbations (moderate or severe) in COPD (COPDCompEx) score, change from baseline in pre- and post-BD FEV₁, St George's Respiratory Questionnaire (SGRQ) score, E-RS or CAT score, BOD Index, mMRC dyspnoea scale score, 5-level EuroQoL-5 Dimension, and/or reporting of a worsening event, e.g., dyspnea, sputum volume, and sputum color, blood IgE, eosinophil-derived neurotoxin (EDN), IL-5, CT imaging biomarkers (mucous plugging, airway lumen dimensions, air trapping, emphysema progression, airway remodeling).

[0171] In one embodiment, the administration improves one or more symptoms of COPD including, but not limited to, number of or severity of COPD exacerbations (e.g., moderate or severe exacerbations), lung function, such as pre- and/or post-bronchodilator forced expiratory volume in 1 second (pre-BD FEV₁), FeNO levels, St George's Respiratory Questionnaire (SGRQ) score, E-RS, and/or CAT score.

[0172] In various embodiments, treatment with anti-TSLP modulates the levels of one or more biomarkers of COPD, 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.

[0173] In various embodiments, treatment with the anti-TSLP antibody delays the time to a COPD exacerbation or flare up compared to a subject not receiving the anti-TSLP antibody.

[0174] Also contemplated 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, antibiotic or COPD therapy (see Figure 1).

[0175] In various embodiments, the subject is also receiving treatment with corticosteroids. In various embodiments the corticosteroids are oral corticosteroids or inhaled corticosteroids. In various embodiments the oral corticosteroids are selected from

the group consisting of one or more of prednisone, prednisolone, cortisone, hydrocortisone, methylprednisolone, triamcinolone, betamethasone, dexamethasone, and deflazacort, fluticasone, budesonide or combinations thereof. In various embodiments, the inhaled corticosteroids include fluticasone, budesonide, mometasone, ciclesonide, and beclomethasone or combinations thereof.

[0176] In various embodiments, the method comprises administering anti-TSLP antibody or antibody variant in conjunction with a co-administered therapy, e.g., bronchodilator and/or an oral or inhaled corticosteroid or triple inhaled maintenance therapy.

Formulations

[0177] In some embodiments, the disclosure contemplates 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.

[0178] 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. Genmo, ed.), 1990, Mack Publishing Company.

[0179] 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.

[0180] 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.

[0181] 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.

[0182] In various embodiments, the anti-TSLP antibody or antibody variant is in a formulation 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.

[0183] In various embodiments, the anti-TSLP antibody or antibody variant 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. In various embodiments, tezepelumab 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.

[0184] When parenteral administration is contemplated, 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

[0185] 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.

[0186] 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 2 Study to Evaluate the Effect of Tezepelumab in chronic obstructive pulmonary disease (COPD)

[0187] The purpose of this study is to evaluate the efficacy and safety of tezepelumab 420 mg administered by subcutaneous (SC) injection every 4 weeks (Q4W) in adults with moderate to very severe COPD receiving triple inhaled maintenance therapy (inhaled corticosteroid/long-acting β 2 agonist and long acting muscarinic antagonist [ICS/LABA/LAMA]) who have had ≥ 2 documented COPD exacerbations in the 12 months prior to study start. The study will evaluate the incidence of COPD exacerbations and other efficacy parameters such as lung function and quality of life and will provide adequate safety information in order to characterize the benefit-risk profile of tezepelumab treatment in subjects with COPD.

[0188] The study planned to randomize approximately 338 subjects 1:1 to either tezepelumab or placebo, stratified by region, and number of prior exacerbations. Approximately 20% of the subjects will be targeted to have ≥ 300 eosinophils/ μ L, 40% of the subjects between ≥ 150 to < 300 eosinophils/ μ L and a maximum of approximately 40% of the subjects with < 150 eosinophils/ μ L at enrollment.

[0189] A subset of patients will participate in a sputum sub study. Performing COPD Exacerbation visit (EXA) for sputum sub-study patients is essential to evaluate exploratory sputum and nasal sub-study endpoints during treatment phase. Patients participating in sputum sub-study are required to perform pre-BD and sputum post-BD spirometry as part of sputum induction, at EXA visits during treatment.

[0190] COPD disease state and COPD exacerbation(s) in the previous year are defined as: Clinic visit (primary or specialist healthcare provider [HCP]) notes or emergency room/hospital records listing COPD as a current diagnosis and providing evidence of ≥ 2 moderate or severe exacerbations in the previous year (52 weeks prior to enrolment); Documented prescription of systemic corticosteroids of at least 3 days duration (or 1 injection of depot formulation) and/or antibiotics for treatment of exacerbation; Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a subject was hospitalized or treated with systemic corticosteroids for a COPD exacerbation.

[0191] Inclusion criteria for the study:

[0192] 1. Written informed consent

[0193] 2. A diagnosis of COPD

[0194] 3. Age 40 years to 80 years inclusive

[0195] 4. History of moderate to very severe documented physician-diagnosed COPD for at least 12 months prior to enrolment with a post-bronchodilator $FEV_1/FVC < 0.70$ and a post-bronchodilator $FEV_1 \geq 20\%$ and $\leq 80\%$ of predicted normal value at Visit 2 (or Visit 1 if Visit 1 and 2 are combined).

[0196] 5. History of at least 2 documented moderate to severe COPD exacerbations, within 2 to 52 weeks prior to enrolment (Visit 1) or re-screening Visit 1.

[0197] -A moderate COPD exacerbation is defined as an exacerbation that required treatment with systemic corticosteroids for at least 3 days duration (or 1 injection of depot formulation) and/or antibiotics.

[0198] -A severe COPD exacerbation is defined as an exacerbation that required hospitalization (defined as an inpatient admission ≥ 24 hours in the hospital, in an observation area, the emergency department or other equivalent healthcare facility depending on the country and healthcare system).

[0199] -Prior use of antibiotics alone does not qualify as a moderate exacerbation unless the antibiotic was specifically prescribed for the treatment of worsening COPD symptoms.

[0200] -Previous exacerbations should be confirmed to have occurred while patient was on stable triple (ICS/LABA/LAMA) background therapy for COPD and not as a result of a step down in therapy, i.e., change from triple to dual therapy.

[0201] 6. Documented treatment with medium or high dose ICS at a total daily dose corresponding to $>250\mu g$ fluticasone propionate dry powder formulation equivalent and

LABA and LAMA for COPD throughout the year prior to enrolment (Visit 1). The dose of ICS should be stable for 3 months prior to Visit 1.

[0202] 7. CAT score ≥ 15 (only based on ePRO questionnaire) at Visit 1.

[0203] 8. Current smoker or ex-smoker with a tobacco history of ≥ 10 pack-years (1 pack year = 20 cigarettes smoked per day for 1 year). Never smokers are not eligible for study entry.

[0204] 9. If on allergen-specific immunotherapy, subjects must be on a maintenance dose and schedule for at least 2 months prior to Visit 1.

[0205] 10. If on theophylline or roflumilast, subjects must be on maintenance treatment for at least 12 months prior to Visit 1 and on stable dose 3 months prior to Visit 1.

[0206] 11. Weight ≥ 40 kg at Visit 1.

[0207] 12. Women of childbearing potential (WOCBP) who are sexually active must use a highly effective form of birth control from enrolment and must agree to continue using such precautions for 16 weeks after the final dose of IP. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

[0208] 13. Compliance with the eDiary completion during the run-in period defined as completing at least 8 EXACT-PRO/E-RS assessments in the 12-day period prior to Visit 3.

[0209] 14. At least 70% compliance with the subject's maintenance therapy (defined as taking all maintenance medication as scheduled for the day) during the run-in period from Visit 2 (or Visit 1 if Visit 1 and 2 are combined) to Visit 3 based on the eDiary.

[0210] 15. Stable FEV₁ during the screening period, defined as a change in pre-BD FEV₁ ≤ 400 mL and/or $\leq 25\%$ compared to baseline pre-BD (Visit 1) assessment. If a patient demonstrates significant change (>400 mL and/or $>25\%$ in either direction) in pre-BD FEV₁ during the screening period, the AZ study physician must be consulted to determine the patient's disposition; randomization may not occur without consultation and agreement with AZ study physician/delegate.

[0211] 16. Acceptable inhaler and spirometry techniques according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005) during the run-in period.

[0212] Exclusion criteria include:

[0213] 1. Clinically important pulmonary disease other than COPD, as judged by Investigator, (e.g., active lung infection, main clinical feature is bronchiectasis or emphysema, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency and primary ciliary dyskinesia) or another diagnosed pulmonary or systemic disease that is associated with elevated peripheral eosinophil counts (e.g., allergic bronchopulmonary aspergillosis (ABPA)/mycosis, eosinophilic granulomatosis with polyangiitis (EGPA), hypereosinophilic syndrome) and/ or radiological and/or laboratory findings suggestive of a respiratory disease other than COPD that is contributing to the subject's respiratory symptoms.

[0214] 2. Current asthma diagnosis according to the Global Initiative for Asthma (GINA) guidelines (GINA 2018) or other accepted guidelines. Patients with a history of asthma, including pediatric asthma or asthma-COPD Overlap Syndrome (ACOS), are not eligible for the study.

[0215] 3. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious (including risk factors for pneumonia), endocrine, metabolic, hematological, immune, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and/or could:

[0216] (a) Affect the safety of the subject throughout the study

[0217] (b) Influence the findings of the study or their interpretation

[0218] (c) Impede the subject's ability to complete the entire duration of study

[0219] Note: Subjects who have epilepsy must be on a stable dose of medication for 28 days prior to randomization.

[0220] 4. Unstable ischemic heart disease, arrhythmia, cardiomyopathy, heart failure, renal failure, uncontrolled hypertension as defined by the Investigator, or any other relevant cardiovascular disorder as judged by the Investigator or any ECG abnormality obtained during the screening period that in Investigator's judgement may put the patient at risk or negatively affect the outcome of the study.

[0221] 5. Treatment with systemic corticosteroids and/or antibiotics, and/or hospitalization for a COPD exacerbation within 14 days prior to enrolment (Visit 1), based on last dose of corticosteroids or last date of hospitalization, whichever occurred later.

[0222] 6. History of clinically significant infection (excluding pneumonia), acute upper or lower respiratory infection, requiring antibiotics or antiviral medication within 14 days prior to

enrolment (Visit 1) based on the last day of antibiotic/antiviral treatment or hospitalization date, whatever occurred later.

[0223] 7. History of pneumonia requiring antibiotics or antiviral medication within 28 days prior to enrolment (Visit 1) or during the screening period, based on the last day of antibiotics or hospitalization date, whatever occurred later or during the enrolment and screening period.

[0224] 8. Known history of allergy or reaction to any component of the investigational product formulation.

[0225] 9. History of anaphylaxis to any other biologic therapy.

[0226] 10. Donation of blood, plasma, or platelets within the past 90 days prior to Visit 1.

[0227] 11. A helminth parasitic infection diagnosed within 24 weeks prior to Visit 1 that has not been treated with, or has failed to respond to, standard of care therapy.

[0228] 12. History of alcohol or drug abuse within the past year, which may compromise the study data interpretation as judged by Investigator or Study Physician.

[0229] 13. History of cancer: Subjects 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. Subjects who have had other malignancies are eligible provided that curative therapy was completed at least 5 years prior to Visit 1.

[0230] 14. Subjects who in the opinion of the Investigator have evidence of active tuberculosis (TB), either treated or untreated, or latent TB without completion of an appropriate course of treatment. Evaluation will be according to the local standard of care as determined by local guidelines and may consist of medical history and physical examinations, chest x-ray, sputum stain and/or culture, and/or TB test (e.g., purified protein derivative or QuantiFeron test).

[0231] 15. Major surgery within 8 weeks prior to Visit 1 or planned surgical procedures requiring general anesthesia or in-patient status for >1 day during the conduct of the study.

[0232] 16. Subjects currently receiving background therapy that is not locally approved for COPD are not eligible for the study (refer to Section 6.5.1)

[0233] 17. Long term oxygen therapy (LTOT) with signs and/or symptoms of cor pulmonale and/or right ventricular failure, or subjects receiving LTOT >4.0 litres/minute (L/min), or saturation <89% despite LTOT.

- [0234]** 18. Use of any non-invasive positive pressure ventilation device (NIPPV). Note: Subjects using continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) for Sleep Apnea Syndrome are allowed in the study.
- [0235]** 19. Use of systemic immunosuppressive medication (including but not limited to methotrexate, cyclosporine, maintenance systemic steroid treatment, any experimental anti-inflammatory therapy) within 3 months prior to enrolment (Visit 1) or throughout the screening period. Use of systemic steroids for treatment of exacerbations is allowed (see exclusion criterion 5).
- [0236]** 20. Receipt of immunoglobulin or blood products within 30 days prior to enrolment (Visit 1).
- [0237]** 21. Receipt of any investigational non-biologic product within 30 days or 5 half-lives whichever is longer, prior to Visit 1.
- [0238]** 22. Receipt of any marketed (e.g., omalizumab) or any investigational monoclonal or polyclonal antibody therapy (e.g., gamma globulin) taken for any reason within 4 months or 5 half-lives prior to Visit 1, whichever is longer.
- [0239]** 23. Receipt of live attenuated vaccines 30 days prior to first IP administration.
- [0240]** 24. Chronic use of macrolide or other antibiotics for prophylactic use of COPD exacerbation if duration of treatment is < 9 months prior to enrolment (Visit 1) or re-screening visit. If the patient was previously on prophylactic treatment but is no longer taking it, the patient cannot be randomized until 6 weeks after the last dose. Chronic macrolide or other antibiotic therapy is allowed provided the patient has been on a stable dose/regimen for ≥ 9 months prior to enrolment (Visit 1) or re-screening visit and have had at least 2 historical COPD exacerbations while on prophylactic treatment.
- [0241]** 25. Influenza vaccination within 3 weeks before sputum collection (Visit 3) for subset of subjects only. Vaccination prior to that or after that time is acceptable.
- [0242]** 26. Subjects with lung volume reduction surgery within the 6 months prior to Visit 1. Subjects with history of partial or total lung resection (single lobe or segmentectomy is acceptable).
- [0243]** 27. Subjects that have been treated with bronchial thermoplasty or received endobronchial valves in the last 12 months prior to Visit 1.
- [0244]** 28. Subjects participating in, or scheduled for, an intensive (active) COPD rehabilitation program (however subjects who are in the maintenance phase of a rehabilitation program are eligible to take part).

[0245] 29. Employees of the clinical study center or family members (first-degree relatives) of such individuals or anyone involved in the planning and/or conduct of the study.

[0246] 30. Previous treatment with tezepelumab (MEDI9929/AMG157).

[0247] 31. Any clinically significant abnormal findings in physical examination, vital signs, hematology, clinical chemistry, or urinalysis during screening period, which in the opinion of the Investigator, may put the subject at risk because of his/her participation in the study, or may influence the results of the study, or the subject's ability to complete entire duration of the study.

[0248] 32. Evidence of active liver disease (with or without ongoing treatment), including jaundice or aspartate transaminase (AST), alanine transaminase (ALT), or alkaline phosphatase (ALP) > 2 times the upper limit of normal (ULN) at Visit 1.

[0249] 33. Subjects are excluded if they have any of the following: A history of known immunodeficiency disorder including a positive test for human immunodeficiency virus, HIV-1 or HIV-2 at Visit 1. Positive hepatitis B surface antigen, or positive hepatitis C virus antibody serology, or a positive medical history for hepatitis B or C at Visit 1. Patients with a history of hepatitis B vaccination without history of hepatitis B are allowed to enroll.

[0250] Pregnant, breastfeeding, or lactating women.— A serum β -HCG pregnancy test must be drawn for women of childbearing potential at the screening visit. If test result is positive, the subject should be excluded. Since urine and serum tests may miss a pregnancy in the first days after conception, relevant menstrual history and sexual history, including methods of contraception, should be considered. Any subject whose menstrual and/or sexual history suggests the possibility of early pregnancy should be excluded.

[0251] Background (maintenance) COPD medication (ICS/LABA/LAMA) is allowed during the study. Documented treatment with medium or high dose ICS at a total daily dose corresponding to >250 μ g fluticasone propionate dry powder formulation equivalent and a LABA and LAMA for COPD throughout the year prior to enrollment (Visit 1) and throughout the study. The dose of ICS should be stable 3 months prior to V1 and throughout the study. ICS in a separate, single device is permitted if all the following criteria are met: - it is administered at the same dose and schedule as in the fixed dose combination product; - it is not given in combination with a LAMA alone.

[0252] SABA (short-acting β 2-agonists administered by an MDI or nebulizer) or SAMA (short acting muscarinic antagonists = short acting anticholinergics administered by MDI or nebulizer) are allowed as rescue medication and for treatment of acute COPD exacerbation.

Prophylactic use of SABA in the absence of symptoms is discouraged. Use of SABA or SAMA is to be avoided 6 hours before a scheduled ECG, FeNO and spirometry assessment.

[0253] ENDPOINTS AND ASSESSMENTS

[0254] All subjects are required to be treated with maintenance locally approved triple inhaled therapy (ICS/LABA/LAMA) for COPD for at least 12 months prior to enrolment (Visit 1) with a stable dose of ICS for the 3 months prior to Visit 1. The aim of this study is to establish the treatment effect of tezepelumab as add-on therapy.

[0255] Primary endpoints include assessing the effect of tezepelumab compared with placebo on rate of moderate or severe COPD exacerbations in subjects with moderate to very severe COPD. Primary outcome measure includes moderate or severe COPD exacerbation rate ratio (tezepelumab vs placebo). A supportive endpoint includes rate of moderate (excluding exacerbations treated only with antibiotics) or severe COPD exacerbations. Supportive measures include moderate (excluding exacerbations treated only with antibiotics) or severe COPD exacerbation rate ratio (tezepelumab vs placebo).

[0256] *Duration of COPD Exacerbations:* For moderate or severe exacerbations, the duration is defined by the prescribed treatment or duration of hospitalization: The start date will be defined as the start date of prescribed treatment with a systemic corticosteroid and/or systemic antibiotic or hospital admission, which occurs earlier. The stop date will be defined as the last day of prescribed treatment with a systemic corticosteroid and/or systemic antibiotic or hospital discharge, which occurs later. A single depot injectable dose of corticosteroids will be considered equivalent to at least 3-day course of systemic corticosteroids. The corresponding stop date for this treatment will consequently be determined as the date of administration plus 2 days. If multiple treatments are prescribed for the same exacerbation, the earliest start date and the latest stop date will be used. For a severe COPD exacerbation with no documented corticosteroid or antibiotics treatment, hospitalization admission/discharge dates, or emergency visit date will be used as start/stop dates. A new COPD exacerbation event must be preceded by at least 7 days between the last COPD exacerbation.

[0257] The subject will use the eDiary for daily symptom reporting, entering symptoms twice daily as. If symptoms meet a specific threshold (i.e., 1 major COPD symptom and at least 1 other major or minor symptom for 2 consecutive days), the eDiary generates an alert to the subject and the investigational site. Major COPD symptoms: dyspnea, sputum volume, and sputum color; Minor COPD symptoms: cough, wheeze, sore throat, cold symptoms (rhinorrhea or nasal congestion), and fever without other cause.

[0258] Secondary endpoints include:

[0259] Evaluation of the effect of tezepelumab compared with placebo on time to first moderate/severe exacerbation. Outcome variables include time to first moderate or severe COPD exacerbation; proportion of subjects with ≥ 1 moderate or severe COPD exacerbation. Supportive outcome measures include Hazard Ratio (tezepelumab vs placebo) and Odds Ratio (tezepelumab vs placebo).

[0260] Evaluation of the effect of tezepelumab as compared with placebo on severe COPD exacerbations. Secondary outcome variables include rate of severe COPD exacerbations. Outcome measures include Rate ratio (tezepelumab vs placebo) and supportive outcome variables include time to first severe COPD exacerbation and proportions of patients experiencing a severe COPD exacerbation. Supportive outcome measures include Hazard Ratio (tezepelumab vs placebo) and Odds Ratio (tezepelumab vs placebo).

[0261] Evaluation of the effect of tezepelumab as compared with placebo on pre-bronchodilator (BD) lung function. Outcome variables include change from baseline in pre-BD forced expiratory volume in 1 second (FEV₁) at Week 52. Outcome measures include mean difference in change from baseline (tezepelumab vs placebo) at Week 52.

[0262] Evaluation of the effect of tezepelumab as compared with placebo on respiratory health status/health-related quality of life. Outcome variables include proportion of subjects achieving an MCID of 4 units or more in SGRQ total score at Week 52 and change from baseline in SGRQ at Week 52; and change from baseline in COPD assessment tool (CAT) at Week 52. Outcome Measures include Odds Ratio (tezepelumab vs placebo) and mean difference in change from baseline (tezepelumab vs placebo) at Week 52.

[0263] Evaluation of the pharmacokinetics (PK) and immunogenicity of tezepelumab as measured by PK, Serum trough concentration, and Immunogenicity, Incidence of anti-drug antibodies (ADA).

[0264] Additional outcome metrics include the following:

[0265] Evaluation of the effect of tezepelumab on COPD Composite Exacerbations (COPDCompEx) event: Time to COPDCompEx event and Rate of COPDCompEx events. Outcome measures include Hazard Ratio (tezepelumab vs placebo) and Odds Ratio (tezepelumab vs placebo);

- [0266]** Evaluation of the effect of tezepelumab on time to a Clinically Important Deterioration (CID) event, as measured by time to CID event and Hazard Ratio (tezepelumab vs placebo);
- [0267]** Assessment of the effect of tezepelumab compared with placebo on blood eosinophil (EOS) and neutrophil levels as measured by change in baseline at week 52;
- [0268]** Assessment 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), mean difference in change from baseline (tezepelumab vs placebo) at Week 52;
- [0269]** Evaluation of the effect of tezepelumab on respiratory symptoms and on the frequency, duration, and severity of EXACT-PRO defined events variables include, change from baseline in Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms (EXACT-PRO/E-RS™: COPD) and rate of EXACT-PRO defined exacerbations, measured by mean difference in change from baseline (tezepelumab vs placebo) at Week 52, and EXACT-PRO defined exacerbation rate ratio (tezepelumab vs placebo);
- [0270]** Evaluation of tezepelumab's effect on COPD-related healthcare resource; Outcome variable: Rate of COPD-specific resource utilization (e.g., unscheduled physician visits, unscheduled phone calls to physicians, use of other COPD medications); Outcome measure: Difference in rate of COPD-specific resource utilizations (tezepelumab vs placebo) over 52 weeks;
- [0271]** Assess the effect of tezepelumab on airway inflammation Outcome variable: Fractional exhaled nitric oxide (FeNO) Outcome measure: Mean difference in change from baseline (tezepelumab vs placebo) at Week 52;
- [0272]** Assess the effect of tezepelumab on total serum immunoglobulins, e.g., total IgG and/or IgE, IgA, IgM, IgG and biomarkers based on mean difference in change from baseline (tezepelumab vs placebo) at Week 52;
- [0273]** Evaluate the effect of tezepelumab on sputum biomarkers, sputum cell counts and sputum microbiome, in subjects participating in sub-study, at baseline, end of treatment, and at the start of all exacerbations during treatment phase; measuring Sputum biomarkers of inflammation and remodeling, sputum cell counts and cell differentials from cytopins, and sputum microbiome;
- [0274]** Evaluate the effect of tezepelumab on nasal lining fluid biomarkers, urine biomarkers, relationships between pharmacogenomic DNA markers and response/exposure

to tezepelumab, the effect of tezepelumab on the blood and/or nasal epithelial cell and/or sputum cell transcriptome for pharmacodynamic (PD) markers of exposure or response to tezepelumab and pre-and post-dose predictive markers of clinical response;

[0275] *Spirometry*: Lung function (FEV₁; forced vital capacity [FVC]) will be measured by spirometry at the study site using equipment provided by a central vendor. 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:

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

[0276] *Post-BD spirometry*: 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 administered between 15 and 45 minutes of the final pre-BD spirometry measurement. SABA administration should start at least 15 minutes after final pre-BD spirometry and should end no later than 45 minutes after final pre-BD spirometry. Post-BD spirometry will be performed 15-30 minutes after last SABA inhalation. SABA administration can start earlier (less than 15 minutes of the final pre-BD spirometry) for safety reasons.

[0277] *Sputum post-BD spirometry*: Sputum post-BD spirometry should be performed per schedule in Table 2 (Visit 3, Visit 16, IPD and EXA) as part of induced sputum procedures if subject is participating in the sputum sub-study, after post-BD spirometry (where applicable, refer to Section 8.1.2.2). It is conducted solely to ensure patient safety in inducing sputum and results will neither be captured for the eCRF, nor for study endpoints. More details will be provided in applicable sputum sub-study manual.

[0278] *Fractional exhaled nitric oxide (FeNO)*: 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). 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 and/or SAMA medication 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.

[0279] *COPDCompEx*: COPDCompEx is a composite endpoint for exacerbations (moderate or severe) in COPD. COPDCompEx combines exacerbations with events defined

from patient daily diaries. The definitions for both types of exacerbation are as follows:
Exacerbations: episodes leading to one or more of the following: hospitalization, emergency room visit, treatment with systemic corticosteroids, or treatment with antibiotics. Diary events: defined by threshold and slope criteria using the following diary variables: individual domains of the breathlessness, cough, sputum scale, sleep, chest tightness and rescue medication use. The analysis of this endpoint will primarily be time to first COPDCompEx event, but the events may also be analyzed with models addressing event rates or time to recurrent event. More details on the derivation and analysis of this variable will be given in the Statistical Analysis Plan (SAP).

[0280] *Clinically Important Deterioration (CID)*: CID is a composite endpoint measuring worsening of the key clinical features of COPD, namely lung function, patient-reported outcomes and exacerbations. CID is defined as 1) a decrease of ≥ 100 mL from baseline in trough FEV₁, 2) a deterioration in health-related quality of life defined as ≥ 4 -unit increase from baseline in SGRQ total score, 3) the occurrence of an on-treatment moderate-to-severe COPD exacerbation (defined as an acute worsening of COPD symptoms requiring the use of additional treatment including oral corticosteroids, antibiotics, emergency department treatment, or hospitalization).

[0281] Patient reported outcomes are also collected.

[0282] *Major/Minor Symptom Worsening Assessment and Alert System*: Symptoms will be assessed each morning for the purposes of a symptom worsening alert. The purpose of this alert is to notify both the subject and the site of a potential symptom worsening event that warrants contact between the subject and Investigator/authorized delegate for further evaluation.

[0283] Each morning the subject will complete 3 questions pertaining to the major symptoms of a worsening event (dyspnea, sputum volume, and sputum color). Subject reported worsening of 1 or more of these symptoms will trigger assessment of the minor symptoms of a worsening event (sore throat, cold, fever without other cause, cough, and wheeze). All questions will have a 24-hour recall period. Questions pertaining to the severity of symptoms vs. their usual state will have 3 response options (e.g., How breathless have you been in the last 24 hours? Less breathlessness than usual, Usual level of breathlessness, more breathless than usual) whereas questions related to the presence or absence of a symptom will have a dichotomous response (e.g., Have you had a sore throat in the last 24 hours? No, Yes, I had a sore throat).

[0284] An alert will be triggered if two or more major symptoms (dyspnea, sputum volume, and sputum color) worsen for two consecutive days or if one major symptom and one minor symptom (e.g., sore throat, cold, fever without other cause, cough, and wheeze) worsen for at least two consecutive days. When either of these criteria is met the subject will be alerted via the ePRO device to contact the site as soon as possible for further evaluation. Likewise, the site will be alerted to contact the subject within approximately 24-72 hours if he or she has not yet contacted the site for further evaluation.

[0285] *COPD Assessment Test (CAT)*: The CAT is an 8-item PRO developed to measure the impact of COPD on health status (Jones et al 2009). The instrument uses semantic differential six-point response scales which are defined by contrasting adjectives to capture the impact of COPD. Content includes items related to cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep and energy. Each item response ranges from 0 to 5 with 0 having the least impact and 5 having the greatest impact on health status. A CAT total score is the sum of item responses. Scores range from 0-40 with higher scores indicative of greater COPD impact on health status. The CAT will be measured at Visits 1, 3, 6, 9, 12, IPD and 16/EOT. A clinically relevant improvement in CAT score includes a reduction in score by 2 or more compared to baseline levels, or compared to placebo group.

[0286] *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. SGRQ a responder will be defined as an individual with a ≥ 4 -point decrease (improvement) in SGRQ total score at Week 52). Specific details on the scoring algorithms are provided by the developer in a user manual (Jones et al 2009). A clinically relevant improvement in SGRQ score includes a reduction in score by 4 or more compared to baseline levels, or compared to placebo group.

[0287] *Exacerbations of Chronic Pulmonary Disease Tool– Patient-reported Outcome (EXACT-PRO) and Evaluating Respiratory Symptoms in COPD (E-RS™:COPD)*: The

EXACT-PRO is a 14-item PRO instrument developed to assess the frequency, severity, and duration of COPD exacerbations (Jones et al 2011, Leidy et al 2011). The instrument was developed for daily, at home, administration using a handheld electronic device.

Respondents are instructed to complete the diary each evening just prior to bedtime and to answer the questions while considering their experiences “today”. The daily EXACT-PRO total score has a range of 0-100 with higher scores indicative of greater severity. Total score changes are used to identify the onset and recovery from an EXACT-PRO defined exacerbation event. In identifying event onset and recovery, the EXACT-PRO can provide information on event frequency and duration as well as event severity.

[0288] The E-RS™: COPD is an 11-item PRO developed to evaluate the severity of respiratory symptoms of COPD (Sexton et al 2010, Sexton et al 2011). The E-RS™: COPD is a subset of items from the EXACT-PRO. The E-RS™: COPD was designed to be captured as part of the daily EXACT-PRO assessment. Summation of E-RS™: COPD item responses produces a total score ranging from 0 to 40, with higher scores indicating greater severity. In addition to the total score, symptom domain scores can be calculated for breathlessness (5 items; score range: 0–17), cough and sputum (3 items; score range: 0–11) and chest symptoms (3 items; score range: 0–12) by summing the responses of items within a respective domain. As with the total score, higher domain scores indicate greater severity. Individual daily E-RS: COPD total and domain scores are calculated and summarized as biweekly (14 days) means, derived by the following rules: The biweekly mean is calculated as the sum of all non-missing daily measures/scores over 14 sequential days divided by the number of non-missing daily measures/scores. If more than 7 -daily measures/scores (>50%) within that period are missing, then the mean daily measure/score for that period is set to missing. A clinically relevant improvement in E-RS™ includes a reduction in score by 2 or more compared to baseline levels, or compared to placebo group.

[0289] For participants in the sputum study:

[0290] *Nasal Epithelial Cell and Sputum Cell Transcriptomics*: Nasal epithelial cell transcriptomic samples and/or sputum cell transcriptomic samples will be obtained, in accordance with the schedule provided in Table 2 in the SoA, in a subset of subjects only participating in the sub-study. If sputum and nasal collections occur at the same visit, nasal sampling should occur before sputum collection. If the subject is not able to produce sputum (spontaneous or induced) at Visit 3, then the subject should be withdrawn from the sub-study only and nasal samples should be discarded. Please note that the subject can continue in the main study. Nasal epithelial and/or sputum cell RNA may be used in the analyses of host gene expression research using quantitative methods that may include but not be limited to

RNA microarrays, RNA-Seq and quantitative reverse-transcriptase polymerase chain reaction technologies and stored for future analyses.

[0291] *Sputum Induction:* The aim of sputum induction is to obtain satisfactory samples of sputum originating from the lower airways. Sputum induction will be performed in accordance with the schedule provided in a subset of subjects only participating in the sub-study. If sputum and nasal collections occur at the same visit, nasal sampling should occur before collection of spontaneous or induced sputum. Attempts will be made to perform sputum induction as close to the baseline assessment time at each of the scheduled visits. If the subject is not able to produce sputum (spontaneous or induced) at Visit 3, then the subject should be withdrawn from the sub-study and nasal samples should be discarded. Please note that the subject can continue in the main study. For other sub-study visits, sputum sub-study samples will be collected if sub-study laboratory kits and supplies are available within visit window. In the event of missing supplies, sites should make reasonable effort to collect and process samples where feasible, and with the approval of Study Physician.

[0292] Sputum induction is conducted by inhalation of nebulized sterile saline solution followed by coughing and expectoration of airway secretions. Since saline inhalations may cause bronchoconstriction lung function will be monitored during the process. If spontaneous sputum is produced immediately prior to beginning the induced sputum procedure, it may be used as a secondary option for outcome measures if an adequate volume of induced sputum is not acquired. Sputum biomarkers may be measured to evaluate the pharmacology of tezepelumab, microbiome and to evaluate changes in biomarkers related to COPD, inflammation and the TSLP pathway. Baseline levels of sputum biomarkers will also be used to explore for potential predictive biomarkers of response or exposure to tezepelumab. The specific biomarkers that may be analyzed may include but are not limited to cytokines, chemokines and inflammatory mediators associated with COPD and the TSLP pathway. Drug concentrations may also be measured in the sputum samples, if feasible. If appropriate, urea concentrations may be measured to correct for the dilution factor of the sputum samples.

[0293] *Nasal Lining Fluid:* The nasal lining fluid procedure is a quick and simple technique for sampling nasal secretions. Nasal lining fluid samples will be obtained in accordance with the schedule provided in a subset of subjects only participating in the sputum sub-study, and if nasal lining fluid sampling supplies are available. If sputum and nasal collections occur at the same visit, nasal sampling should occur before spontaneous/sputum induction. Nasal lining fluid biomarkers will be measured to evaluate the pharmacology of tezepelumab and to

evaluate changes in biomarkers related to COPD, inflammation and the TSLP pathway. Baseline and early post-dose levels of nasal lining fluid biomarkers may also be used to explore for potential predictive biomarkers of response or exposure to tezepelumab. The specific biomarkers that may be analyzed include but are not limited to cytokines, chemokines and inflammatory mediators associated with COPD and the TSLP pathway. Drug concentrations may also be measured in the nasal lining fluid samples, if feasible. If appropriate, urea concentrations may be measured to correct for the dilution factor of the nasal lining fluid samples.

[0294] Participants report any of the following in the eDiary:

[0295] • Rescue medication usage including reliever inhaler and nebulizer use will be captured twice daily. Inhaler usage will be reported as the number of puffs, (i.e., the sum of different relievers, if applicable) in a given period whereas nebulizer use will be reported as the number of times. Rescue medication usage at night will be assessed in the morning and rescue medication used during the day will be assessed in the evening;

[0296] • Subjects will be asked to report the occurrence of nocturnal awakenings due to COPD symptoms each morning using the ePRO device. A single question with yes/no response options will be used.

[0297] *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.

[0298] *Pharmacokinetic Assessments:* Whole blood samples of approximately 5 mL are collected for measurement of serum concentrations of tezepelumab.

[0299] STATISTICAL ANALYSIS

[0300] 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% confidence intervals (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.

[0301] The COPD exacerbation rate and the corresponding 90% confidence interval (CI) within each treatment group will be presented. The estimated treatment difference from placebo (i.e., the absolute difference between tezepelumab and placebo, and the rate ratio

of tezepelumab versus placebo), corresponding 90% CI, and 1-sided p-value for the rate ratio will be presented. The 95% CI, and 2-sided p-value for the rate ratio will also be presented. Marginal standardization methods will be used on the model estimates for all negative binomial analyses, unless otherwise specified.

[0302] Annual rate of severe COPD exacerbations will be analyzed using a Negative Binomial Model as outlined for the primary efficacy variable.

[0303] Time to first severe COPD exacerbation will be analyzed using a similar model for time to first COPD exacerbation.

[0304] Change from baseline in pre-dose/pre-BD FEV1 at Week 52 will be compared between tezepelumab and placebo using a repeated measures analysis on subjects with a baseline pre-dose/pre-BD FEV1 and at least one post-randomization pre-dose/pre-BD FEV1 in the FAS. The dependent variable will be the change from baseline in pre-bronchodilator FEV1 at post-baseline protocol-specified visits (up to the EOT visit). Treatment group will be fitted as the explanatory variable, and region, visit, baseline pre-bronchodilator FEV1 and the interaction between visit and treatment will be fitted as covariates. Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance covariance matrix will be used instead. The model is:

*Change in FEV1 = Treatment group + baseline FEV1 + region + prior exacerbation strata + visit + treatment*visit*

[0305] Changes from baseline in SGRQ total score and CAT total score at Week 52 will be analyzed using a similar model for change from baseline in pre-dose/pre-BD FEV1; the appropriate baseline value will be used in each model.

[0306] *Results:* The study was completed to high quality: 85% of subjects completed study as of CDL. 4 patients were randomized in error and not dosed (all on Teze), and are not counted in Full Analysis Set. 17% of patients discontinued IP, discontinuations were balanced across arms and spread generally uniformly over study follow-up time. Demographics and baseline characteristics were generally well balanced across treatment arms, with a small imbalance in baseline eosinophils. However, this imbalance was not present in screening eosinophils. Rates of IPDs were balanced across arms.

[0307] The Phase 2 study was completed with the following patient profiles receiving treatment and completing the study (Table 2):

Table 2

Number (%) of subjects	Teze 420 mg Q4W	Placebo
Subjects who completed treatment	138 (81.7)	137 (81.5)
Subjects who discontinued treatment	27 (16.0)	31 (18.5)
Subjects who discontinued treatment but completed study	10 (5.9)	14 (8.3)
Subjects who completed study ^b	142 (84.0)	146 (86.9)
Subjects withdrawn from study	23 (13.6)	18 (10.7)

[a] Informed consent received.

[b] Includes subjects who completed treatment and study, and subjects who discontinued treatment but completed study assessments up to follow up to Visit 16.

[0308] The demographic characteristics of the patients were generally balanced across the treatment groups. Subject characteristics at baseline, including Baseline blood eosinophil count (cells/ μ L), baseline blood eosinophil count group (cells/ μ L) n (%), and Baseline FeNO (ppb), are described in Figure 3.

[0309] The primary endpoint, rate of moderate or severe COPD exacerbations, was not met in the overall population (17% reduction (90% CI: -6% to 36%), p [1-sided]=0.1042). The rate of moderate or severe COPD exacerbations was 1.75 (95% CI: 1.45 to 2.11) in tezepelumab and 2.11 (95% CI: 1.77 to 2.53) in placebo.

[0310] Effects in the primary endpoint (% reduction and 95% CI) and rate of moderate or severe COPD exacerbations (FAS) were observed across baseline biomarkers and subgroups as shown in Figure 4 and Table 3. The effects were not necessarily consistent between different subgroups.

Table 3

Subgroup		% Reduction in exacerbations vs placebo (95% CI)
EOS	<150	-19% (-90%, 25%)
	150-300	34% (-4%, 58%)
	$\geq$ 300	46% (-15%, 75%)
FENO	<25 ppb	1% (-43%, 31%)
	$\geq$ 25 ppb	54% (2%, 78%)
Historical exacerbations	2	4% (-45%, 36%)
	>2	30% (-7%, 54%)
Age group	40-<65 yrs	45% (8%, 67%)

>=65 -80	0% (-44%, 30%)
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[0311] Improvement in the percent reduction in rate of COPD exacerbation as analysed by eosinophil counts at baseline were -19% (-90%, 25%) for patients with <150 cells/μL eosinophil at start of treatment, 34% (-4%, 58%) in patients having between 150-300 cells/μL eosinophil at start of treatment and 46% (-15%, 75%), >=300 cells/μL eosinophil at start of treatment groups respectively. Thus, treatment may be improved in patients having eosinophil counts over 150 cells/μL at the beginning of treatment.

[0312] Rate of exacerbations as analysed based on FeNO levels showed a reduction in exacerbation of 1% (-43%, 31%) and 54% (2%, 78%) in <25 ppb and >=25 ppb patient groups respectively. Thus, treatment may be improved in patients having FeNO equal to or greater than 25 ppb at the beginning of treatment.

[0313] Historical exacerbations were measured resulting in 4% (-45%, 36%) and 30% (-7%, 54%) reduction in those with 2 prior and >2 prior exacerbations, respectively.

[0314] Analysis of the rate of moderate or severe COPD exacerbations by age group: showed 45% (8%, 67%) reduction in patients 40-<65 and 0% (-44%, 30%) in patients 65+.

[0315] Reduction as assessed in relation to incidence of bronchitis was 2% (-47%, 34%) and 34% (-4%, 58%) in patients with and without bronchitis.

[0316] However, a clinically meaningful numerical reduction was observed in the rate of severe exacerbations compared with placebo (48% (95% CI: -11%, 76%) in the all-comer population, although low number of events were observed (Figure 5).

[0317] Numerical improvements from baseline to Week 52 was observed for pre-BD FEV1 (55 mL, 95% CI: 14 to 96mL), SGRQ (-2.93, 95% CI: -6.23 to 0.36) and CAT (-1.855, 95% CI: -3.314 to -0.395), compared with placebo in the all-comer population (Figure 6). There was no meaningful difference vs placebo in E-RS.

[0318] Subgroup analyses of pre-BD FEV1 and SGRQ generally showed numerical improvements regardless of subgroup, however with greater magnitude of effect in the higher EOS, higher FeNO, >=2 exacerbations, 40-<65 groups (Figure 7).

[0319] Reductions in blood EOS and FeNO were observed with no meaningful effect on neutrophil levels (Figure 8).

[0320] The mean trough concentrations in the study was as expected following administration of 420 mg SC Q4W and given the linear PK of tezepelumab.

[0321] Further analysis showed that though the primary endpoint of annualized rate of moderate or severe COPD exacerbations was not met in the overall population (17% reduction [90% CI –6%, 36%], P [1-sided] = 0.1042), the analyses of pre-specified subgroups showed a numerical reduction in participants with BEC $\geq$ 150 cells/ μ L (37% reduction [95% CI – 7%, 57%]. Participants treated with tezepelumab had a numerical (48%) reduction versus placebo in severe COPD exacerbations. Treatment with tezepelumab showed a numerical improvement versus placebo at Week 52 in pre-BD FEV₁ (LS Mean difference 0.055 L [55 mL]), SGRQ total score (LS mean difference -2.933), and CAT total score (LS mean difference -1.855) (**Error! Reference source not found.**). As expected, tezepelumab reduced BEC, FeNO, and IgE. Tezepelumab did not impact the level of neutrophils. Tezepelumab was generally well tolerated in the moderate to very severe COPD population.

Example 2—A Phase 3 Study to Evaluate the Effect of Tezepelumab in Chronic Obstructive Pulmonary Disease (COPD)

[0322] The Phase 2a proof-of-concept study COURSE (NCT04039113) studied efficacy and safety of tezepelumab (at a dose of 420 mg Q4W SC by APFS) in adult participants with moderate to very severe COPD. Tezepelumab demonstrated a numerically greater improvement versus matching placebo on annual exacerbation rates, lung function, and HRQL in a COPD population with blood eosinophils (BEC) > 150 cells/ μ L compared to the overall population (Singh et al 2024). Tezepelumab 420 mg Q4W was well tolerated in participants with COPD, and no new safety concerns were identified compared to its known safety profile from asthma studies.

[0323] This study analyzes the efficacy and safety of tezepelumab administered 420 mg and 210 mg Q4W, SC using APFS, as add-on treatment to inhaled maintenance therapy in the COPD population with a history of exacerbations and $\geq$ 150 cells/ μ L BEC, where currently treatment options are limited. The dose regimen for this study will inform the efficacy and safety of the dose studied in the COURSE (420 mg Q4W) and the lower dose regimen used for asthma (210 mg Q4W).

[0324] Objectives and Endpoints:

[0325] The primary, secondary, and safety objectives, with their associated endpoints, are listed below. The population and estimands are presented in **Error! Reference source not found.**.

Table 4

Objective	Endpoints
Primary	
To compare the effect of tezepelumab with placebo on moderate or severe COPD exacerbations in participants with moderate to very severe COPD	Annualized rate of moderate or severe COPD exacerbations up to 76 weeks
Key Secondary	
To compare the effect of tezepelumab with placebo on pre-BD lung function in participants with moderate to very severe COPD	Change from baseline in pre-BD FEV₁ at Week 52.
To compare the effect of tezepelumab with placebo on HRQL in participants with moderate to very severe COPD	- Change from baseline in the SGRQ total score over 52 weeks. - Participants achieving a clinically meaningful improvement from baseline in SGRQ total score (4-point score decrease) at Week 52.
To compare the effect of tezepelumab with placebo on moderate or severe COPD exacerbations in participants with moderate to very severe COPD and screening BEC $\geq$ 300 cells/ μ L	Annualised rate of moderate or severe COPD exacerbations up to 76 weeks among participants with screening BEC $\geq$ 300 cells/μL
To compare the effect of tezepelumab with placebo on severe COPD exacerbation	Annualised rate of severe COPD exacerbations up to 76 weeks
Other Secondary	
To compare the effect of tezepelumab with placebo on COPD health status in participants with moderate to very severe COPD	- Change from baseline in the CAT total score at Week 52 - Participants achieving a clinically meaningful improvement from baseline in CAT total score (2-point score decrease) at Week 52
To compare the effect of tezepelumab with placebo on time to first moderate or severe COPD exacerbation	Time to first moderate or severe COPD exacerbation up to 76 weeks
To compare the effect of tezepelumab with placebo on time to first severe COPD exacerbation	Time to first severe COPD exacerbation up to 76 weeks
To compare the effect of tezepelumab with placebo on mucus plugging	Change from baseline in mucus score as assessed by CT at Week 52
To explore the effect of tezepelumab on post-BD lung function	Change from baseline in post-BD FEV₁ at Week 52
To compare the effect of tezepelumab with placebo on airway inflammation	Change from baseline in FeNO (ppb) at Week 52
To assess the PK and immunogenicity of tezepelumab in participants with moderate to very severe COPD	- PK: Serum trough concentrations - Immunogenicity: Incidence of anti-drug antibodies and neutralising antibodies
To compare the effect of tezepelumab with placebo on blood eosinophils	Change from baseline in BEC (cells/μL) at Week 52

Objective	Endpoints
Safety	
To compare the safety and tolerability of tezepelumab with placebo in participants with moderate to very severe COPD	Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory, 12-lead ECGs, and physical examination Assessments related to AEs cover: • Occurrence/Frequency • Intensity • Seriousness • Death • AEs leading to discontinuation of study intervention • AESI

ADA, anti-drug antibody; AE, adverse event; AESI, adverse event of special interest; BD, bronchodilator; BEC, blood eosinophil count; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; CT, computed tomography; ECG, electrocardiogram; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in the first second; HRQL, health-related quality of life; PK, pharmacokinetic; SGRQ, St. George's Respiratory Questionnaire.

[0326] Additional endpoints include the following endpoints in Table 5.

Table 5

Exploratory	
To evaluate the effect of tezepelumab with placebo on respiratory symptoms	• Change from baseline in weekly E-RS:COPD score at Week 52 • Participants achieving MCID (2 point score decrease from baseline) in E-RS:COPD total score at Week 52
To explore the effect of tezepelumab on airway structure and function ^a	Change from baseline in CT parameters at Week 52 for: • Quantitative CT mucus plugging assessments • Airway lumen dimensions • Air trapping
To explore an early treatment effect on mucus plugging and airway structure and function ^a	Change from baseline at Week 12 for: • CT mucus score and quantitative mucus plugging assessments • Airway lumen dimensions • Air trapping
To explore the effect of tezepelumab on disease modification in moderate to very severe COPD ^a	Change from baseline in CT parameters at Week 52 for: • Emphysema progression (volume adjusted PD15) • Airway remodelling (airway wall area %)
To explore the effect of tezepelumab on participants perception of COPD health status	• Participants in PGI-S categories and in PGI-C categories at Week 52
To explore the effect of tezepelumab on HRQL	• Change from baseline in Health State Valuation index EQ-5D-5L • Change from baseline in EQ-5D-5L VAS at Week 52

To explore the impact of tezepelumab on blood neutrophil counts	Change from baseline over time in blood neutrophil counts over 52 weeks
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[0327] Eligible participants will be 40 to 80 years of age, have CAT score of ≥ 15 with a history of ≥ 2 moderate or ≥ 1 severe COPD exacerbations within 12 months before Visit 1, and treatment with maintenance inhaled triple (ICS+LABA+LAMA) or dual (LABA+LAMA, ICS+LABA, ICS+LAMA) background therapy. At least one of the 2 historical moderate exacerbations must have required treatment with systemic corticosteroids.

[0328] The study will randomise approximately 990 participants. Eligible participants (as per criteria listed in Section **Error! Reference source not found.**) will be randomised in a 1:1:1 ratio to receive tezepelumab (at doses of either 420 mg Q4W or 210 mg Q4W), or matched placebo Q4W given as an SC injection.

[0329] Inclusion criteria:

1. Adult patients 40 to 80 years of age at the time of signing the informed consent.
2. Documented physician-diagnosed COPD for at least 12 months before Visit 1.
3. A post-BD $FEV_1/FVC < 0.70$ and a post-BD $FEV_1 \geq 20\%$ and $\leq 70\%$ of the predicted normal value during screening.
4. Documented stable dose of triple (ICS+LABA+LAMA) or dual (LABA+LAMA, ICS+LABA, ICS+LAMA) inhaled therapy for at least 3 months before Visit 1.
5. Documented history ≥ 2 moderate or ≥ 1 severe COPD exacerbations within 12 months before Visit 1. At least one of the two moderate exacerbations must have been treated with systemic corticosteroids. An exacerbation will be considered moderate if it requires treatment with systemic corticosteroids (oral or injectable) of at least 3 days (or a single depo injection) and/or antibiotics and does not result in hospitalisation. An exacerbation will be considered severe if it results in hospitalisation (inpatient admission ≥ 24 hours in the hospital, in an observation area, the ER or other equivalent healthcare facility depending on the country and healthcare system).
6. $BEC \geq 150$ cells/ μ L during the screening period.
7. CAT total score ≥ 15 at Visit 1.
8. Current or former smokers (with smoking cessation ≥ 6 months before Visit 1) have a history of at least 10 pack-years of tobacco smoking (1 pack year = 20 cigarettes smoked per day for 1 year).
9. Body weight ≥ 40 kg at Visit 1.
10. Capable of giving signed informed consent as described in Appendix **Error! Reference source not found.** which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
11. Provision of signed and dated, written ICF prior to any mandatory study-specific procedures, sampling, or analysis.

12. $\geq 70\%$ compliance with participant's maintenance COPD therapy within 2 weeks immediately before Visit 2.

[0330] Exclusion criteria: Participants are excluded from the study if any of the following criteria apply

1. Clinically important pulmonary disease other than COPD (eg, active lung infection, clinically significant bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency and primary ciliary dyskinesia) or another diagnosed pulmonary or systemic disease that is associated with elevated peripheral eosinophil (eg, allergic bronchopulmonary aspergillosis/mycosis, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome).
2. Radiological findings suggestive of a respiratory disease other than COPD that is significantly contributing to the participant's respiratory symptoms. Radiological findings of pulmonary nodules suspicious for lung cancer, as per applicable guidance, (eg, ACR Lung-RADS v2022, (**Error! Reference source not found.**)) without appropriate follow up before Visit 2.
3. Radiological findings suggestive of acute infection.
4. Current physician diagnosed asthma according to the Global Initiative for Asthma (**Error! Reference source not found.** and onwards versions) guidelines or other accepted guidelines, past physician diagnosed asthma including paediatric asthma, or asthma-COPD overlap syndrome.
5. Any unstable disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, immune, psychiatric, or major physical/or cognitive impairment that is not stable in the opinion of the investigator or the sponsor and/or could: Affect the safety of the participant throughout the study; Influence the findings of the study or their interpretation; or Impede the participant's ability to complete the entire duration of the study and/or comply with the study visit schedule and procedures.
6. Unstable cardiovascular disorder (including but not limited to ischemic heart disease, arrhythmia, cardiomyopathy, severe right and/or left heart failure (NYHA class IV)), renal failure, uncontrolled hypertension, as defined by the Investigator, or any other relevant cardiovascular disorder or ECG abnormality that in the Investigator's judgment may put the participant at risk or negatively affect the outcome of the study.
7. Acute upper or lower respiratory infection requiring antibiotics or systemic antiviral medication within 2 weeks before Visit 1 (based on the last day of antibiotic/antiviral treatment, whichever occurred later). Lower respiratory infection requiring hospitalisation less than 4 weeks before Visit 1 (based on the date of discharge from hospital).
8. COPD exacerbation treated with systemic corticosteroids and/or antibiotics within 2 weeks before Visit 1 (based on the last dose of corticosteroids or antibiotics, whichever occurred later), or/and requiring hospitalisation for COPD within 4 weeks before Visit 1 (based on the date of discharge from hospital).

9. A helminth parasitic infection within 6 months before Visit 1 that has not been treated with, or has failed to respond to, the standard of care therapy, or diagnosed during the screening period.
10. Immunodeficiency disorder including a positive human immunodeficiency virus test before Visit 1 or during the screening period.
11. Tuberculosis requiring treatment within the 12 months before Visit 2.
12. Anaphylaxis or documented immune complex disease (Type III hypersensitivity reactions) following any biologic therapy.
13. Chronic alcohol or drug abuse within 12 months before Visit 1 or during screening, which may compromise the interpretation of the study data as judged by investigator.
14. Major surgery within 8 weeks before Visit 1 or planned surgical procedures requiring general anesthesia or hospitalization for > 1 day during the study.
15. Malignancy, current or past (within 5 years before Visit 1), except for basal cell carcinoma, localized squamous cell carcinoma of the skin, or in situ carcinoma of the cervix provided when a curative therapy was completed at least 12 months before Visit 1.
16. Past or planned partial or total lung volume reduction (single lobe or segmentectomy is acceptable). Surgical or endoscopic (e.g., valves) lung volume reduction within 6 months before Visit 1 or a planned procedure.
17. Treatment with systemic immunosuppressive/immunomodulating medications including maintenance use of systemic corticosteroids within the last 12 weeks or 5 half-lives before Visit 1 or during the screening for other reasons than COPD exacerbation. Expected need for chronic use during the study for any reason.
18. LTOT with signs and/or symptoms of cor pulmonale and/or right ventricular failure, or LTOT > 4.0 litres/minute (L/min) at rest or an oxyhaemoglobin saturation < 89% despite LTOT.
19. Use or need for chronic use of any non-invasive positive pressure ventilation device. Stable use of non-invasive ventilation for the treatment of Obstructive Sleep Apnoea is permitted.
20. Treatment with maintenance allergen-specific immunotherapy initiated < 30 days before Visit 1.
21. Maintenance treatment with macrolides or other antibiotics for COPD if the duration of the treatment is < 6 months before Visit 1.
22. Treatment with any marketed respiratory biologic or investigational biologic within 4 months or 5 half-lives before randomisation.

Note: Treatment with marketed ocular biologics is allowed. Other marketed biologics that are not likely to interfere with the safety assessment and/or efficacy of tezepelumab might be allowed upon a prior AZ study physician/delegate approval.
23. Receipt of immunoglobulin or blood products within 30 days before randomisation.
24. Receipt of live attenuated vaccines 30 days before first IP administration.
25. Receipt of any COVID-19 vaccine within 28 days before first IP administration.

26. 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.
27. Concurrent enrolment in another IP-related interventional clinical trial.
28. Previous receipt of tezepelumab. A participant randomised to the placebo arm in previous tezepelumab studies may be allowed to participate following agreement with AZ study physician/delegate.
29. Involvement in the planning and/or conduct of the study (applies to AZ staff and/or site staff), or participants employed by or relatives of the employees of the site or sponsor.
30. Any clinically significant abnormal findings in physical examination, vital signs, hematology, clinical chemistry, or urinalysis during screening, 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 the entire duration of the study.
31. Evidence of active liver disease, including jaundice or AST, ALT, or ALP greater than twice the ULN (laboratory results during screening and/or before first dose).
32. Positive hepatitis B surface antigen, or hepatitis C virus antibody serology, or a positive medical history for hepatitis B or C. Participants with a history of hepatitis B vaccination without history of hepatitis B are allowed to enrol.
33. Non-leukocyte-depleted whole blood transfusion within 120 days of genetic sample collection.
34. Previous allogenic bone marrow transplant.
35. Pregnant (confirmed with positive pregnancy test), breastfeeding, or lactating participants.
36. Taking part in, or are scheduled for, an intensive (active) COPD rehabilitation program (however participants who are in the maintenance phase of a rehabilitation program are eligible to take part).
37. Inability to follow the study procedures or restrictions, in the opinion of the investigator (e.g., use of ePRO device or app, an acceptable inhaler techniques, and spirometry techniques according to the ATS/ERS 2019 guidelines (**Error! Reference source not found.**)).
38. Donation of blood, plasma, or platelets within the past 90 days before randomisation

[0331] All participants are required to be treated with stable maintenance triple inhaled therapy (ICS+LABA+LAMA) or dual (LABA+LAMA, ICS+LABA, ICS+LAMA) throughout at least 3 months before Visit 1 and during the VTP. Dual or triple maintenance inhaled therapy components may be used in fixed-dose combination(s) or separate devices. Additional COPD maintenance therapies (such as macrolides or other antibiotics, xanthines, roflumilast, mucolytics, LTRA, antitussives) are allowed in the study.

[0332] SABA and/or SAMA and/or SABA/SAMA combination may be used during the study in the event of worsening of COPD symptoms, as per local SoC. Rescue medication

use is restricted before spirometry. Rescue medication use will be reported via ePRO device or app by a participant and the use will be monitored by the Investigator/delegate.

[0333] The participant will be required to complete PRO measures using an ePRO device or an app downloaded on his/her own device. The measures to be collected include: SGRQ, CAT, CED, BCSS, COPD maintenance therapy and rescue medication use.

[0334] The primary endpoint in this study is the annualized rate of moderate or severe COPD exacerbations.

[0335] Assessment of COPD Exacerbation

[0336] A moderate or severe COPD exacerbation will be defined as a worsening in the participant's usual COPD symptoms that is beyond normal day-to-day variation, is acute in onset, lasts 2 or more days (or less if the worsening is so rapid and profound that the treating physician judges that intensification of treatment cannot be delayed), may warrant a change in regular medication, and leads to any one of the following:

- Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids
- Use of antibiotics to treat COPD exacerbation
- An inpatient hospitalization due to COPD (defined as an inpatient admission $\geq$ 24 hours in the hospital, an observation area, the emergency department, or other equivalent healthcare facility depending on the country and healthcare system)
- Results in death

[0337] Severity of COPD Exacerbations

[0338] A COPD exacerbation will be considered moderate if it requires treatment with systemic corticosteroids for at least 3 days and/or antibiotics and does not result in hospitalization or death. Moderate severity also includes use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids

[0339] A COPD exacerbation will be considered severe if it results in hospitalization (defined as an inpatient admission $\geq$ 24 hours in the hospital, an observation area, the ER, or other equivalent healthcare facility depending on the country and healthcare system) or death due to COPD.

[0340] The start and stop of a moderate or severe exacerbation is defined as: the start date of systemic corticosteroids or antibiotic treatment or hospital admission, whichever occurs earlier, and the stop date is defined as the last day of systemic corticosteroids or antibiotic treatment or hospital discharge, whichever occurs later.

[0341] A single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids. The corresponding stop date for this treatment will consequently be determined as the date of administration plus 2 days. If multiple treatments are prescribed for the same exacerbation, the earliest start date and the latest stop date for systemic corticosteroids or antibiotics will be used. For a severe COPD exacerbation with no documented corticosteroid or antibiotics treatment, hospitalization admission/discharge dates, or ER visit dates will be used as start/stop dates.

[0342] Spirometry (pre-BD and post-BD) are measured using techniques as described in Example 1.

[0343] Composite endpoint for Exacerbations in COPD (COPDCompEx) is measured using techniques as described in Example 1

[0344] Patient Reported Outcomes

[0345] Participants will complete all PRO assessments at home and/or at site visits at time points specified in the SoA using a handheld ePRO device or an app on the participant's own device.

[0346] The daily at-home ePRO assessments will be completed by the participant at home. If a scheduled ePRO has not been completed at the time of a site visit, site personnel will ask the participant to complete it on-site prior to completing other study procedures.

[0347] St. George's Respiratory Questionnaire (SGRQ), BOD index, mMRC and COPD Assessment Test are measured using techniques as described herein.

[0348] Breathlessness, Cough, and Sputum Scale

[0349] The BCSS® is a 3-item PRO that assesses the severity of 3 symptoms: breathlessness, cough, and sputum, each on a scale of 0 to 4. Item scores can be reported individually and can also be summed to yield a total score. Higher scores for each item, and thus for the total score, indicate more severe symptoms. The BCSS will be completed each evening via ePRO device or app as the recall period is "today" (Leidy et al 2003).

[0350] COPD Exacerbation Diary

[0351] The severity of COPD symptoms will be assessed daily via the CED for the purposes of a symptom worsening alert. The purpose of this alert is to notify both the participant and the study site of a potential symptom worsening that warrants contact between the patient and site for further evaluation.

[0352] Each day the participant will complete 3 questions pertaining to COPD symptoms: breathlessness, cough, and mucus (phlegm) volume. Worsening of at least 1 of these symptoms will trigger assessment of 5 additional symptoms: mucus (phlegm) color, wheeze, sore throat, cold and fever. All questions have a 24-hour recall period. Questions pertaining to the severity of symptoms compared with their usual state have 3 response options (e.g., How breathless have you been in the last 24 hours? Less breathlessness than usual, Usual level of breathlessness, more breathless than usual), whereas, questions related to the presence or absence of a symptom have a dichotomous response (e.g., Have you had a sore throat in the last 24 hours? No or Yes, I had a sore throat).

[0353] If COPD symptoms worsen for at least 2 consecutive days, the ePRO device or app generates an COPD worsening alert to the participant and the investigational site. This alert should trigger contact between the participant and the investigational site. The investigator then makes the decision whether or not to initiate (or escalate, as appropriate) treatment (i.e., with systemic corticosteroids and/or antibiotics, and/or hospitalization).

[0354] COPD maintenance therapy use will be recorded by the participants in the ePRO device or app each evening. The participant is asked a single question on whether they took their regularly scheduled COPD medicine (yes/no) and instructed not to consider instances of rescue medication use when answering this question.

[0355] Rescue medication use (e.g., SABA and/or SAMA) will be recorded by the participants in the ePRO device or app each evening. The participant is asked whether they used a rescue medication in response to worsening symptoms. If they indicate that they used a rescue inhaler, they are asked to provide the number of puffs of a rescue inhaler in the past 24 hours. If they indicate that they used a nebulizer, they are asked to provide the number of times they used a nebuliser over the last 24 hours.

[0356] 5-level EuroQoL-5 Dimension

[0357] The EQ-5D-5L assesses 5 dimensions of health including 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 unable to/extreme problems; the participant indicates his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The EQ-5D-5L also includes a VAS, where the

participant rates his/her current health status on a scale of 0 to 100, with 0 being the worst imaginable health state (Brooks 1996, EuroQol Group 1990, EuroQol Research Foundation 2021, Kind et al 1991, Rabin and de Charro 2001).

[0358] Clinically Important Deterioration (CID) is measured as described herein.

[0359] Biomarkers

[0360] Blood, serum and plasma samples will be collected to evaluate the pharmacology of tezepelumab and to evaluate changes in biomarkers related to COPD, inflammation, and the TSLP pathway. Blood, serum, and plasma biomarkers may also be used as predictive biomarkers of response or exposure to tezepelumab.

[0361] The biomarkers analyzed include cytokines, chemokines and inflammatory mediators associated with COPD and the TSLP pathway, such as:

- BEC:
- Serum IgE: Serum EDN - Baseline and early post-dose levels of serum EDN levels
- TSLP
- Fibrinogen
- Serum IL-5 and IL-13
- Proteomics analysis to evaluate additional protein markers related to Th1, Th2, Th17 and other inflammatory immune pathways and airway re-modelling
- Transcriptomics - Whole blood samples will be collected in PAXgene® tubes for RNA sample preparation. RNA may be used in the analyses of host gene expression and microbiome research using quantitative methods that may include but not be limited to RNA microarrays, RNA-Seq and quantitative reverse-transcriptase polymerase chain reaction technologies and stored for future analyses.
- FeNO
- Blood samples for the determination of ADA and neutralizing antibodies in serum.
- BMI, Airflow Obstruction, Dyspnoea Index is also measured.
- CT imaging biomarkers (mucous plugging, airway lumen dimensions, air trapping, emphysema progression, airway remodeling).

[0362] To analyze the primary endpoint, participants with moderate to very severe COPD receiving a stable dose of triple inhaled maintenance therapy (ICS+LABA+LAMA) or dual

therapy (LABA+LAMA, ICS+LABA, ICS+LAMA) with ≥ 2 moderate or ≥ 1 severe documented COPD exacerbation(s) in the 12 months before Visit 1 and ≥ 150 BEC / μ L during screening. Patients are randomized into treatment groups of tezepelumab (420 mg Q4W or 210 mg Q4W) or matching placebo Q4W.

[0363] To monitor the secondary endpoints, participants with moderate to very severe COPD receiving a stable dose of triple inhaled maintenance therapy (ICS+ LABA+LAMA) or dual therapy (LABA+LAMA, ICS+LABA, ICS+LAMA) with ≥ 2 moderate or ≥ 1 severe documented COPD exacerbation(s) in the 12 months before Visit 1 and $\geq 150/\mu$ L BEC during screening are measured for pre-BD FEV₁ change from baseline at Week 52. All participants are monitored for their SGRQ change from baseline over 52 weeks.

[0364] The minimum study duration is 67 weeks, and the maximum is 98 weeks.

[0365] The population to be studied in this Phase 3 study has been defined based on results of completed Phase 2a study COURSE in which a numerical effect of tezepelumab versus placebo was observed on annual exacerbation rates, lung function, and HRQL in symptomatic participants (CAT ≥ 15), on the triple inhaled COPD therapy, with moderate to very severe COPD with a history of exacerbations (≥ 2 moderate COPD exacerbations) and BEC ≥ 150 cells/ μ L regardless of a smoking status (former or current) (Section **Error! Reference source not found.**).

[0366] The primary endpoint (rate of COPD exacerbations) is a well-accepted measure for drug efficacy in a registrational study with a COPD population.

[0367] The control group in this study is placebo. Both tezepelumab and placebo will be given on top of maintenance COPD inhaled therapy; therefore, the placebo group's treatment will correspond to the current SoC for patients with COPD. The double-blind design will allow for an unbiased assessment of the effect of tezepelumab.

[0368] Based on the COURSE data, the BEC eligibility criterion (≥ 150 cells/ μ L during screening) will be confirmed at the central laboratory measurement at Visit 1. The COPD MAP observational cohort study showed that approximately 70% of patients with two blood eosinophil measurements remained in the same BEC category (< 100 , 100 to 300 and ≥ 300) over 1 year and that small numerical movements across BEC thresholds should not change the initial clinical interpretation based on blood eosinophil count and provides reassurance regarding treatment decisions using this biomarker in COPD (**Error! Reference source not found.**). A post hoc analysis of IMPACT a large inhaled therapy trial, found that single blood eosinophil count was as good as two for prediction of an ICS response (**Error!**

Reference source not found.). A higher BEC stability is expected in COPD patients with less than 340 cells/ μ L (**Error! Reference source not found.**).

[0369] Numerous modifications and variations of the invention as set forth in the above illustrative examples are expected to occur to those skilled in the art. Consequently only such limitations as appear in the appended claims should be placed on the invention.

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What is Claimed:

1. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering an anti-TSLP antibody to the subject in a dose of 210 mg 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.
2. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering an anti-TSLP antibody to the subject in a dose of 210 mg 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 comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

4. The method of any one of claims 1 to 3, wherein the antibody is administered every 2 weeks.

5. The method of any one of claims 1 to 4, wherein the antibody is administered every 4 weeks.

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 5, wherein the antibody is administered at a dose of 420 mg.

8. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering an anti-TSLP antibody to the subject in a dose of 420 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 chronic obstructive pulmonary disease (COPD) in a subject comprising, administering an anti-TSLP antibody to the subject in a dose of 420 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. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering 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.

11. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering 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.

12. The method of any one of claim 8 to 11, wherein the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

13. The method of claim 10 wherein the antibody further comprises an IgG2 domain.

14. 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.

15. The method of any one of the preceding claims, wherein the 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.

16. The method of any one of the preceding claims, wherein the antibody is an IgG2 antibody.

17. The method of any one of the preceding claims, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

18. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering an anti-TSLP antibody to the subject in a dose of 210 mg at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

19. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering an anti-TSLP antibody to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

20. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg to 420 mg at an interval of every 2 weeks or 4 weeks, wherein both

binding sites of the antibody are identical binding sites that bind 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.

21. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg to 420 mg at an interval of every 2 weeks or 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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.

22. The method of claim 20 or 21, wherein the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

23. The method of claim 22 wherein the antibody further comprises an IgG2 domain.

24. The method of any one of claims 20 to 23, wherein the antibody or antibody variant is administered every 2 weeks.

25. The method of any one of claims 20 to 23, wherein the antibody or antibody variant is administered every 4 weeks.

26. The method of any one of claims 20 to 25, wherein the antibody is an IgG2 antibody.

27. The method of any one of claims 20 to 26, wherein the antibody or antibody variant is administered at a dose of 210 mg.

28. The method of any one of claims 20 to 27, wherein the antibody or antibody variant is administered at a dose of 420 mg.

29. The method of any one of claims 20 to 28, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

30. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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.

31. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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.

32. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering 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 are identical binding sites that bind 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.

33. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering 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 are identical binding sites that bind 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.

34. The method of any one of claims 30 to 33, wherein the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

35. The method of claim 34, wherein the antibody further comprises an IgG2 domain.

36. The method of any one of claims 30 to 35, 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.

37. The method of any one of claims 30 to 36, wherein 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 IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody.

38. The method of any one of claims 30 to 37, wherein the antibody is an IgG2 antibody.

39. The method of any one of claims 30 to 38, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

40. The method of any one of claims 30 to 39, wherein the antibody or antibody variant is a human antibody.

41. A method for treating chronic obstructive pulmonary disease (COPD) in a subject in need thereof comprising, administering an anti-TSLP antibody to the subject in a dose of 210 mg 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 human IgG2 antibody.

42. A method for treating chronic obstructive pulmonary disease (COPD) in a subject in need thereof comprising, administering an anti-TSLP antibody to the subject in a dose of 210 mg 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, wherein the antibody is an human IgG2 antibody.

43. The method of claim 41 or 42, wherein the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

44. The method of any one of claims 41 to 43, wherein the antibody is administered every 2 weeks.

45. The method of any one of claims 41 to 43, wherein the antibody is administered every 4 weeks.

46. The method of any one of claims 41 to 45, wherein the antibody is administered at a dose of 210 mg.

47. The method of any one of claims 41 to 45, wherein the antibody is administered at a dose of 420 mg.

48. The method of any one of claims 41 to 47, wherein the has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

49. A method for treating chronic obstructive pulmonary disease (COPD) in a subject in need thereof comprising, administering an anti-TSLP antibody to the subject in a dose of 420 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, wherein the antibody is an human IgG2 antibody.

50. A method for treating chronic obstructive pulmonary disease (COPD) in a subject in need thereof comprising, administering an anti-TSLP antibody to the subject in a dose of 420 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, wherein the antibody is an human IgG2 antibody.

51. A method for treating chronic obstructive pulmonary disease (COPD) in a subject in need thereof comprising, administering 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, wherein the antibody is an human IgG2 antibody.

52. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, administering 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, wherein the antibody is an human IgG2 antibody.
53. The method of any one of claims 49 to 52, wherein the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.
54. The method of any one of claims 49 to 53, wherein the antibody is administered for a period of at least 4 months, 6 months, 9 months, 1 year, 2 years or more.
55. The method of any one of claims 49 to 54, wherein the has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.
56. The method of any one of the preceding claims wherein, the antibody or antibody variant is administered to the subject in a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient.
57. The method of any one of the preceding claims, wherein the COPD is moderate to very severe COPD.
58. The method of any one of the preceding claims, wherein the subject is an adult.
59. The method any one of the preceding claims, wherein the method improves one or more measures of COPD in a subject selected from moderate to severe COPD exacerbation, time to first COPD exacerbation, rate of COPD exacerbations associated with emergency room (ER) visit, urgent care visit or hospitalization, FeNO level, COPD Assessment Test (CAT) score, Clinically Important Deterioration (CID) score, Exacerbations of Chronic Pulmonary Disease Tool– Patient-reported Outcome (EXACT-PRO) score, E-RS, composite endpoint for exacerbations (moderate or severe) in COPD (COPDCompEx)

score, change from baseline in pre- and post-BD FEV₁, St George's Respiratory Questionnaire (SGRQ) score, E-RS or CAT score, BOD Index, mMRC dyspnoea scale score, 5-level EuroQoL-5 Dimension score, and/or reporting of a worsening event, e.g., dyspnea, sputum volume, and sputum color, blood IgE, eosinophil-derived neurotoxin (EDN), IL-5, CT imaging biomarkers (mucous plugging, airway lumen dimensions, air trapping, emphysema progression, airway remodeling).

60. The method any one of the preceding claims, wherein the administration improves one or more symptoms of COPD as measured by a patient symptom diary.

61. The method of any one of the preceding claims, 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.

62. The method of any one of the preceding claims wherein the subject is also receiving a co-administered therapy.

63. The method of claim 62, wherein the co-administered therapy is selected from the group consisting of a short-acting β 2 agonist (SABA), long-acting β 2 agonist (LABA), inhaled corticosteroids, oral corticosteroids, short acting muscarinic antagonist (SAMA), long acting muscarinic antagonist (LAMA), triple inhaled maintenance therapy (inhaled corticosteroid/long-acting β 2 agonist and long acting muscarinic antagonist [ICS/LABA/LAMA]), and combinations thereof.

64. The method of claim 62 or 63, wherein the co-administered therapy is triple inhaled maintenance therapy (inhaled corticosteroid/long-acting β 2 agonist and long acting muscarinic antagonist [ICS/LABA/LAMA]).

65. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody to the subject in a dose of 210 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.

66. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody to the subject in a dose of 210 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).

67. The method of claim 65 or 66, wherein the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

68. The method of claim 67, wherein the antibody further comprises an IgG2 domain.

69. The method of any one of claims 65 to 68, wherein the antibody is administered every 2 weeks.

70. The method of any one of claims 65 to 68, wherein the antibody is administered every 4 weeks.

71. The method of any one of claims 65 to 70, wherein the antibody is administered at a dose of 210 mg.

72. The method of any one of claims 65 to 70, wherein the antibody is administered at a dose of 420 mg.

73. The method of any one of claims 65 to 72, wherein the antibody is administered for a period of at least 4 months, 6 months, 9 months, 1 year, 2 years or more.

74. The method of any one of claims 65 to 73, wherein the 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.

75. The method any one of claims 65 to 74, wherein the antibody is an IgG2 antibody.

76. The method of any one of claims 65 to 75, wherein the antibody is a human antibody.

77. The method of any one of claims 65 to 76, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

78. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody to the subject in a dose of 420 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.

79. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody to the subject in a dose of 420 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).

80. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering 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 antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2.

81. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody to the subject in a dose of 210 mg at an interval of every 2 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).

82. The method of any one of claims 78 to 81, wherein the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

83. The method of claim 82, wherein the antibody further comprises an IgG2 domain.

84. The method of any one of claims 78 to 83, wherein the antibody is administered for a period of at least 4 months, 6 months, 9 months, 1 year, 2 years or more.

85. The method of any one of claims 78 to 84, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

86. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody to the subject in a dose of 210 mg at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

87. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

88. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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.

89. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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).

90. The method of claim 88 or 89, wherein the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

91. The method of claim 90, wherein the antibody further comprises an IgG2 domain.

92. The method of any one of claims 88 to 91, wherein the antibody or antibody variant is administered every 2 weeks.

93. The method of any one of claims 88 to 91, wherein the antibody or antibody variant is administered every 4 weeks.

94. The method of any one of claims 88 to 93, wherein the antibody or antibody variant is administered at a dose of 210 mg.

95. The method of any one of claims 88 to 93, wherein the antibody or antibody variant is administered at a dose of 420 mg.

96. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 210 mg to 420 mg at an interval of every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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.

97. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering 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 are identical binding sites that bind 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).

98. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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.

99. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein both binding sites of the antibody are identical binding sites that bind 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).

100. The method of any one of claims 88 to 99, 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.

101. The method of any one of claims 88 to 100, wherein the 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.

102. The method any one of claims 88 to 101, wherein the antibody or antibody variant is an IgG2 antibody.

103. The method of any one of claims 88 to 102, wherein the antibody or antibody variant is a human antibody.

104. The method of any one of claims 88 to 103, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

105. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody to the subject in a dose of 210 mg to 420 mg at an interval of every 2 weeks or every 4 weeks, 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, and wherein the antibody is an human IgG2 antibody.

106. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody or antibody variant to the subject in a dose of 210 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), and wherein the antibody is an human IgG2 antibody.

107. The method of claim 105 or 106, wherein the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

108. The method of any one of claims 105 to 107, wherein the antibody is administered every 2 weeks.

109. The method of any one of claims 105 to 107, wherein the antibody is administered every 4 weeks.

110. The method of any one of claims 105 to 109, wherein the antibody is administered at a dose of 210 mg.

111. The method of any one of claims 105 to 109, wherein the antibody is administered at a dose of 420 mg.

112. The method of any one of claims 105 to 111, wherein the antibody is administered for a period of at least 4 months, 6 months, 9 months, 1 year, 2 years or more.

113. The method of any one of claims 105 to 112, wherein the has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

114. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody to the subject in a dose of 420 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, wherein the antibody is an human IgG2 antibody.

15. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering an anti-TSLP antibody to the subject in a dose of 420 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 is an human IgG2 antibody.

116. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering 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 antigen binding protein specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO:2, wherein the antibody is an human IgG2 antibody.

117. A method of reducing the frequency of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in a subject having COPD comprising, administering 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 is an human IgG2 antibody.

118. The method of any one of claims 114 to 117, wherein the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

119. The method of any one of claims 114 to 118, wherein the antibody is administered for a period of at least 4 months, 6 months, 9 months, 1 year, 2 years or more.

120. The method of any one of claims 114 to 119, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

121. The method of any one of the preceding claims wherein the method delays the time to a COPD exacerbation compared to a subject not receiving the anti-TSLP antibody.

122. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD) and administering an anti-TSLP antibody to the subject in a dose of 210 mg to 420 mg at an interval of every 2 weeks or 4 weeks, 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.

123. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD) and administering an anti-TSLP antibody to the subject in a dose of 210 mg to 420 mg at an interval of every 2 weeks or 4 weeks, 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.

124. The method of claim 122 or 123, wherein the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

125. The method of claim 124, wherein the antibody further comprises an IgG2 domain.

126. The method of any one of claims 122 to 125, wherein the antibody is administered every 2 weeks.

127. The method of any one of claims 122 to 125, wherein the antibody is administered every 4 weeks.

128. The method of any one of claims 122 to 127, wherein the antibody is an IgG2 antibody.

129. The method of any one of claims 122 to 128, wherein the antibody or antibody variant is administered at a dose of 210 mg.

130. The method of any one of claims 122 to 128, wherein the antibody or antibody variant is administered at a dose of 420 mg.

131. The method of any one of claims 122 to 130, wherein the has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

132. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD) and administering an anti-TSLP antibody to the subject in a dose of 420 mg at an interval of every 4 weeks, 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.

133. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD) and administering an anti-TSLP antibody to the subject in a dose of 420 mg at an interval of every 4 weeks, 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.

134. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD) and administering an anti-TSLP antibody to the subject in a dose of 210 mg at an interval of every 4 weeks, 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.

135. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD) and administering an anti-TSLP antibody to the subject in a dose of 210 mg at an interval of every 4 weeks, 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.

136. The method of anyone of claims 132 to 135, wherein the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

137. The method of claim 136, wherein the antibody further comprises an IgG2 domain.

138. The method of any one of claims 132 to 137, wherein the antibody is administered for a period of at least 4 months, 6 months, 9 months, 1 year, 2 years or more.

139. The method of any one of claims 132 to 138, wherein 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.

140. The method of any one of claims 132 to 139, wherein the antibody is an IgG2 antibody.

141. The method of any one of claims 132 to 140, wherein the antibody is a human antibody.

142. The method of any one of claims 132 to 141, wherein the has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

143. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD) and administering an anti-TSLP antibody to the subject in a dose of 210 mg at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

144. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD) and administering an anti-TSLP antibody to the subject in a dose of 420 mg at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

145. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD) and administering an anti-TSLP antibody to the subject in a dose of 210 mg to 420 mg at an interval of every 2 weeks or 4 weeks, 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 human IgG2 antibody.

146. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD) and administering an anti-TSLP antibody to the subject in a dose of 210 mg to 420 mg at an interval of every 2 weeks or 4 weeks, 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, wherein the antibody is an human IgG2 antibody.

147. The method of claim 145 or 146, wherein the light chain variable domain comprises the amino acid sequence set forth in in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

148. The method of any one of claims 145 to 147, wherein the antibody is administered every 2 weeks.

149. The method of any one of claims 145 to 147, wherein the antibody is administered every 4 weeks.

150. The method of any one of claims 145 to 149, wherein the antibody or antibody variant is administered at a dose of 210 mg.

151. The method of any one of claims 145 to 149, wherein the antibody or antibody variant is administered at a dose of 420 mg.

152. The method of any one of claims 145 to 151, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

153. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD) and administering an anti-TSLP antibody to the subject in a dose of 420 mg at an interval of every 4 weeks, 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 human IgG2 antibody.

154. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD) and administering an anti-TSLP antibody to the subject in a dose of 420 mg at an interval of every 4 weeks, 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, wherein the antibody is an human IgG2 antibody.

155. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD) and administering an anti-TSLP antibody to the subject in a dose of 210 mg at an interval of every 4 weeks, 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 human IgG2 antibody.

156. A method for treating chronic obstructive pulmonary disease (COPD) in a subject comprising, selecting a subject in need of treatment for chronic obstructive pulmonary disease (COPD) and administering an anti-TSLP antibody to the subject in a dose of 210 mg at an interval of every 4 weeks, 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, wherein the antibody is an human IgG2 antibody.

157. The method of anyone of claims 153 to 156, wherein the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

158. The method of any one of claims 145 to 157, wherein the antibody is administered for a period of at least 4 months, 6 months, 9 months, 1 year, 2 years or more.

159. The method of any one of claims 145 to 158, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

160. The method of any one of the preceding claims, wherein the subject has a baseline eosinophil count of 100 cells/ μ L or greater.

161. The method of any one of the preceding claims, wherein the subject has a baseline eosinophil count of 150 cells/ μ L or greater.

162. The method of any one of the preceding claims, wherein the subject has a baseline eosinophil count between 100 cells/ μ L to 300 cells/ μ L.

163. The method of any one of the preceding claims, wherein the subject has a baseline eosinophil count between 150 cells/ μ L to 300 cells/ μ L.

164. The method of any one of the preceding claims, wherein the subject has a baseline eosinophil count of 300 cells/ μ L or greater.

165. The method of any one of the preceding claims, wherein the subject has FeNO levels greater than or equal to 25 ppb.

166. The method of any one of the preceding claims, wherein the subject is between 40 and 65 years of age.

167. The method of any one of the preceding claims, wherein the subject has improvement in pre- and post-BD FEV1 levels, SGRQ score, E-RS and/or CAT score compared to baseline at Week 52.

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

169. A composition comprising an anti-TSLP antibody for treating chronic obstructive pulmonary disease (COPD) in a subject, wherein the composition is administered in a dose of 210 mg 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.

170. A composition comprising an anti-TSLP antibody for treating chronic obstructive pulmonary disease (COPD) in a subject, wherein the composition is administered in a dose of 210 mg 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.

171. Use of a composition comprising an anti-TSLP antibody in the manufacture of a medicament for treating chronic obstructive pulmonary disease (COPD) in a subject, wherein the composition is in a dose of 210 mg to 420 mg for administration 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.

172. Use of a composition comprising an anti-TSLP antibody in the preparation of a medicament for treating chronic obstructive pulmonary disease (COPD), wherein the composition is in a dose of 210 mg to 420 mg for administration 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.

173. The composition or use of any one of claims 169 to 172, wherein the light chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:12 and the heavy chain variable domain comprises the amino acid sequence set forth in SEQ ID NO:10.

174. The composition or use of any one of claims 169 to 173, wherein the antibody is administered every 2 weeks.

175. The composition or use of any one of claims 169 to 173, wherein the antibody is administered every 4 weeks.

176. The composition or use of any one of claims 169 to 175, wherein the antibody is an IgG2 antibody.

177. The composition or use of any one of claims 169 to 176, wherein the antibody or antibody variant is administered at a dose of 210 mg.

178. The composition or use of any one of claims 169 to 176, wherein the antibody or antibody variant is administered at a dose of 420 mg.

179. The composition or use of any one of claims 169 to 178, wherein the has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

180. A composition for treating chronic obstructive pulmonary disease (COPD) in a subject comprising an anti-TSLP antibody, wherein the antibody is administered in a dose of 210 mg at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

181. A composition for treating chronic obstructive pulmonary disease (COPD) in a subject comprising an anti-TSLP antibody, wherein the antibody is administered in a dose of 420 mg at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

182. Use of a composition comprising an anti-TSLP antibody in the preparation of a medicament for treating chronic obstructive pulmonary disease (COPD), wherein the composition is in a dose of 210 mg for administration at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.

183. Use of a composition comprising an anti-TSLP antibody in the preparation of a medicament for treating chronic obstructive pulmonary disease (COPD), wherein the composition is in a dose of 420 mg for administration at an interval of every 4 weeks, wherein the antibody has a full-length heavy chain amino acid sequence set forth in SEQ ID NO: 13 and a full-length light chain amino acid sequence set forth in SEQ ID NO: 14.